# British Dietetic Association (BDA), British Nutrition Foundation (BNF) and Diabetes UK

# Insight Document on Low- and No-Calorie Sweeteners

This paper aims to update the low- and no-calorie sweeteners (LNCS) insights document for the British Dietetic Association (BDA), British Nutrition Foundation (BNF) and Diabetes UK position statement published in 2019.

A working group from the three organisations has undertaken a narrative rapid review (completed 29 February 2024), to assess the evidence on the association between LNCS and health outcomes including dental health, obesity, cardiovascular disease, type 2 diabetes (T2D), cancer, and associated disease risk markers including appetite and the gut microbiome. The purpose of this insight document is to provide a summary of the evidence. It is not a systematic review, and the outcomes considered were selected by the working group (comprising dietitians, public health nutritionists and academics and including specialists in diabetes) as those of greatest public health and consumer concern.

This Insight document should be considered alongside the 2025 Scientific Advisory Committee on Nutrition (SACN) statement on non-sugar sweeteners (see SACN Recommendations in Appendix H).

## Contents

# Introduction

## The need for sugar reduction

Tackling obesity is a major public health challenge in the UK and globally in adults and children. In England, around two-thirds (64%) of adults in England are living with overweight, with over one in four living with obesity (NHS England 2024). In children aged 10 – 11 years, 23.4% are living with obesity, with a strong association identified between obesity and deprivation (NHS England 2023). There is a similar picture in the devolved nations[1]. Obesity is associated with reduced life expectancy and an increased risk of developing (or exacerbation of) a number of chronic diseases and conditions including cardiovascular disease (e.g., coronary heart disease), T2D, various cancers, as well as liver and respiratory disease, and can impact mental health (DHSC 2016; NICE 2025).

Reduction in sugar intake has emerged as a key target for intervention to tackle childhood obesity and is a focus of many UK and global public health nutrition policies. Excess intake of free sugars[2] is widely believed to be a contributing factor to obesity risk and is the primary dietary risk factor in the development of dental caries. Although largely preventable, nearly a quarter of 5-year-olds in England have experienced tooth decay, affecting 3 – 4 teeth on average (OHID 2022). In countries like the UK and US, sugar sweetened beverages (SSBs) are a major source of free sugars in the diet (DiFrancesco *et al.* 2022; PHE 2020). The average intake of free sugars for all age groups in the UK exceeds the Scientific Advisory Committee on Nutrition[3] (SACN) recommendation of no more than 5% of energy intake. The UK *National Diet and Nutrition Survey* (NDNS) data 2019 to 2023 reported average intakes of 10.2% energy intake in children aged 4 – 10 years, 11.4% in 11 – 18-year-olds, and 10.0% in 19 – 64-year-olds) (OHID 2025). Reducing current intakes to recommended amounts will likely require a concerted approach with a broad range of population-based interventions including product reformulation. Use of low- or no-calorie sweeteners (LNCS) presents a practical strategy to decrease the sugar content of some foods and beverages.

## What are 'sweeteners'?

The term 'sweetener' can be used to describe any sweetening agent including sugar, syrups, and honey, but it is most often used to describe ingredients added to food in small amounts to create a sweet taste, with limited calories. The term 'artificial' sweeteners can be used to define synthetically derived chemicals and can also include 'natural' extracts (e.g. stevia) that may or may not be chemically modified. Other terms used in the scientific literature include high-intensity sweeteners, non-sugar sweeteners (NSS), non-nutritive sweeteners (NNS) and non-caloric sweeteners.

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[1] Devolved nations refers to the UK nations with devolved powers. Devolution is the decentralisation of governmental power. In the UK, this refers to the separate legislatures and executives in Scotland, Wales and Northern Ireland that have powers to make laws and deliver public services (GOV.UK)

[2] These are sugars that are added to food/drink items and those naturally occurring in honey, syrups, fruit juices and fruit juice concentrates (WHO, 2015). In the UK, it is currently recommended that free sugar consumption is limited to no more than 5% of total dietary intake (SACN, 2015).

[3] SACN is the independent body of experts that advises and provides independent scientific advice on, and risk assessment of, nutrition and related health issues to government on nutrition and related health matters.

In this paper, the term low- or no- calorie sweeteners (LNCS)[4] will be used but will not include polyols (see definition below). LNCS are used in beverages (e.g. flavoured carbonated and non-carbonated drinks/soft drinks), and in pre-packaged foods such as yogurts, desserts, jams and as well as table-top sweeteners which are added directly by the consumer. Each sweetener has a unique structure and metabolic fate, technical characteristics, and taste profile *(*EFSA 2011*;* Garba *et al., 2024,* Magnuson *et al.,* 2016).

**Polyols**
Sugar alcohols, or polyols, defined as 'alcohols containing more than two hydroxyl groups', are low calorie 'bulk' sugar replacers. Typically derived from sugars, they are the main class of compounds used as bulk sugar replacers. However, they can be used for purposes other than sweetening as they exert wider technological functions in food (Lenhart & Chey 2017). Polyols do contain calories but are less energy dense than sugar (2.4 kcal/g compared with 4.0 kcal/g sugar).

*Polyols are not considered within the scope of this document.*

The data describing global LNCS consumption patterns are limited and incomplete (Martyn et al., 2018) and there is currently no national monitoring of LNCS intakes. Data suggests consumption of low- or no-calorie sweetened beverages (LNCBs) has generally risen over time (BSDA 2025 DEFRA 2023, Sylvetsky & Rother 2016) (*see Chapter 3: LNCS Intake and Diet Quality*), applied to UK-produced or imported sugar-sweetened beverages, has contributed to an increase in the use of LNCS in the soft drinks market. However, consumer concerns persist regarding the safety of LNCS in relation to potential links to adverse health effects such as cancer (see *LNCS and Cancer* section). Additionally, their role in weight management remains a controversial issue. The Soft Drinks Industry Levy (SDIL), applied to UK-produced or imported sugar-sweetened beverages, has contributed to an increase in the use of LNCS in the soft drinks market (Luick *et al.* 2024). However, consumer concerns persist regarding the safety of LNCS in relation to potential links to adverse health effects such as cancer. Additionally, their role in weight management remains a controversial issue (*see Chapter 2 Health Outcomes*).

In the UK, Government dietary advice is based on recommendations from Scientific Advisory Committee on Nutrition (SACN) and the Food Standards Agency (FSA) and considers guidelines and associated evidence from authoritative health bodies including the World Health Organization (WHO). In 2023, WHO released a guideline with a conditional recommendation[5] suggesting that LNCS should not be used to control body weight or reduce risk of non-communicable disease (NCDs) (WHO 2023a). The Office for Health Improvement and Disparities (OHID) for England, part of the government's Department of Health and Social Care, stated in a draft consultation response to WHO (WHO 2022) that the recommendation

[4] For consistency, the term LNCS will be used throughout this paper, even if this is not the term used by the author in the original research or document. This paper will note when the sweeteners being described in the paper differ from those referred to as LNCS in this document.
[5] Conditional recommendations are those recommendations for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, substantive discussion amongst policymakers may be required before a conditional recommendation can be adopted as policy.

may be too strong given the limitations of the evidence base, and raised concerns regarding study design and the potential for reverse causality. OHID emphasise that the use of LNCS should not be considered a ‘magic bullet’ for reducing energy intake, as excess intake of free sugars is just one factor that impacts body weight and body mass index (BMI) (Anderson *et al.*, 2017). It remains appropriate to recommend dietary patterns that lower intakes of free sugars, saturated fats and salt, choosing foods that help to achieve a healthy dietary pattern. SACN has subsequently reviewed the WHO statement and published a position statement in April 2025 (SACN 2025). It reiterates reducing free sugars to ≤5% energy and advises minimising LNCS, aiming to limit both overall, and recommends that LNCS-sweetened drinks should not be consumed by younger children. For older children and adults, swapping sugars for LNCS may help reduce sugar in the short term, with the evidence suggesting there may be some benefit in using LNCS to help reduce weight gain in the short to medium term. SACN emphasised that LNCS are not the only option and emphasised the importance of following UK government dietary guidance, as summarised in the Eatwell Guide to support weight maintenance and long-term health.

It seems timely to review the Diabetes UK insights document (an expert consensus document from BDA, BNF and Diabetes UK, originally published in December 2018) to consider the role of LNCS and whether these may be a useful tool for some individuals to reduce overall calorie and sugar intake.

# Chapter 1: Safety

Authoritative regulatory bodies at national, regional and international levels are responsible for evaluating the safety of food additives before they are approved for use. These are periodically re-evaluated and reviewed in light of new scientific information. Data required for risk assessment includes reproductive and developmental toxicity, mutagenicity, genotoxicity, carcinogenicity immunotoxicity and neurotoxicity (FAO/WHO 2009, Serra-Majem *et al.* 2018). Nevertheless, consumer concerns persist regarding the safety of additives and their potential negative impacts on health (Farhat *et al.* 2021).

This section provides the regulatory context on the safety of LNCS, including conclusions from key authoritative regulatory bodies.

## Regulation of LNCS

Food safety authorities have extensively reviewed and (re)evaluated the safety of LNCS as additives, assessing several toxicological properties (see *Appendix A*). Such authorities include the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority (EFSA) and national authorities such as the FSA and the US Food and Drug Administration (FDA).

There are 11 LNCS currently approved for use in the UK and EU (EC 2023, SACN 2025). As well as adherence to the general regulatory requirements of food additives, LNCS are additionally subject to other regulations including that they must serve either as substitutes for sugars in the production of energy-reduced food, non-cariogenic food, or food without added sugars (EC 2023).

*Table 1: LNCS approved for use in the UK and EU*

| E number | Name | Latest evaluation status |
|---|---|---|
| E 950 | Acesulfame K | Evaluated in 2025[6] |
| E 951 | Aspartame | Evaluated in 2013 |
| E 952 | Cyclamates<br>Cyclamic acid, and its Na and Ca salts | Re-evaluation ongoing |
| E 954 | Saccharins<br>Saccharin and its Na, K and Ca salts | Evaluated in 2024[7] |
| E 955 | Sucralose | Re-evaluation ongoing |
| E 957 | Thaumatin | Evaluated in 2021 |
| E 959 | Neohesperidine dihydrochalcone (DC) | Evaluated in 2022 |
| E 960 | Steviol glycosides, including: | |
| E 960a | Steviol glycosides from Stevia | Evaluated in 2010 |
| E 960c | Enzymatically produced steviol glycosides | Evaluated in 2019 |
| E 960d | Glucosylated steviol glycosides | Evaluated in 2022 |
| E 961 | Neotame | Evaluated in 2025[8] |
| E 962 | Salt of aspartame-acesulfame | Re-evaluation ongoing |
| E 969 | Advantame | Evaluated in 2013 |

*NOTE: EFSA has committed to, and is currently undertaking, a re-evaluation of the safety of all LNCS that were already permitted for use in foods in the EU before 20 January 2009 (EFSA 2024). Recent re-evaluations in 2024/2025 for* Acesulfame K, Neotame and Saccharins have confirmed safety and increased the ADIs from the previous EFSA evaluation.

For each sweetener, EFSA reviews the evidence on chemical and biological properties, potential toxicity, estimates of the human dietary exposure and other additive-specific measures of safety (EFSA 2021). A revised protocol for hazard identification and hazard characterisation of LNCS was published in 2023 (EFSA 2023a) setting out the strategy to be applied for collecting and selecting data, appraising the relevant evidence, and analysing and integrating the evidence in order to draw conclusions that will form the basis for the scientific opinions (see *Appendix B*).

Since leaving the EU[9], the FSA's Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (CoT) assumed responsibility for assessing the evidence and the safety of additives in the UK. The FSA and OHID continue to endorse EFSA's scientific opinion on the safety and use of LNCS and will consider any EFSA advice or changes to the legislation and the relevance and applicability to the UK. The FSA ensures that "the science on additives is strictly reviewed, the law is strictly enforced, action is taken where problems are found" and "investigate any information that casts reasonable doubt on the safety of an additive" (FSA 2024).

[6] ADI for acesulfame K (E 950) of 10 mg/kg bw per day replaced the previous ADI of 9 mg/kg bw/d

[7] ADI for Saccharin (E954) increased from 5mg/kg bw to 9mg/kg

[8] ADI for neotame (E 961) of 10 mg/kg bw per day replaced the previous ADI of 2mg/kg bw/d

[9] Following Great Britain's exit from the European Union (EU) on 31st January 2020, EU food safety legislation was retained to provide legal continuity. GB legislation dictates the amount of LNCS that can be used in which products. Northern Ireland remains part of the EU and is therefore subject to its legislation.

## Acceptable Daily Intakes

As part of the safety evaluation process, each LNCS is given an Acceptable Daily Intake (ADI) level.[10] ADI's are set at one hundredth of the amount, in milligrams per kilogram of body weight, that can be safely consumed on a daily basis over a person's lifetime without incurring health risks (see *Appendix C* for ADIs for specific LNCS). It is extremely difficult for individuals consuming a typical diet to reach the ADI for any LNCS. In an international example, WHO, following the Joint Expert Committee on Food Additives 2023 aspartame hazard and risk assessment, illustrated that, for "a can of diet soft drink containing 200 or 300mg of aspartame, an adult weighing 70kg would need to consume more than 9 to 14 cans per day to exceed the acceptable daily intake, assuming no other intake from other food sources" (WHO 2023b). This provides an indication of the level of consumption required to reach maximum recommended daily intakes. A review published in 2018 (including European studies form 2008-2017) suggests that the available data on LNCS intake raises no concern with respect to the exceedance of individual LNCS ADIs among the general global population (see *Chapter 3: LNCS intake and Diet Quality*) (Martyn *et al.* 2018).

## Cancer

Regulatory bodies evaluate the association between LNCS and cancer as part of the safety assessment. Currently, regulatory bodies (including JECFA, FSA and EFSA) as well as cancer health charities such as Cancer Research UK, have concluded that observational research suggesting approved LNCS when consumed within the ADI may increase the risk of cancer in humans, is unconvincing (*see LNCS and Cancer , Chapter 2) (American Cancer Society 2023; CRUK 2023; WCRF 2022; WHO 2023a).*

## Safety for Infants and Young Children

In the UK, and in line with EU regulation, LNCS are not permitted in foods for infants (under 12 months old) and young children (1-3 years old), including infant and follow-on formulae, processed cereal-based foods and baby foods (COT 2019).

## LNCS and Phenylketonuria: Aspartame

It is a legal requirement for food products to clearly state 'contains a source of phenylalanine' on the label if they contain aspartame or salt of aspartame-acesulfame (NHS 2023a). This type of labelling is of particular importance for consumers with phenylketonuria (PKU); a rare genetic disorder in which the amino acid phenylalanine cannot be metabolised due to the deficiency of the enzyme phenylalanine hydroxylase. For people with PKU, phenylalanine can accumulate to harmful levels if not controlled with diet, and they are therefore advised against consuming LNCS that contain phenylalanine.

[10] These apply to the whole population, except infants and young children for whom it is not recommended LNCS are consumed (see *Safety for Infants and Young Children*)

## Safety during pregnancy

Since their approval, the safety of LNCS in Europe has been reviewed by the European Scientific Committee on Food (1984, 1988, 1994, 1997 and 2002) and concerns regarding possible reproductive and developmental toxicity have not been identified (EFSA 2011b). EFSA consider approved LNCS safe within their ADIs, which apply to the general population, including pregnancy. Regulatory bodies have stated that approved LNCS are considered safe for consumption during pregnancy within the ADIs and continue to monitor and evaluate the evidence around any new safety issues (EFSA 2023). However, some concern has been raised around the possible association of LNCS consumption during pregnancy with an adverse impact on the infant gut microbiome and increased body weight in children. To date the research for this is very limited, as is the scientific understanding of the health effects of changes in the gut microbiome (see *LNCS and Reproductive health, Chapter* 2) (Azad *et al.* 2016; Goran *et al.* 2019; Zhu *et al.* 2017). WHO has more recently reported that associations observed between birth weight or weight of offspring later in life and LNCS use during pregnancy were inconsistent, and no conclusions can be drawn.

## Allergy

Despite anecdotal reports suggesting that LNCS like aspartame may be associated with allergic/hypersensitivity-type reactions, adverse reactions are rare. The American Academy of Allergy, Asthma and Immunology report that only a few studies show adverse reactions to food additives and most reports of these are in single patients or small clusters of patients (AAAAI 2015, Babbel *et al*., 2021).

LNCS are evaluated for potential allergenicity during the regulatory process for approval for use. One of the most researched LNCS in this area is aspartame, with early reviews of potential allergenicity reporting mixed findings (Butchko *et al.* 2002; Hill & Belsito 2003; Jacob & Stechschulte 2008). Although isolated case studies have been reported (Czarnecka *et al.* 2021), in their most recent re-evaluation, EFSA concluded that the weight of the evidence shows that aspartame is not associated with allergic-type reactions in experimental models or in humans, but they have committed to monitor emerging research (EFSA 2013). In a randomised, double-blind placebo-controlled food challenge trial, 48 individuals with self-reported sensitivity to aspartame were compared to 48 matched aspartame non-sensitive individuals. Participants consumed an aspartame containing (100mg) or control snack bar randomly at least 7 days apart. Fourteen symptoms were rated repeatedly over 4 hours after consuming the snack bars. No differences between aspartame and placebo reactivity in individuals with self-reported aspartame reactions were reported (Sathyapalan *et al.* 2015).

# Chapter 2: Health Outcomes

Evidence suggests that high dietary sugar intake increases overall energy intake which can lead to weight gain, and is associated with a greater risk of developing dental caries (SACN 2015, WHO 2015). In addition, high intake of SSBs are associated with weight gain and an increase in BMI (SACN 2015; WHO 2023c). Such research has led to interest in LNCS as a potential alternative, to reduce sugar consumption and therefore support weight management and reduce obesity-related health risks. However, mixed findings from observational studies, some of which suggest that LNCS may have adverse effects on health outcomes, including weight gain, have contributed to public concern.

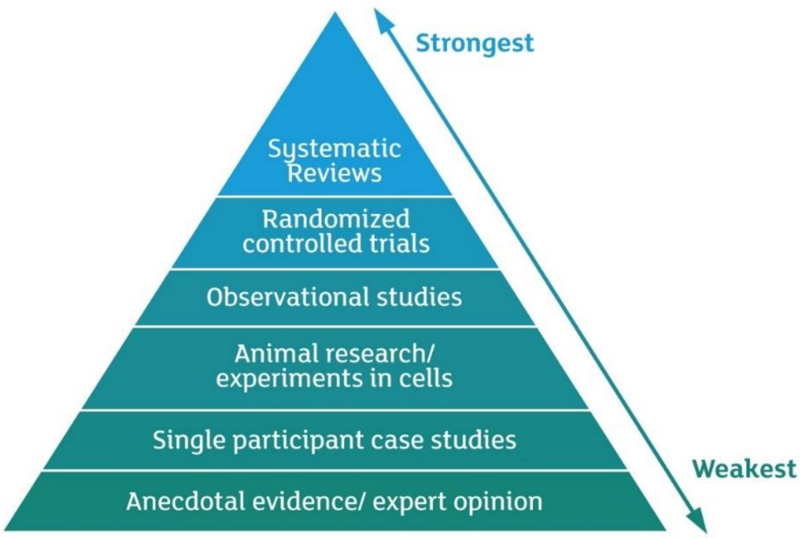
The five-year multidisciplinary SWEET project, funded by the European Commission Horizon 2020 programme, brought together 29 organisations across Europe to develop and review evidence on long term benefits and potential risks of transitioning to LNCS (referred to as 'sweeteners and sweetness enhancers' within the project) in relation to public health, safety, obesity and sustainability. Publications from this project are ongoing (see SWEET Project Publications). A notable aspect of this project involves examining the environmental footprint of sweeteners, which is crucial in the shift towards promoting healthier and more sustainable dietary practices.

## Hierarchy of Evidence

In this chapter, the evidence base for LNCS and the following health outcomes will be discussed: cancer, weight management and obesity, T2D, CVD, and effects on dental health, the gut microbiome and reproductive health. Central to discussion of evidence-based nutrition practice is the ability to appraise research. Research designs offer different levels of confidence about the findings of the research, and the idea of a hierarchy of evidence has been used widely from weaker to stronger study designs (see Box 1). These hierarchies provide a framework for clinicians and researchers to interpret the best available evidence. This is an important and recurrent theme in the interpretation of the evidence base regarding LNCS and health outcomes.

**Box1 Hierarchy of Evidence**

There is a general agreement on the relative strengths of the principal types of research studies. Typically, 'expert opinion' and *in vitro* or animal models are placed at the bottom of the hierarchy of evidence, followed by 'observations in individuals or small groups of humans' (e.g. case reports, case series), followed by 'observational studies' in the middle (case–control, cohort (retrospective), cohort (prospective), followed by 'RCTs' (randomised controlled trials) and finally 'systematic reviews' and meta-analyses of RCTs at the very top of the hierarchy (Gallagher et al. 2021, Hickson et al. 2024).




**For further information on study designs, strength of evidence and limitations, see Appendix G**

For an intervention to be useful it must be both efficacious (i.e. able to produce the desired result under controlled, ideal circumstances) and effective (i.e. able to produce the desired result in the 'real-world' conditions while considering acceptability, adherence and feasibility). A combination of study designs is typically required to thoroughly understand the implementation and impact of an intervention. Therefore, the 'best' method by which to acquire evidence depends on the research question. Different types of evidence are required to answer different types of research questions, such as an intervention's timeliness, equity, cost-effectiveness or patient centeredness. Furthermore, the amalgamated findings of the systematic review itself are only as good as the rigour of the review (strength of search terms, comprehensive search strategy, relevant eligibility criteria etc) and the design of the individual studies included. A systematic review of case-control studies (a weak study design) cannot provide the same level of evidence certainty as a systematic review of RCTs. Nevertheless, hierarchies of the most appropriate study designs remain part of the quality framework with adequately powered multi-centre trials and systematic reviews of any kind of human study design considered to provide the most powerful evidence.

## Examples of study limitations with regards to LNCS (Gallagher *et al.* 2021, SACN 2025)

- SACN, in its review of the evidence for LNCS, noted that consumption of some products containing LNCS, particularly some brands of 'diet' or 'zero' drinks, may be associated with particular dietary patterns, leading to potential residual confounding.

- Many of the cohort studies were conducted in the 1980/90s when LNCS-containing foods and drinks may have been marketed as 'diet' foods and drinks or foods and drinks to aid weight loss. Consumers of LNCS in this time period may be different to current consumers of LNCS.

- Assessments of intakes often consider only certain sources of LNCS (e.g. in drinks only) and/or LNCS as a homogenous group (despite having distinct individual chemical structures and different metabolism). This has the potential of not adequately capturing intakes of individual LNCS or allowing for a reliable estimation of overall LNCS intakes. There may be differences in the mechanism of action for LNCS in drinks (e.g. satiety) compared to foods or as a tabletop additive.

- The design and study quality of RCTs should also be carefully considered. Many RCTs of LNCS are of low quality and/or short duration (under 3 months). The distinction between fixed calorie designs (where participants consume a predefined amount of dietary energy) and *ad libitum* designs *(where participants* eat until satiation is reached) is important. In a fixed-calorie design, it is not possible to show how LNCS may influence appetite, food intake or body weight in the long term. In contrast, an *ad libitum* study design will be able to demonstrate whether a certain LCS increases, decreases or has no effect on appetite, food intake, glycaemic control or body weight compared with a control situation (e.g. sucrose or water).

Overall, the majority of studies in LNCS, including RCTs are of low or very low quality. There is also a need for research specifically focused on people with diabetes, as this population was not considered by the WHO review.

## LNCS and Cancer

Although, as indicated in the safety section, regulatory bodies consider carcinogenicity in safety assessments, stories on the link between LNCS and cancer are still raised in the media and social media (CRUK 2023). Interest in the association between LNCS and cancer risk initially arose from early rodent studies, which were subsequently dismissed after assessment by regulatory bodies. This was in part due to inconsistent results and low quality research but also due to substantial biological and mechanistic variances between rodents studied and humans. Of particular note, some species of laboratory rodents can develop spontaneous tumours and housing conditions can affect outcomes (Park *et al.* 2016). In 1981 saccharin was listed in the US National Toxicology Program's (NTP) Report on Carcinogens as a 'substance reasonably anticipated to be a human carcinogen', after laboratory studies linked high doses of saccharin with the development of bladder cancer in rats (National Toxicology Program 2021). However, it was removed from the list in 2000 after mechanistic studies showed that the ways in which saccharin causes cancer in rats do not apply in humans.

Between 1997 and 2007, the Ramazzini institute conducted a series of laboratory studies that suggested exposure to aspartame and sucralose was associated with increased carcinogenic effects and risk of malignant tumours in rodents (Belpoggi *et al.* 2006; Landrigan & Straif 2021; Soffritti *et al.* 2006; Soffritti *et al.* 2010; Soffritti *et al.* 2007). These findings were assessed by EFSA, which concluded that the available data did not support the conclusions of the authors and "did not give reason to reconsider the previous evaluations of aspartame or of other food additive sweeteners authorised in the European Union" (EFSA 2011b).

There have been several meta-analyses in recent years to investigate the link between different LNCS and various cancers in humans (see *Table 2*), which overall do not suggest a direct association between LNCS intake and cancer risk and mortality when consumed within recommended limits. Evidence on the associations between individual LNCS and specific cancer outcomes can be found in *Appendix D.*

More recently, the concern around the association between LNCS and cancer has been revived following a WHO International Agency for Research on Cancer (IARC) assessment published in 2023. Citing *limited evidence* (with a lower level of certainty) IARC concluded that aspartame is 'possibly carcinogenic to humans' (WHO 2023b). The WHO/IARC assessment is a hazard assessment which means it identifies an exposure that has the potential to harm people, but it does not assess the risk of this occurring. Following this assessment, the Joint FAO/WHO Expert Committee on Food Additives, JECFA, completed its risk assessment report on the consumption of aspartame and concluded that the "data evaluated indicated no sufficient reason to change the previously established ADI". Having reviewed the evidence, the FDA disagreed with IARC conclusion, and noted JECFA's findings support the view that aspartame continues to be safe to consume at current permitted levels of use (FDA, 2023).

*Table 2: Summary of systematic reviews and meta-analyses of the evidence on LNCS intake and cancer (all cancers and multiple cancer types)*

| **Study** | **Type of study** | **Studies included*** | **Outcome** | **Association and Results** |
|---|---|---|---|---|
| **Liu et al., 2021** | Meta-analysis | 10 case control studies | Cancer risk | LNCS intake was not associated with an increase in all cancers (OR 0.91, 95% CI:0.75-1.11). In sub-analysis of gender LNCS use was inversely associated with urinary system cancer risk in women, but not men (OR 0.76, 95% CI:0.60-0.97). |
| **Pan et al., 2022** | Systematic review and meta-analysis | 7 prospective cohort studies | Cancer mortality | Based on low certainty of evidence, there was no association between LNCBs intake and cancer mortality (HR 1.01, 95% CI:0.98-1.05). |
| **Rios-Leyvraz & Montez, 2022** *(see Appendix E)* | Systematic review and meta-analysis | 39 case control studies and 9 cohort studies | Cancer incidence and mortality | No significant association between higher intakes of LNCBs and any type of cancer as assessed in prospective cohort studies (HR 1.02 (0.95,1.09)). 3 cohort studies found no significant association between higher intake of LNCBs and cancer mortality (HR 1.02 (0.92, 1.13). As assessed in case–control studies only (very low quality), a 31% increase in risk of bladder cancer was observed with NSS intake. |
| **Yan et al., 2022** | Meta-analysis | 25 prospective cohort studies | Cancer incidence and mortality | LNCS intake was not associated with overall cancer incidence and mortality. However, in regional sub analysis suggested LNCS intake may be associated with a higher risk of cancer in incidence European populations (6 studies, HR/RR 1.07, 95% CI:1.02,1.12) but authors conclude more data from well-conducted studies and clinical trials are required to confirm the association. |
| **Pan et al. 2023** | Systematic review and meta-analysis | 11 prospective cohort studies | Cancer risk | 11 articles reported on the association between LNCBs and cancer.<br><br>Low certainty evidence from two studies showed that a higher consumption of LNCBs (250mL/day was significantly associated with a greater risk of |

| | | | | |
|---|---|---|---|---|
| | | | | leukaemia. (RR 1.16, CI:1.00-1.35).<br>No significant associations were found between LNCBs consumption and other types of cancer. |
| **Pavanello et al., 2023** | Review of toxicology and systematic review | 18 cohort studies | Cancer incidence and mortality | 18 cohort studies investigated LNCS and cancer incidence, with 11 finding there was no association and 6 reported an HR between 1.12 and 3.36. and 1 study found an association only in a subgroup.<br>6 cohort studies evaluated the relationship between LNCS intake (all using LNCBs) and cancer mortality. 5 out of 6 did not find an association. A meta-analysis of mortality from all cancers (4 studies) pooled estimate was 1.01 (95% CI: 0.96, 1.06) indicating no excess risk for the highest level of consumption. |

***See hierarchy of evidence Box 1**

## The Role of LNCS in Weight Management and Obesity

Obesity is associated with an increased risk of many health conditions including T2D, various cancers (at least 13 different types according to WCRF) and heart disease (DHSC 2020). The risk of obesity is influenced by a number of complex factors including genetics, dietary intake, physical activity, socio-economic status and the food environment, now often termed “the obesogenic environment”, reflecting an environment which presents barriers to managing energy intake, being more active and less sedentary. Poverty is one of the most significant causes of health inequalities in the UK. Notably prevalence of obesity is highest in those living in the most deprived areas (NHS 2019). Increasing numbers of people in the UK are living in food poverty, unable to access a healthy, balanced diet. The most deprived fifth of the UK population would need to spend 45% of their disposable income on food to meet the cost of the Government’s recommended nutritional guidelines, rising to 70% for those households with children (Food Foundation 2025).

In relation to energy intake, SACN concluded that higher intakes of free sugars increases the risk of consuming too many calories, and this is supported by observations of the associations between increased sugar consumption from sources such as sugar sweetened beverages, fruit juice, jams desserts and cakes and the risk of living with overweight and obesity reported in the scientific literature (SACN 2015; Te Morenga *et al.* 2012). Therefore, there is particular interest in the role that LNCS play in displacing energy from sugar sweetened foods and drinks, although there are currently no EU or UK authorised health claims that state that replacing sugar with LNCS leads to the maintenance or achievement of normal body weight (EFSA 2011). Nonetheless, the key interest in LNCS in respect of weight management is focussed on replacement or reduction of sugars in the diet.

The effects of LNCS on weight have been explored but evidence has been inconclusive and is conflicting, leading to debate around its interpretation (see *Table 3*). There are particular areas of consideration including the quality of evidence and the role of the comparator.

### *WHO Guideline on the use of LNCS: Adiposity*

In 2023, the WHO released a guideline on the use of LNCS based upon the analysis of a commissioned systematic review and meta-analysis (Rios-Leyvraz & Montez 2022) (*Appendix F*). The review included over 280 studies of different designs, primarily RCTs (50 studies with 45 RCTs conducted in adults, prospective cohort studies (97 studies) and case control studies (47 studies).

A total of 32 RCTs and 13 prospective cohort studies reporting on measures of adiposity were included in the meta-analyses (Table 4). This included studies that compared LNCS consumption with no or lower doses of LNCS consumption, and trials that compared the intervention of LNCS with a variety of different comparators which included any type of sugar, placebo, plain water or no intervention, thus adding a risk of bias, and potentially reducing the reliability of any data. A further caveat is that most of the trials provided foods and beverages containing free sugars or LNCS in addition to the existing diet, i.e., they are not direct substitution studies.

*Table 3: Summary of systematic reviews and meta-analyses of the evidence on LNCS intake and weight management; adults and children*

| **Study** | **Type of study** | **Studies included** | **Adiposity Outcome** | **Participants** | **Association and Results** |
|---|---|---|---|---|---|
| Miller & Perez, 2014 | Systematic review & meta-analysis | 15 RCTs & 9 prospective cohort studies | Body weight, BMI & body composition | Child & adolescent studies: 4<br>Adult studies: 11 | In RCTs, replacement of caloric sweeteners with LNCS significantly reduced body weight 0.80 kg (95% CI: −1.17, −0.43; fixed-effect WGMD = −0.61) BMI −0.24 kg/m2; (95% CI: −0.41, −0.07; fixed-effect WGMD = −0.24), and waist circumference (−0.83 cm; 95% CI: −1.29, −0.37; fixed-effect WGMD = −0.83). (95% CI: -1.29, -0.37; fixed effect = -0.83). Among prospective cohort studies, LNCS intake was not associated with body weight or fat mass but was significantly associated with slightly higher BMI (0.03; 95% CI: 0.01, 0.06) |
| Rogers et al., 2016 | Systematic review & meta-analysis | 12 PCS (9 used in analysis) | BMI | Children studies: 5 comparisons | Random effects model showed no change in BMI with LNCS consumption. With a high level of heterogeneity. Fixed effect model showed a slightly lower BMI with |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Adult studies: 6 comparisons | LNCS consumption (−0.008 kg/m$^2$per year, 95% CI: −0.010, −0.006) |
| Rogers et al., 2016 | Systematic review & meta-analysis | 10 RCTs ⩾ 4 weeks duration | Body weight change | Children studies: 1 comparison<br>Adult studies: 8 comparisons | Meta-analysis of randomized controlled trials (4 weeks to 40 months) showed that consumption of LNBS versus SSB led to relatively reduced body weight (nine comparisons (−1.35 kg, 95% CI: –2.28, −0.42) |
| Azad et al. 2017 | | 7 RCTs (>6 months) & 30 cohort studies | BMI | Adults only<br>3 RCTs<br>2 Cohorts | Meta-analysis of 3 RCTS (using only water/placebo as comparators) showed MD −0.37 kg/m$^2$ (95% CI: −1.10 to 0.36); meta-analysis of 2 cohort studies, LNCS intake was associated with an increase in BMI (mean correlation 0.05, 95% CI: 0.03, 0.06) |
| McGlynn et al., 2022 | Systematic review & meta-analysis | 12 RCTs - LNCSBs were a substitute for | Body weight and other measures of adiposity | Adults only Mean age: | Substitution of LNCSBs for SSBs was associated with reduced body weight, MD −1.06 kg (95% CI: −1.71, –0.41 kg), BMI (MD, −0.32 |

| | | | | | |
|---|---|---|---|---|---|
| | | SSBs ⩾ 2 weeks duration | | 33.1 years (SD 6.6) | kg/m$^2$; 95% CI: −0.58, –0.07), percentage of body fat (MD, −0.60%; 95% CI: −1.03%, –0.18%) |
| Laviada-Molina et al., 2020 | Systematic review & meta-analysis | 20 RCTs ⩾ 4 weeks duration | Body weight change and BMI | Children & adolescent studies: 4<br>Adult only studies: 16 | When comparing LNCS vs sucrose, significant lower weight gain/BMI differences in overweight adults on unrestricted energy diets, but not in weight-reduction diets. Studies evaluating NNS consumption vs all comparators in children/adolescents showed no significant weight/BMI effect (SDM: −0.29; 95% CI: −0.61, 0.02; *P* = 0.07; $I^2$ = 63%) |

* Sustained = studies with an LNCS exposure of >1 day.

**Table 4: A comparison of the findings from RCTs and cohort studies from the WHO review**

| Randomised control trials | Cohort-case control studies |
|---|---|
| **Adiposity**<br>â Body weight: MD -0.71 kg (95% CI -1.13, 0.28) (low) – mostly in LNCS -> sugars<br>â BMI: MD -0.14 kg/m$^2$ (95% CI -0.30, 0.02) (low) – mostly in LNCS -> sugars<br>Ø Other measures: waist-to-hip ratio, waist circumference, fat/lean mass | **Adiposity**<br>á Incident obesity: HR 1.76 (95% CI 1.25, 2.49) (low)<br>á BMI: MD +0.14 kg/m$^2$ (95% CI 0.03, 0.25) (very low)<br>Ø Other measures |

MD: Mean difference

### *Results from WHO Review: RCTs*

In the general adult population:

- 29 RCTs (majority ≤3 months) showed higher intakes of LNCS resulted in a reduction in body weight of 0.71 kg (MD), 95% CI: -1.13, -0.28).
- Twenty-three RCTs showed a reduction in BMI, with a mean difference of -0.14 kg/m$^2$ (MD, 95% CI (-0.30, 0.02), but this was not statistically significant.
- 

Subgroup analyses suggested that the effect of LNCS on body weight may be greatest in those living with overweight, and those trying to lose weight. Differences were observed for individual subgroups for body weight and BMI by comparator but were more pronounced when LNCS consumption was compared to sugar consumption.

- Subgroup analyses showed that, when adding LNCS to the diet compared to nothing (or placebo), there was a decrease in body weight (MD -0.29 95% CI: -1.20,0.62) and BMI (MD -0.98 95% CI: -1.48, -0.48).
- adding LNCS to the diet compared with free sugars (either LNCS replacing sugars, or both LNCS and sugars being added to the diet in separate arms of the trial) resulted in a decrease in weight and BMI: sugar MD -0.76 95% CI (-1.18, -0.34) and BMI -0.21 (-0.36, -0.06).
- adding LNCS to the diet compared with water showed no effect on body weight (MD -0.51 95% CI (-2.40, 1.37) and a non-significant increase in BMI (HD 0.37 95% CI: -0.02, 0.77).

The observed change in body weight and BMI was likely due to a reduction in energy intake as all studies that compared LNCS to sugar showed a reduction in body weight and BMI when energy intake was reduced. In contrast studies not comparing LNCS to sugars did not collectively show a reduction in energy intake.

The effect of LNCS on total energy intake (kJ/day) varied depending on the comparator used in RCTs. When LNCS were compared to sugar, there was a reduction in total energy intake (MD -1008.35 95% CI: -1397.11, -619.60). However, when LNCS were compared to water, the effect on energy intake was not significant (MD 183.53 95% CI: -234.86, 601.92). Lastly, when no comparator was used, the reduction in energy intake (MD-477.92 95% CI: -1426.30, 470.46) was not statistically significant.

In four RCTS, when LNCS were used specifically as replacement for sugars (mostly in the form of replacing SSB with LNCS sweetened beverages), there was a smaller reduction in body weight and BMI. This reduction was not statistically significant, with a MD-0.01 (95% CI: -0.38, 0.35).

Greater weight reduction in RCTs of longer duration was suggested by subgroup analysis and meta-regression but these results were not statistically significant for either. However, with many of the RCTs being short in duration (only four lasting longer than a year) and the heterogeneity of the trials, it is difficult to interpret the data with confidence. No significant effects were observed for other measures of adiposity as assessed in RCTs.

*Results from WHO Review: Observational Studies*

In the prospective cohort studies, with follow-up periods up to 10 years, higher intakes of LNCS were associated with a higher BMI, with a MD of 0.14 kg/m$^2$ (95% CI: 0.01, 0.04). Additionally, these studies indicated a 76% increase in the risk of developing obesity, as evidenced by a HR of 1.76 (95% CI: 1.25, 2.49) across two studies. However, these findings are based on very low certainty of evidence, and no other significant associations were observed in prospective cohort studies.

Whilst observational studies provide useful information on long term health outcomes further research is needed to determine whether the observed associations are genuine or a result of reverse causation and/or residual confounding and cannot be used to infer causality.
Another limitation is that there was a paucity in the evidence for long term data on the use of LNCS in weight management as only four of the trials lasted for more than a year. Because of the limitations of the available research, the WHO guideline is considered conditional and is based on evidence of low certainty.

The WHO review indicated replacing free sugars with LNCS in food and beverages does not assist weight loss in the long term though the evidence is graded of low certainty. Similarly, Mathur and Bakshi's narrative analysis based on systematic reviews reported that where the bulk of the studies were observational, the use of LNCS appears to be associated with a gain in weight although there was insufficient evidence to conclude any long-term impact~~s~~ on weight management (Mathur & Bakshi 2023).

The meta-analysis of the RCTs provides us with the highest level of evidence because confounding factors are randomised into the different arms of the trial for comparison and can indicate whether the intervention caused the outcome. The evidence from the prospective cohort studies was weaker and can only show an association. The WHO recommended that LNCS should "not be used as a means of achieving weight control or reducing the risk of non-communicable diseases (conditional recommendation)". The evidence in individuals who already have diabetes was not appraised and so the recommendation applies to all individuals, except those with pre-existing diabetes.

### *Systematic Reviews: LNCS as a substitution for sugars*

A systematic review and meta-analysis restricted to prospective cohort studies where substitution analysis modelling of LNCS as a replacement for caloric sugars was used, reported an inverse association between LNCS intake and body weight (3 cohorts, n=165,579) and waist circumference (1 cohort, n=173) over the follow-up period (Lee *et al.* 2022). The pooled results support the suggestion that LNCS use can contribute to weight reduction by reducing or displacing excess calories from sugar. Likewise, a systematic review and meta-analysis (McGlynn *et al.* 2022) provided supporting evidence on the impact of LNCS as a substitution for SSBs (12 RCTs, n=601) in adults living with obesity or overweight. The analysis revealed that replacing SSBs with LNBS resulted in a modest reduction in body weight, with a MD of -1.06kg (95% CI: -1.71 to -0.41), supported by moderate certainty of evidence. The review also found a reduction in BMI with a MD -1.07kg (95% CI: -1.95, -0.19), although the certainty of this evidence was low. In contrast, when LNCS were substituted for water, the effect on body weight was similarly modest, with an MD of -1.07 kg (95% CI: -1.95,-0.19), but this finding was based on low-certainty evidence. The impact on BMI in this context was negligible, with an MD of 0.02 kg/m² (95% CI: -0.46 to 0.51), again with low certainty of evidence.

### *Children and adolescents*

Children, particularly adolescents, are amongst the highest consumers of SSBs (PHE 2020). Data from the *National Diet and Nutrition Survey* (NDNS), which reports UK food and nutrient intake and nutritional status, suggested average consumption of SSBs (including non-consumers) amongst 11 to 18 years to be 124g/day (OHID 2025). Replacing them with LNCBs may therefore be a useful strategy to reduce sugar intake for regular consumers amongst this age group.

Data on the effect of LNCS on children are limited. In a systematic review and meta-analysis by Miller and Perez, 4 RCTs were identified for children and a decrease in body weight reported with LNCS use (-1.06 kg; 95% CI: -1.57, -0.56) (Miller & Perez 2014). More recently Rios-Leyvraz and Montez's (see *Appendix E*) meta-analysis of 2 RCTs and 14 cohort studies reported on the effects of LNCS intake on measures of adiposity in children (Rios-Leyvraz & Montez 2022). Meta-analyses of the small number of studies with amenable data yielded no significant results for any measure of adiposity., in one 18-month RCT (SSBs vs LNCS sweetened beverages) in 641 mostly normal weight primary school aged children who commonly drank SSBs, demonstrated 1.01kg (95% CI: 1.65-0.48) lower body weight increase amongst those receiving the LNCBs compared to SSBs and a non-significant difference in BMI z-score of -0.04 ( 95% CI: 0.10 -0.02) (de Ruyter *et al.* 2012).

Childhood obesity has been highlighted by the government as a major public health concern. The Soft Drinks Industry Levy (SDIL) on sugar sweetened beverages introduced as part of the government's initiative to tackle childhood obesity has seen an increase in reformulation to replace sugars with LNCS in SSBs, with reduction in sugar content in soft drinks in scope, with modelling studies suggesting that the levy may support obesity reduction (see *LNCS Public Health Policy, Chapter 4)*.

Whilst LNCS on the market are deemed safe, there is some concern around children's consumption from health professionals and the general public (Schermbeck *et al.* 2019). Evidence on long term health benefits and potential risks in children is lacking. However, it should be noted that Infants and young children, especially those under 3 years old, should not be encouraged to consume products with LNCS, and these are currently not recommended for this age group. Current school food standards in school in relation to beverages are shown in *Table 5.* These typically permit water, milk/dairy alternative and unsweetened fruit/vegetable drinks and have some restrictions pertinent to SSBs and LNCBs. The Soil Association *Food for Life* School award certification scheme does not permit LNCS – describing them as 'undesirable' without providing any evidence for this requirement (Soil Association 2019).

*Table 5: school food policies on drinks, including LNCBs in the UK as defined in government legislation*

| Country/Region | Permitted Drinks | Drinks not permitted or not advised |
|---|---|---|
| **Wales**<br>The Healthy Eating in Schools (Nutritional Standards and Requirements) (Wales) Regulations 2013 | Primary Schools<br>• Plain water – still or carbonated<br>• Plain milk – semi skimmed or skimmed<br>• Fruit juice – still or carbonated<br>• Vegetable juice– still or carbonate<br>• Plain soya, plain rice or plain oat drinks<br>• Fruit juice combined with wate<br>• Vegetable juice combined with water<br>• Blended drinks – singly or in combination with a blend or puree of fruit, vegetables, fruit juice or vegetable juice<br>Secondary Schools:<br>*As above*, plus:<br>• Fruit juice or vegetable juice combined with plain milk or plain yogurt (e.g. dairy smoothies)<br>• Fruit juice or vegetable juice<br>• combined with plain soya, plain rice or plain oat drinks<br>• Flavoured milk, yogurt or soya, rice or oat drinks<br>• Tea and coffee<br>• Hot chocolate | • Squash of any kind, including sugar free squash<br>• Flavoured waters including sugar free flavoured water<br>• Sports or energy drinks<br>• Fizzy soft drinks including diet or sugar free fizzy drinks, e.g. cola, lemonade |
| **Northern Ireland**<br>Nutritional Standards for School Lunches (2007) and the Nutritional Standards for Other Food and Drinks in Schools (2008) | • Plain water (still or sparkling)<br>• Milk<br>• Unsweetened fruit or vegetable juices<br>• Yogurt or milk drinks (with less than 5% added sugar)<br>• Drinks made from combinations of the above (e.g. smoothies)<br>• Tea, coffee and low-calorie hot chocolate (these drinks are not suitable for the nursery sector) | Artificial sweeteners are only permitted in combination drinks |

| | | |
|---|---|---|
| | • Combination drinks must contain at least 50% milk, yogurt or fruit juice<br>• Fresh drinking water, i.e. tap water, must be provided free every day | |
| **England**<br>2014 No. 1603 Education, England [The requirements for School Food Regulations 2014]() | • Plain water (still or carbonated)<br>• Lower fat milk or lactose reduced milk<br>• Fruit or vegetable juice (maximum 150mls)<br>• Plain soya, rice or oat drinks enriched with calcium<br>• Plain fermented milk (for example yogurt) drinks<br>• Combinations of fruit or vegetable juice with plain water (still or carbonated, with no added sugars or honey)<br>• Combinations of fruit juice and lower fat milk or plain yogurt, plain soya, rice or oat drinks enriched with calcium; cocoa and lower fat milk; flavoured lower fat milk, all with less than 5% added sugars or honey<br>• Tea, coffee, hot chocolate | You can avoid drinks containing preservatives, flavourings, colourings and sweeteners |
| **Scotland**<br>The Healthy Eating in Schools Guidance (2020) | Primary Schools:<br>• Plain still or sparkling water<br>• Plain lower fat milk and calcium enriched milk alternatives<br>• No added sugar, lower fat milk drinks<br>• No added sugar, lower fat drinking yogurt<br><br>Secondary Schools:<br>• Plain still or sparkling water<br>• Plain lower fat milk and calcium enriched milk alternatives<br>• Tea and coffee<br>• No added sugar, lower fat milk drinks (e.g. flavoured and hot chocolate)<br>• No added sugar, lower fat drinking yogurts<br>• Sugar-free drinks (excluding high caffeine – 150 mg per litre) | Advice on the use of sweeteners<br>'While sweeteners are safe for consumption, their use in school food and drink should be carefully considered to ensure that we do not simply replace sugary products with sweetened products that continue to teach children's and young people's palates to expect sweet tasting food and drink and may lead to them making less healthy choices outside of school.' |

## The role of LNCS in the Risk of Type 2 Diabetes and in Diabetes Management

### *Sugar and sugar sweetened beverage intake*

Although there is little evidence for sugar as a direct causal factor for T2D, the risk of developing T2D is often mediated through the effects of overweight and obesity, among other risk factors. Higher sugars intake increases the risk of higher energy intake, and subsequent obesity risk.–'Age, family history and ethnicity are non -modifiable risk factors for the development of T2D,. However, obesity is a modifiable risk factor and an increase in visceral adiposity and ectopic fat is a significant risk factor for the development of T2D because it causes both insulin resistance and beta cell dysfunction (Klein *et al.* 2022; Sattar & Gill 2014). Therefore, measures that reduce overweight and obesity will reduce the risk of developing T2D, and associated complications.

In SACN's Carbohydrates and Health review, the included cohort studies provided no evidence of an association between individual or total intake of sugar and incidence of T2D. However, a positive association between greater consumption of SSB and increased risk of T2D was shown. The results from a meta-analysis, which included results from several large cohort studies, reported (RR=1.23, 95% CI: 1.17, 1.30 for each 330ml/day increase; $p<0.001$), with a heterogeneity of $I^2=65\%$). (SACN 2015). There are a number of proposed mechanisms to explain how SSB consumption may contribute to increased risk of T2D, including their effect on satiety, additional liquid calories to the diet, hyperinsulinaemia induced by the rapid absorption of glucose, adverse glycaemic effects and through hepatic metabolism of excess fructose from sugars in SSBs (DellaValle *et al.* 2005; Malik & Hu 2022; Malik *et al.* 2010).

International guidelines advise limiting free sugars in the diet for the general population, and those living with diabetes. The Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) recommends that intakes of free or added sugars should not exceed 10% of total energy intake in people living with or at risk of diabetes. WHO recommends free sugars account for less than 10% of total energy intake across the life course (strong recommendation), with a conditional recommendation for a lower intake of less than 5% of total energy.

### *LNCS and Risk of Type 2 Diabetes*

Given that the evidence indicates that SSBs and living with overweight or obesity are associated with a higher risk of developing T2D and, lowering sugars intake may confer health benefits, sugar reduction is an important dietary recommendation and the use of LNCS can be a means to do this. LNCS contain little to no carbohydrate and therefore do not cause a direct postprandial increase in blood glucose levels as is seen with sugars (Greyling *et al.* 2020). There is an approved health claim (in the EU and UK) that LNCS help to reduce postprandial glucose levels if consumed in place of sugars (EFSA 2011), i.e., this can induce a lower blood glucose rise after consumption compared to sugar-containing foods/drinks.

However, some studies have indicated an association between the consumption of LNCBs and increased risk of developing T2D (Azad *et al.* 2017; Imamura *et al.* 2015; Nettleton *et al.* 2009), although as yet the quality of evidence is limited and associations are not well established, making it challenging to draw definitive conclusions. It has been suggested that reverse causality (e.g. people living with overweight and obesity use LNCBs to manage body weight) may explain part of the association(Drewnowski & Rehm 2014; Greenwood *et al.* 2014; Imamura *et al.* 2015, Pereira 2013) and there are several potential confounding factors(Romo-Romo *et al.* 2016).

RCTs typically only measure intermediate markers or metabolic parameters of diabetes including fasting glucose. Although RCTs provide a higher quality of evidence, shorter term trials assessing relationships between LNCS intake and health outcomes that develop over time like T2D can miss dietary exposures captured in longer term observational studies. Moreover, in real-world settings, consumers may use different types of LNCS, in greater quantities and in different food sources than provided in controlled trials. However, confounding factors and bias that may occur in observational research but are better, accounted for in RCTs, means that results from observational studies should be interpreted with caution, and considered within the totality of evidence, notably alongside the RCT evidence.

### *Randomised controlled trials – Intermediate markers of type 2 diabetes*

Santos et al.'s meta-analysis of twelve randomised controlled clinical trials assessed the effect of the LNCS aspartame consumption (versus control or sucrose) on metabolic parameters of diabetes (Santos *et al.* 2018). Pooled mean differences were calculated using a random or fixed-effects model for heterogeneous and homogenous studies respectively. When comparing LNCS with the control there was no association with changes in blood glucose levels (MD −0.03 mmol/L; 95% CI: −0.21, 0.14) or to sucrose (MD 0.31 mmol/L; 95% CI: −0.05, 0.67). Similarly, there was no significant difference in insulin levels compared to control (0.13 µU/mL; 95% CI: −0.69, 0.95) or to sucrose (2.54 µU/mL; 95% CI: −6.29, 11.37). Body weight did not change after aspartame consumption compared to control (5.00 kg; 95% CI: −1.56, 11.56) or to sucrose (3.78 kg; 95% CI: −2.18, 9.74). Energy intake was not altered by aspartame consumption compared to control (−0.49 MJ; 95% CI: −1.21, 0.22) or to sucrose (−0.17 MJ; 95% CI: −2.03, 1.69).

Nichol et al. conducted a meta-analysis of 29 RCTs to estimate and track changes in blood glucose concentration over time following consumption of LNCs after an overnight fast(Nichol *et al.* 2018). LNCS consumption was not found to increase blood glucose levels and blood glucose levels decreased over the 210-minute observation. To assess impact of heterogeneity of LNCS type and study participants a meta-regression was conducted. No difference in the glycaemic impact of LNCS consumption was found by type of LNCS but a moderate change was observed with age, BMI and whether living with diabetes. An additional year of age was associated with a decrease in the glycaemic impact of LNCS 150-179 minutes after consumption, with a MD of 0.026 mmol/L in blood glucose levels (95% CI: 0.002, 0.051). An increase in BMI was found to be associated with a decrease in blood glucose levels, with MDs of 0. 049 mmol/L (95% CI: 0.008, 0.091) 120-149 minutes after consumption and 0.074 mmol/L (95% CI: 0.008, 0.140) 180-210 minutes following consumption.

Tucker and Tan's systematic review tested the hypothesis that LNCS improve glucose regulation postprandially and included 41 studies in their systematic review(Tucker & Tan 2017). The review concluded, after weighing the totality of the evidence that sweet taste receptor activation from LNCS do not affect acute postprandial glucose levels when tested alone, or when added to energy or carbohydrate-matched meals or drinks, or as preloads.

The recent WHO systematic review included 21 RCTs (including parallel, mixed and cross over study design) reporting on intermediate markers (glucose, insulin, HOMA-IR, HbA1c) for meta-analysis(Rios-Leyvraz & Montez 2022). No significant effects were observed for any measure of glycaemic control as assessed in these RCTs.

### *Observational Studies*

Observational studies and reviews of these (Azad *et al.* 2017; Mathur & Bakshi 2023; Rios-Leyvraz & Montez 2022), have indicated an association between the consumption of LNCS drinks and increased risk of developing T2D; however the quality of evidence is limited, making it challenging to draw definitive conclusions. It has been suggested that reverse causality (e.g. people living with overweight and obesity use LNCBs to manage body weight) may explain part of the association. In a recent large cohort study (n=105,588) using the NutriNet-Sante cohort aiming to limit the effects of reverse causality through sensitivity analysis, a positive association between LNCS and the risk of T2D (HR 1.69; 95% CI: 1.45, 1.97; $p<0.001$; Debras et al., 2022a) was reported. The authors recognise that the results may still be limited by residual confounding.

The recent WHO systematic review of observational data reported higher intakes of LNCS to be associated with an increased risk of developing T2D. As assessed in prospective cohort studies, higher intakes of LNCS in beverage form were associated with increased risk of developing T2D [13 cohorts HR 1.23 (95% CI: 1.14, 1.32)] or similarly with LNCS in tabletop form [2 cohorts HR 1.34 (95% CI: 1.21, 1.48)]. To address reverse causation, the included prospective cohort studies included adjusted for relevant confounders, including BMI, and most performed a number of relevant sensitivity analyses, including the exclusion of diabetes cases in the first 3–7 years of follow-up from baseline.

Contrary to findings reported from the RCT evidence on intermediate markers of T2D higher intakes of LNCS, as assessed in three prospective cohort studies, were associated with an increase in risk of high fasting glucose (defined as ≥5.5 mmol/L (HR 1.21; 95% CI: 1.01, 1.45). The WHO systematic review (Rios-Leyvraz & Montez 2022) reported that from 16 RCTs that assessed the effect of LNCS on fasting glucose (mmol/L) indicated that there was no significant effect (MD –0.01; 95% CI: –0.05, 0.04). The methodology of the WHO review has been called into question by Khan et al. who criticised the reliance on prospective cohort studies, calling for a re-evaluation of the results and recommendations (Khan *et al.* 2023). The WHO did acknowledge the limitations of the conditional findings and reported that short term RCTs failed to establish significant effects of LNCS use on intermediate markers such as fasting glucose, fasting insulin and blood lipid levels (WHO 2023a).

The mechanisms by which LNCS may increase risk of T2D are unclear, and trials investigating LNCS intake on glucose metabolism are contradictory and difficult to compare because of the differences in outcome measures, use of different types of LNCS and different lengths of follow-up times (Johnson et al. 2018). Overall, current evidence that intake of LNCS on a regular basis increases risk of T2D is inconclusive. Further, higher quality trials are needed to evaluate specific LNCS, with an adequate sample size, a uniform study group, sufficient exposure time and adjustment for potential confounding factors including previous consumption of LNCS (Romo-Romo *et al.* 2016).

### *LNCS and Management of Diabetes*

There is limited research on the use of LNCS to maintain blood glucose within a healthy range for people living with diabetes. A Cochrane systematic review and meta-analysis of RCTs investigated the effect of LNCS consumption for HbA1c, body weight and adverse events in people living with type 1 or T2D (Lohner *et al.* 2020). The review included nine RCTs with a duration of at least four weeks. Most studies compared LNCS with sugar or placebo. The findings did not show a clear difference in HbA1c, body weight, or side effects in individuals with type 1 or T2D, indicating that the impact of LNCS on these outcomes remains uncertain in the context of diabetes management.  Data on health-related quality of life are lacking.

## Cardiovascular disease

Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels and includes all cardiac and cerebrovascular events (often defined as Major Adverse Cardiovascular Events [MACE]) which can include myocardial infarctions, unstable angina, heart failure, stroke, and cardiovascular death. However, the definition is applied inconsistently throughout the literature (Bosco *et al.* 2021).

In a review by Azad et al., prospective cohort studies comparing highest versus lowest LNCS intake reported associations between drinks containing LNCS with hypertension, higher risk of metabolic syndrome, stroke and cardiovascular events (Azad *et al.* 2017). However, the authors concluded that these associations have not been confirmed in experimental studies and may be influenced by publication and confounding bias.

The findings from the WHO systematic review on cardiovascular outcomes (cohort data) and biomarkers of cardiovascular risk (RCTs) are summarised in Table 6 (WHO 2023a). (In terms of study types, refer to Box 1 – Hierarchy of Evidence for quality of evidence with respect cohorts and RCTs).

*Table 6: Findings from the WHO systematic review on LNCS and cardiovascular outcomes*

| Measure of CVD (unit) | Number of studies/cohorts | Effect estimate (95% CI) | $I^2$ (%) |
|---|---|---|---|
| CVD mortality | 5 cohorts | **HR 1.19 (1.07, 1.32)** | 25 |
| Cardiovascular events | 3 cohorts | **HR 1.32 (1.17, 1.50)** | 0 |
| Coronary heart disease | 4 cohorts | HR 1.16 (0.97, 1.39) | 75 |
| Stroke | 6 cohorts | **HR 1.19 (1.09, 1.29)** | 0 |
| Hypertension | 6 cohorts | **HR 1.13 (1.09, 1.17)** | 48 |
| Systolic blood pressure (mmHg) | 14 RCTs | MD −1.33 (−2.71, 0.06) | 38 |
| Diastolic blood pressure (mmHg) | 13 RCTs | MD −0.51 (−1.68, 0.65) | 40 |
| Total cholesterol (mmol/L) | 14 RCTs | MD 0.01 (−0.09, 0.11) | 32 |
| LDL cholesterol (mmol/L) | 12 RCTs | MD 0.03 (−0.03, 0.09) | 32 |
| HDL cholesterol (mmol/L) | 13 RCTs | MD 0.00 (−0.03, 0.03) | 45 |
| Total cholesterol:HDL cholesterol | 4 RCTs | **MD 0.09 (0.02, 0.16)** | 0 |
| Triglycerides (mmol/L) | 14 RCTs | MD −0.04 (−0.11, 0.04) | 55 |

CVD: cardiovascular diseases; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
*Note:* Bold font indicates a statistically significant effect.

Post-WHO review, a recently published NutriNet Sante prospective cohort study of French adults investigated total artificial sweetener intake (including drinks, tabletop LNCS and LNCS sweetened dairy) (Debras *et al.* 2022b). Individuals with greater LNCS consumption reported a higher body mass index, lower total energy intake, lower dietary fat (both saturated and polyunsaturated), fibre, carbohydrate, fruit and vegetable intakes, and higher intakes of sodium, red and processed meat and SSBs. They also found an association with increased risk of cardiovascular diseases (1502 events, HR 1.09, 95% CI: 1.01 to 1.18,); absolute incidence rate in higher consumers (above the sex specific median) and non-consumers was 346 and 314 per 100,000 person years, respectively. This study also reported a significant association with cerebrovascular disease (including stroke; 777 events HR 1.18, 95% CI: 1.06 to 1.31), and found different associations of aspartame, acesulfame K and sucralose. However, the authors could not rule out residual confounding and/or reverse causality.

The study also included a sub-analysis on different types of LNCS. Aspartame intake was found to be associated with an increased risk of cerebrovascular events, while acesulfame potassium and sucralose were linked to a higher risk of coronary heart disease. However, the study did not explore the mechanistic or metabolic explanations for these differences between the various sweetener types.

Comparative analysis of the impact of SSB versus LNCBs has been published from the Health Professionals' Follow Up Study and the Nurses' Health Study cohorts in the US. These analyses indicated that, compared to individuals who never or rarely consumed SSBs or LNCBs the HR for CVD among those consuming ≥2 servings/d was 1.21 (95% CI: 1.12, 1.32; P-trend < 0.001) for SSBs, and 1.03 (95% CI: 0.97, 1.09; P-trend = 0.06) for those consuming ≥2 servings/d of LNCBs (Pacheco *et al*., 2024). Therefore, while consuming unsweetened beverages may be the healthiest choice, consuming LNCBs appears to offer a potential benefit over SSBs in reducing CVD risk.

## Dental Health

Sugar is known to adversely affect dental health, for example through the development of dental caries, a common infection caused by cariogenic bacteria in the mouth that metabolise sugar to produce acid that demineralises tooth structure. It has been hypothesised that LNCS do not promote tooth decay as they are not metabolised by oral bacteria (Sachdev, 2018). However, LNCS are typically consumed within acidic sweetened drinks; therefore it is possible that LNCS consumption in this matrix could lead to an increased risk of poor oral health (Giacaman *et al.* 2018).

In adults, the Rios-Leyvraz and Montez's systematic review (Rios-Leyvraz & Montez 2022) (see *Appendix E*) included a single 6-month RCT (dental health not a primary outcome), where participants were assigned to consume sugar-sweetened or NSS-sweetened soft drinks, and checks were carried out for caries or acid erosion of the enamel throughout the intervention. Neither group developed caries nor experienced acid erosion of the enamel at any point during the intervention (Maersk et al. 2012). In children, two RCTs on LNCS intake and dental caries (Vandana *et al.* 2017) (Cocco *et al.*2019) were included. Despite improvements in the prevalence of dental caries among children in the UK over the past 30 years, it continues to be a public health burden with significant oral health inequalities. Dental caries remains the most common reason for hospital admission for children aged 6–10 years old, with many receiving dental care under general anaesthetic (Kaddour *et al.* 2023). Limited research in children generally suggests that LNCS are less harmful to dental health, and in some instances could be beneficial, compared to sugar containing products.

An RCT involving high risk children aged 6–9 years (n=271) found that over a 6-week period, the concentrations of cariogenic (dental caries producing or promoting) bacteria and lactobacilli, and the probability of developing caries (measured via cardiogram) was reduced for those consuming snacks containing a LNCS (stevia) (Cocco *et al.*, 2019). Comparatively, there were no significant changes for the group eating snacks containing sugar. In an RCT, adolescent girls in Nellore, India (n=108, 12–15-year-olds) used 1 of 4 daily mouth rinses: chlorhexidine gluconate-based, sodium fluoride-based, LNCS containing stevioside-based or a placebo for 6 months (Vandana *et al.* 2017). Whilst all groups showed improvements in the short term, the stevioside-based mouthwash was found to be the most effective in reducing plaque and gingivitis by the end of the study period. This is likely because stevia is nonfermentable by oral bacteria and contains tannins, xanthines and flavonoids, which have antiplaque activity. Consequently, these findings may not be generalisable to all LNCS.

The WHO also reported on a limited number of observational studies. A prospective cohort study of children aged 1-5 (n=642) found that a low intake of LNCBs was associated with fewer dental caries, compared with no intake. However, the association with high LNCBs intake was not investigated (Marshall *et al.* 2003). Contrastingly, research from a cross-sectional study (Mihrshahi *et al.* 2017) (n=3671) found that in adolescents, the adjusted OR for toothache for adolescents drinking one or more cups of LNCBs a day (OR=5.21 [2.67-10.18]) was higher than those who drank one or more cups of soft drinks (AOR=1.95 [1.22-3.12]), fruit juice (AOR=1.32 [0.76-2.31]), sports (AOR=3.60 [1.93-6.73]) or energy drinks (AOR=2.14 [1.44-3.19]), or flavoured water (AOR=1.63 [0.74-3.59]). Findings from observational studies of this nature require careful interpretation, as the possibility of reverse causality cannot be ruled out (refer to Box 1 – Hierarchy of Evidence).

While LNCS may not directly increase the risk of dental erosion, their frequent consumption in acidic, sweetened beverages could potentially contribute to it. However, other components of these beverages, rather than LNCS, might be responsible for the elevated risk.

**A note on Polyols on Dental Health**

Sugar alcohols (polyols), although not covered in the scope of this document, are commonly used as a sugar replacement in products that are intended to be kept in the mouth for a long while, including chewing gums and breath mints. This is due to the fact they also do not contribute to dental caries as they are not as readily fermented by oral bacteria (Sachdev 2018). Lohner et al's systematic review found 16 intervention studies (14 RCTs and 2 non-RCTs) all of which reported either no effect (*n*=2) or found that the oral pH was higher for LNCS consuming participants, compared with a sugar containing control group (Lohner *et al.* 2020). It is generally agreed that a neutral oral pH is ideal, but that a high pH is less damaging than a low, acidogenic pH (Baliga *et al.* 2013).The findings of a 2019 systematic review (Newton *et al.* 2020) provide tentative evidence that chewing sugar free gum reduces caries increment in comparison to nonchewing controls. However, there is a considerable degree of variability in the effect and the trials included were generally of moderate quality. There is a need for future research to explore the acceptability and feasibility of the use of sugar free gum as a public health intervention.

## The Effect of LNCS on the Gut Microbiome

The potential effect of LNCS on gut health has been a topic of recent interest with a small number of intervention studies investigating the effects of different LNCS on both diversity of bacteria in the colon and effects on wider metabolism. This appears to have stemmed from interest in defining a potential biological mechanism to explain findings of the effect of LNCS suggested in cohort studies. Early research largely in animal models has suggested alterations to the colonic microbiome are linked to altered glycaemia, lipid profile and weight gain (Turner *et al.* 2020). Therefore, if LNCS do affect the microbiome, such metabolic changes may be observed.

However, the RCTs assessing gut microbiome and LNCS are inconclusive. An often-cited intervention study suggests that sucralose and saccharin, when consumed in quantities over the ADI, may alter the gut microbiome in some individuals (Suez *et al.* 2014). Ten individuals, supplemented with LNCS for 14 days showed altered glucose metabolism. This was proposed to be a result of an alteration to the gut microbiome, as evidenced by dysglycemia being observed following faecal transplants from responders into sterile rodent models. However, a randomised double-blind trial (n=34 healthy males) did not observe an alteration to the gut microbiome or glycaemic control following sucralose ingestion over a seven-day period (Thomson *et al.* 2019). In a study where the primary outcome was to determine the effect of sucralose and aspartame, in doses reflective of common consumption, on glucose metabolism in healthy individuals (n = 17), no effect was seen on gut microbiome or the profile of short chain fatty acids they produce consuming normal intakes of LNCS (Ahmad *et al.* 2020).

Any advice pertaining to LNCS and gut health should caveat that there is limited evidence and reflect the short term and modest nature of the effects on gut microbiome that would likely differ between individuals and with different types of LNCS. More research is needed and is being undertaken (see clinicaltrials.gov). For example, a four-week intervention has recently been completed to assess the effect of replacing SSBs with LNCBs, versus water on glucose tolerance, gut microbiome and cardiometabolic risk in adult SSB consumers living with overweight or obesity (Ayoub-Charette *et al.* 2023).

## LNCS and Reproductive Health

In safety assessments for LNCS (see *Chapter 1*), as with other additives, developmental and reproductive toxicity testing (including teratogenicity) and evaluation of the evidence around any new safety issues is required before they are introduced into the market.

The interest in LNCS consumption in pregnancy has investigated risks in delivery and birthweight but the available research in humans is limited. A prospective cohort study of Danish pregnant women (n=59,334) suggested that the daily intake of LNCBs may be associated with a small but significant increased risk of preterm delivery, primarily driven by medically induced delivery (Halldorsson et al. 2010). A Norwegian prospective study (Englund-Ögge *et al.* 2012) (n=60,761) found that the association of pre-term spontaneous delivery with >1 portion of LNCBs per day was much weaker (adjusted OR 1.11 (95% CI: 1.00, 1.24) and was exceeded by the association with consumption of SSB (>1 portion per day; adjusted OR: 1.25; 95% CI: 1.08, 1.45). These studies were considered by EFSA as part of their scientific opinion on the re-evaluation of aspartame (EFSA 2013). EFSA concluded that currently available epidemiological data do not suggest that consumption of LNCBs are a cause of preterm delivery, but further research would be needed to confirm or reject the association. Further to s the EFSA re-evaluation, Petherick et al.'s prospective cohort study (n=8914) reported no relationship between daily LNCS cola beverage consumption and preterm delivery irrespective of the amount consumed per day, whereas there was an increased risk for mothers consuming more than 4 cups of SSBs a day compared to women who consumed none (Petherick *et al.* 2014).

A systematic review and meta-analysis of prenatal effects of LNCS consumption evaluated 10 cohort studies and 1 RCT of 'low' and 'very low' certainty (Cai *et al.* 2021). This found that daily consumption of LNCS was associated with a small increase in birth weight (3 cohort studies; RR = 1.18, 95% CI 1.09, 1.28) compared with no consumption, corresponding to a mean difference of 23.74g (95% CI 0.89, 45.58). The analysis also indicated a small decrease in gestational age (3 cohort studies; mean difference: -0.11 weeks, 95% CI -0.19, -0.03). Other areas of reproductive health include LNCS intake and age of menarche. A prospective cohort study (n=2,379) found that greater consumption of LNCBs was associated with a higher risk of early menarche (RR for 1 serving per day increment: 1.43; 95% CI: 1.08, 1.88), and specifically for consumption of aspartame (RR for 1 serving per day increment: 1.20; 95% CI: 1.10, 1.31) (Mueller *et al.*, 2015). However, a plausible explanation for these observed effects could be weight gain, dietary patterns, or efforts at weight loss in these girls during the menarche or pubarche phases, prior to the age at which data were collected for this study (Kleinman 2015).

Human studies investigating at the association of LNCS with male fertility are scarce. A systematic review of 9 studies assessing male fertility in rodents (Kearns *et al.* 2022) reported inconclusive results but the authors highlighted the lack of research in this area.

# Chapter 3: LNCS Intake, and Impact on Diet Quality

## LNCS Intake

Quantifying intakes of both total and individual LNCS is challenging. In the UK, there are no national dietary surveys that measure LNCS intake, including the NDNS, although low calorie soft drinks have been used as a proxy measurement within research (Gibson *et al.* 2016). Furthermore, manufacturers are not required to declare LNCS quantities on labels or packaging, meaning that they are not publicly shared. SACN recently discussed monitoring of LNCS as part of dietary surveys (SACN 2025). The NDNS collects information about use of tabletop and other LNCS as part of 24-hour recalls (using Intake24's digital tool) and previously as part of the food diary but there are a number of important limitations to this data collection. Information is held on the presence of LNCS at food code level and the current coding frame for foods and drinks is not designed to assess exposure to LNCS. For the new NDNS contract (2024 to 2029 Years 16-20), OHID and FSA are considering inclusion of one or more general questions about use of LNCS, but it is unknown whether this will be sufficient to provide the robust data needed for future research.

UK intake data has been investigated from a cross-sectional study (UK Fenland cohort, n=9991), and reported that higher intakes of LNCBs ( 'low calorie or diet fizzy soft drinks'.) was associated with being female (OR 1.6, 95%CI:1.34-1.96), those who reported to be on weight loss diets (OR 2.58, 95%CI:2.05-3.24) and those reporting to have higher incomes (OR 1.53, 95%CI:1.16-2.00) (Barrett *et al.* 2017). In a survey of the US National Weight Control Registry (individuals who had lost ≥13.6 kg and maintained that weight loss for at least 1 year) (Catenacci et al. 2014), 53% reported regular consumption of LNCBs, where regular was defined as ≥ once a day.

A review of available data on intake of the major LNCS globally over a decade (from 2008, based on a literature search conducted in October 2017) showed that overall global intakes were below ADIs (Martyn et al., 2018). The authors commented that the most detailed exposure assessments were conducted in Europe, and that Japan and Korea similarly had up-to-date and regular intake data available. However, the data for other Asian countries, Latin America, Australia/New Zealand and global estimates, evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), while available, were shown to be more limited in terms of design (Martyn et al., 2018). The review highlighted the need for a more standardised approach to monitor potential changes in exposure, especially in response to sugar reduction recommendations. This is particularly important for more vulnerable groups, such as children, and to ensure risk management decisions are based on high quality intake data. Consumer perceptions vary with regard to LNCS, but concern has been noted over their potential adverse health effects (Ashwell *et al*., 2020; Farhat et al., 2021; Tang *et al*. 2020). This may have been heightened with the World Health Organization's conditional recommendation against LNCS for weight management, and the IARC classification of aspartame as possibly carcinogenic to humans. Consumer research also suggests a preference for sweeteners perceived as 'natural' (e.g. stevia and monk fruit sweeteners, honey, agave syrup, coconut sugar, brown sugar) to those referred to as 'artificial' (e.g. aspartame, sucralose). This aligns with an association of 'natural with healthiness and artificial with a higher health risk. It is also interesting that all foods and beverages containing LNCS are classified as *Ultra processed Foods* (UPF) under the NOVA definition. In a 2024-2025 FSA Consumer Insight tracker year review, 76% - 78% respondents indicated concern about ultra-processed, or the over-processing of food, second only to food prices (86% - 88% ), and with food poverty and inequality exhibiting a comparable level of concern. In the year review, it was noted that concern about ingredients and additives in food (70% - 73%) had become a more prevalent concern than animal welfare (68% - 72%) (Gosschalk *et al.* 2025).

## Diet Quality

SACN's *Carbohydrates and Health* report concluded that diets with high intakes of added sugars are associated with a poorer diet quality (SACN 2015)[11]. Sugar reduction is one means of improving overall diet quality. There is some evidence from short term RCTs that replacing sugars with LNCS may be beneficial to weight management (see *The role of LNCS in Weight Management and Obesity* section and *Sugar Reduction in the UK*) and could decrease sugar intake, particularly in high consumers of SSBs. A narrative review evaluating the association between diet quality and LNCS intake reported limited evidence with no clear consensus on the impact of LNCS on dietary patterns, food groups and/or nutrient intakes (Russell *et al*., 2021). However, in analysis of UK NDNS data (2008-2011), those who did not consume SSBs and those consuming "low-calorie beverages" had higher quality diets compared with consumers of SSBs or of both SSBs and LNCBs (Gibson *et al.* 2016).

In three US cross-sectional studies analysing National Health and Nutrition Examination Survey (NHANES) data, those consuming LNCS reported higher diet quality or healthier dietary patterns (measured, for example, through diet index scores) compared to non-consumers (Drewnowski & Rehm 2014; Fulgoni & Drewnowski 2022; Rusmevichientong *et al.* 2018). Conversely, one modelling study, and secondary analysis of the NHANES dataset found LNCBs intake to be associated with a lower overall diet quality (Piernas *et al.* 2015; An 2016). Two further cross-sectional studies, one performed amongst those living with morbid obesity in Norway (n=100) and the other using UK Biobank data (n=116,711), found that LNCBs intake was associated with less healthy dietary habits, including higher intakes of calories, free sugars, red and processed meat, processed snacks, and reduced intake of some vitamins (Maimaitiyiming *et al.* 2023; Winther *et al.* 2017). Other variables, such as how foods containing LNCS are replaced, along with the overall nutritional value and energy content of the diet, are likely to play a role. Consuming LNCBs does not necessarily translate to a higher quality, or a lower quality diet and it is likely that the whole dietary pattern needs to be considered rather than focussing on a single component.

In Nordic countries, LNCS are amongst the disqualifying food components included within the underlying nutrient profiling algorithm of the Keyhole front-of-pack nutrition labelling voluntary scheme which provides aggregated information on the overall nutritional quality of the product. In 2023 the algorithm for the NutriScore nutrition front of pack nutrition labelling system used

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[11] Diet quality refers to the overall nutritional value of an individual's diets, encompassing both the food groups that are encouraged, and those that should be eaten in moderation, and the quantities in which these are consumed. It often includes an assessment of proximity to dietary guidelines, for example the USDA Healthy Eating Index (HEI) score. A high quality diet generally includes a variety of fruits, vegetables, whole grains, lean proteins, and healthy fats, while minimising added sugars and salts, and unhealthy fats (NHS, 2022), or a HEI score of 81 out of 100 or above. A low quality diet generally consists of the opposite nutrients and proportions or has a HEI score of lower than 50.

in a number of European countries (France, Belgium, Switzerland, Germany, Spain, the Netherlands and Luxembourg) was updated for beverages. The algorithm now includes negative points so that the use of LNCS in beverages is not promoted (Sante Publique France 2023).

## Sweet Preferences

Concern has been raised that exposure to sweet ingredients, even LNCS, could contribute to an increased preference for a sweet taste in both the long- and short-term (Drewnowski *et al.* 2012). Whilst evidence shows sweet taste preference is innate to humans, it has been hypothesised that dietary sweetness, including sugars and sweetening ingredients, may initiate a 'learned preference,' that LNCS could disrupt the learned control of energy intake (sweet taste confusion hypothesis) and that exposure to sweetness increases desire for sweetness (sweet tooth hypothesis); (Rogers 2018). However, the research is mixed, with studies showing no consistent relationship between the consumption of LNCS and an increased preference or increased consumption of sweet foods and drinks (Appleton *et al.* 2018; Bellisle 2015; Mela & Risso 2024). There is also some suggestion that the sweetness of LNCS could activate the brain to expect calories and stimulate appetite (Rogers *et al.* 2016; Pepino & Bourne, 2011) . In contrast, other studies hypothesise that consuming LNCS could actually suppress appetite for sweetness and lead to a lower intake of sweet tasting foods or drinks, potentially facilitating weight loss(Appleton *et al.* 2018; Bellisle 2015; Piernas *et al.* 2015).

Most recently Rios-Leyvraz and Montez (*see Appendix E),* as part of their investigation on taste preferences, reviewed the effect of LNCS on sugar intakes with RCT evidence (n=12) indicating that higher intake of LNCS resulted in reduction of sugar intakes of approximately 39g per day (Rios-Leyvraz & Montez 2022). Rios-Leyvraz and Montez also reported on appetite, with three randomised clinical trials, with a high degree of heterogeneity suggesting that LNCS reduced desire to eat, using subjective rating scales (0.23 95% CI: 0.04, 0.42)(Rios-Leyvraz & Montez 2022).Two other studies reported no effects narratively (Raben *et al.* 2002; Kanders *et al.*, 1988).

Innate sweet preference, which is linked to sensations of pleasure, is often combined with measures of desire to eat, desire to initiate eating and delay in ceasing to eat. However, satiety, satiation and appetite are different to sweet preference yet are not always separated in the literature. This is further complicated by the inclusion of traits of liking and food preferences.

In summary, there is inconclusive evidence of the effects of LNCS on appetite or food preferences.

# Chapter 4: LNCS and Sugar Reduction Public Health Policy

There is evidence suggesting that a dietary pattern with high intake of free sugars can contribute to weight gain and obesity, and associated health conditions such as type 2 diabetes, cardiovascular disease (e.g., coronary heart disease) and certain cancers (DHSC 2016). Government strategies across the world to reduce sugars intake range from information provision to consumers (e.g. dietary guidelines, public health campaigns, labelling of sugar content of foods and beverages) to the implementation of financial (dis)incentives, such as taxes on products with high sugar contents to encourage reformulation and dissuade consumers from purchasing or consuming them (Hawkes *et al*., 2013; WHO 2017). Strategies also commonly include a range of activities to influence the 'food environment', for example limiting the availability of foods and beverages with a high sugar content in schools or public environments, and restrictions on the marketing and advertising practices for high sugar foods and beverages (WCRF, 2015; von Philipsborn *et al*., 2019). Furthermore a comprehensive whole system policy, rather than a piecemeal approach is likely to be is needed to reduce sugar consumption at a population level, and mandatory reduction and reformulation policies (that create a level playing field) have been highlighted as more effective than voluntary ones ((Gressier et al. 2025,Hashem *et al.* 2024; Tedstone 2023; WCRF 2015).

## Sugar Reduction in the UK

In the UK, free sugars intake exceeds the government recommendation of providing no more than 5% of total energy intake across the age groups (SACN 2015). NDNS data (OHID 2025) reports mean intakes were around double the recommendation the 11 to 18 years age group, (10.9% energy intake for boys and 11.9% for girls). In the 4 to 10 years and 19 to 64 years age groups, mean intakes were also around double the recommendation (10.2% and 10.0% of energy respectively).

High intakes of sugars, alongside increased recognition of the need to change the food environment, has prompted the government to implement policies such as taxation of SSBs through the Soft Drinks Industry Levy (SDIL) directly to the manufacturer and the voluntary sugar reduction programme (DHSC 2016; DHSC 2021) to reduce population sugar intakes. There has been a particular policy focus on reformulation which aims to reduce free sugars content often without the need for consumer behaviour change. Replacing sugars with LNCS, particularly in SSBs, has been one response to these policies. Technically, it is easier to replace sugar with LNCS in SSBs, compared with other products. In categories such as chocolate and baked goods, sugar can play a technical role, i.e. affecting the texture, structure, appearance and shelf-life of the food item. There are also regulatory conditions for the use of LNCS in products, in terms of maximum levels of use, and types of food in which use is permitted (i.e. restrictions by category) (see Chapter 1: safety) (PHE 2018).

Internationally, as in the UK, taxes on SSBs have been introduced. The WHO global report on the use of SSB taxes note that 105 countries apply excise taxes on sugar-sweetened carbonated beverages (WHO 2023d). Several countries, including Hungary, France, and certain states in the US, have also implemented taxes on LNCBs, in addition to SSBs.

In the UK, since its announcement in 2016 and implementation in 2018, the SDIL has led to a marked reduction (46% average) in sugar content in soft drinks that are in scope of the levy between 2015 and 2020 (HMT-HMRC 2024). Under the current levy structure, 89% of soft drinks sold in the UK do not pay SDIL, as they contain less than 5g sugar per 100ml. Research suggests that this policy could contribute to a reduction in childhood obesity, including data from the National Child Measurement Programme (NCMP)[12], showing a 2.4% (95% CI 1.6, 3.2) reduction in the prevalence of obesity in Year 6 girls, but not in Year 6 boys or reception children (Rogers *et al.* 2023a). A recent modelling study of the impact of the SDIL on health and health inequalities in children and adolescents in England reported that this could lead to medium-term reductions in dental caries and overweight/obesity, with the greatest benefits projected for children and adolescents from more deprived areas (Cobiac *et al.* 2024).

However, attributing any reduction in obesity levels solely to the SDIL is challenging as there are many other factors that will impact on obesity rates. The quality of food environments differ in areas of deprivation and this can limit access to affordable and healthy food options (Social Market Foundation 2018). Any action to reduce sugar intake should be done in conjunction with strategies that aim to tackle the determinants of poor diet, including socioeconomic differences, restrictions to the promotion of food and drinks high in fat, sugar or salt (HFSS), increasing accessibility to healthier foods and wider cross-governmental strategies to tackle drivers of health inequalities.

The influence of reformulation in the food supply chain is a rapidly evolving landscape and innovation in this field may provide new solutions for sugar reduction. It is interesting that even though the public are concerned about sugar intake, more ‘natural’ alternatives, such as honey, agave syrup, and coconut sugar can be perceived as being more acceptable and ‘healthier’ as they are derived from plant-based sources and carry a positive ‘halo’ although they are still classified as free sugars. Likewise novel LNCS that are marketed as ‘natural’ for example stevia may be more acceptable for consumers; other ‘natural’ sweetening products such as monk fruit extract has FDA ‘Generally Recognized As Safe (GRAS) status, but EFSA advises that more research is needed.

[12] This programme is part of the Government’s approach to tackling child obesity by annually measuring the height and weight of children in reception (aged 4–5 years) and year 6 (aged 10–11 years) in mainstream state-maintained schools in England.

# Conclusion

This insights document has highlighted recent research on LNCS but there are many important gaps in the evidence base. One such gap is the limited understanding of LNCS intake consumption patterns. There are few studies that quantify LNCS intakes in the UK and globally, and those available may not reflect the considerable reformulation changes, with increased LNCS use particularly in beverages as part of public health sugar reduction initiatives. As a result of reformulation, it will be important to monitor LNCS consumption and long-term use and ascertain the impact of increased LNCS use on overall diet quality. Food composition data and dietary survey data do not currently provide details of LNCS, yet accurate quantifiable intake data is needed to fully investigate real life effects of LNCS consumption, as well as monitor changes in intake and inform policy. Data from manufacturers regarding LNCS quantities would greatly strengthen data collection efforts.

Approved LNCS consumed within ADIs have been deemed to be safe and can be incorporated into strategies for managing weight and diabetes, although they are unlikely to be a stand-alone solution for the majority of people; thus, the primary focus of dietary advice should be on achieving a healthy eating pattern. However, there is still a need to develop and review evidence on long term benefits and potential risks of different types of LNCS and their role in different food and drink products, in the context of public health. Although it was not in the scope of this review, it is also important to consider the impact of LNCS on environmental sustainability. More high-quality research, including well conducted RCTs of longer duration, is warranted to support a greater understanding of longer-term physiological effects of LNCS on metabolism and energy balance.

Consumer confusion on this topic may be exacerbated by frequent media coverage presenting conflicting opinions. SACN has published its SACN statement on the WHO guideline on non-sugar sweeteners (April 2025) in the context of implications to the UK. SACN agree that a reduction in consumption of free sugars, alongside other positive changes to diet, is likely to be beneficial to health overall. In relation to the use of NSS to reduce free sugars intake, SACN concludes that the evidence indicates that there may be some value in using NSS to help reduce weight gain in the short to medium term, but it is not essential and is not the only option. SACN reiterates the importance of following UK government advice on a healthier diet, based on SACN's recommendations, which is summarised in the UK's national food guide, the Eatwell Guide. The publication of its expert and evidence-based statement could help inform the public. However, SACN would welcome further, more robust, long-term evidence, particularly from RCTs, to explore any association and the possible underlying mechanisms in respect to body fatness and noncommunicable diseases given the range of studies reporting such associations. It is important that regulatory authorities continue to monitor new research on LNCS, disseminating findings in easily understandable outputs for the public. Public health messages focusing on safety and appropriate use of LNCS in the context of a healthy diet should also be communicated.

Maintaining a balanced perspective and avoiding sensationalism is essential as more conclusive findings are awaited. Advice from healthcare professionals needs to be clear, up-to-date and consistent, as well as practical and individualised. There is widespread recognition in the UK that average intake of free sugars is too high and SSBs are a significant contributor for many people. For those consuming SSBs regularly, LNCS sweetened beverages may be a helpful substitute if overall energy intake is reduced. This approach may be particularly helpful for people who are accustomed to a sweet taste and for whom water, at least initially, is an undesirable option.

The National Weight Control Registry in the US reported that people successful at weight loss maintenance primarily consume reduced calorie or non-caloric beverages (including LNCSB) and report low consumption of SSB. The majority (78%) of people who consume LNCSB felt these helped them control or reduce their total food or calorie intake suggesting that these beverages could play a role in a weight control programme. Changes in patterns of beverage consumption (specifically increasing water and to a lesser extent, reducing regular calorie/non diet beverages) may also be important strategies for weight loss and maintenance (Catenacci *et al.* 2014). Encouraging shifts in patterns from sugar sweetened foods to those that are naturally sweet like fruit, as well as healthier unsweetened foods and beverages is important but can be challenging. Food preferences developed in the early years track throughout childhood and beyond and, therefore, it is critical that fruit and vegetable familiarity is promoted at the very earliest opportunity (Chambers et al., 2016).

The aim of this insight report was to inform the development of a position statement from the participating organisations. However, we note some limitations. This report did not have a formal review protocol or predefined methodology. The authors have searched for key research and reviews in this field, with particular reference to the most recent WHO review from 2023, but the search may not be exhaustive. Research studies, reviews and opinion articles present a spectrum of conclusions regarding the potential effects of LNCS, ranging from harmful to beneficial or neutral. Within this current insight document, a hierarchical approach of evidence has been applied. Rigorous research methodologies and careful consideration of evidence representation and weighting are needed to ensure a balanced interpretation and contextual understanding. When reporting research and reviews, it is important to interpret observational and animal data in light of plausible causal pathways and consider the results of any relevant human RCTs.

This report has highlighted substantial limitations in the evidence base have been highlighted, including study design in terms of LNCS exposure and relevant comparators employed. These should be related to the primary outcome being tested whether this is energy reduction or sweetness (which can be largely generalisable to LNCS) or a specific metabolic effect, which may be specific to the properties of individual LNCS. Better quality evidence, including better quality RCTs and the consideration of all relevant evidence from different study designs, may help to reduce inconsistencies in scientific reports and their appraisals as well as reducing misconceptions in the general public and help guide healthcare professionals to give clearer advice.

# Recommendations

## Research Recommendations

- Standardised methods should be developed to accurately monitor both total and individual intakes of LNCS intakes over time. This will support comparisons with ADIs and help identify high consumers. Efforts should include improved and validated nutritional assessment tools and the use of biomarkers through urinary analysis.
- There is a clear need for publicly available, regularly updated food composition databases that reflect product categories and reformulation trends. All dietary sources (not just beverages) must be included, and dietary modelling should be used to assess

the potential impact of LNCS on reducing free sugar intake across the total diet and evaluate the role of LNCS in sugar reduction strategies.

- Research should examine both short- and long-term effects of LNCS, across diverse population groups including variations by ethnicity, age (including infant and young children), sex, life stages (including pregnant and lactating women) and pre-existing health status (such as those living with obesity or with diabetes). Behavioural changes linked to long-term conditions should also be considered.
- Further research is needed to understand biological mechanisms, including the:
    - long-term impact of LNCS on energy balance, appetite, satiety and glucose metabolism, using high-quality RCTs to control for confounding variables;
    - effect of food matrices (e.g. liquid vs. solid) on the physiological processing and utilisation of LNCS;
    - distinct metabolic pathways of individual LNCS compared to collective (in combination) effects, and the potential 'cocktail effect' of different sweeteners when used in combination.
- Research should explore consumer perceptions of different LNCS types, including perceived benefits versus perceived risks, and the impact on dietary behaviour.
- Studies should assess HCPs' understanding of LNCS, including their views on benefits and risks, to support objective, evidence-based dietary guidance.
- Research funding should prioritise research that supports healthy, balanced diets and sugar reduction strategies.

## Policy Recommendations

Authoritative bodies in the UK (such as SACN, DHSC and FSA) should:

- Include LNCS and specific types of LNCS in foods and beverages commonly consumed within the UK's national composition of foods database.
- Find a way to share commercially sensitive data on LNCS and specific types of LNCS in foods and beverages commonly consumed in the UK to support inclusion of LNCS within the UK's national composition of foods database.
- Improve food labelling, and public communication by providing clear, consistent public health messages on LNCS safety and explaining ADIs in the context of typical consumption levels.
- Assess exposure to LNCS by sweetener type and across socio-demographic strata.
- Track intake levels and consumption patterns, including total and specific LNCS types, in light of reformulation policies. Enhanced data collection within the National Diet and Nutrition Survey would support this
- Evaluate the impact of sugar reduction policies on LNCS intakes.
- Continue to monitor the safety of LNCS through regular reviews of emerging research.
- Evaluate the impact of sugar reduction policies on LNCS intakes.
- Continue to monitor the safety of LNCS through regular reviews of emerging research.
- Provide timely and clear responses to influential publications on LNCS, including WHO guidelines, to inform stakeholders such as the public, HCPs and procurement bodies.
- Track intake levels and consumption patterns, including total and specific LNCS types. Enhanced data collection within the *National Diet and Nutrition Survey* and inclusion within the national composition database would support this. This is particularly pertinent in light of government sugar reduction targets, the 2018 NPM's focus on free

sugars, and SACN's precautionary advice on sweeteners. With this clear need for robust consumption data, exploring mechanisms to share commercially sensitive information on the presence and quantity of LNCS in commonly consumed foods and beverages would support both policy evaluation and evidence-based risk assessment.

- Improve public communication and food labelling by providing clear, consistent public health messages on LNCS safety and explaining ADIs in the context of typical consumption levels.

| LNCS | ADI | ADI Equivalent if sweetener used at the maximum permitted level |
|---|---|---|
| ASPARTAME | 0-40 mg/kg bodyweight | For an adult, without any other source of aspartame in the diet, this is equivalent to drinking 16 standard 250ml glasses (around 12 cans) of soft drink sweetened with aspartame at the maximum permitted level every day throughout their life. Soft drinks frequently contain aspartame at less than the maximum permitted level |
| SUCRALOSE | 0-15 mg/kg bodyweight. | For an adult, without any other source of sucralose in the diet, this is equivalent to drinking 12 standard 250ml glasses (around 9 cans) of soft drink sweetened with sucralose at the maximum permitted level every day throughout their life. |
| STEVIOL GLYCOSIDES | 0-4 mg/kg bodyweight. | For an adult, without any other source of steviol glycosides in the diet, this is equivalent to drinking 12 standard 250ml glasses (around 9 cans) of soft drink sweetened with steviol glycosides at the maximum permitted level every day throughout their life. |

Table 7: Illustrated quantity of intake of soft drinks needed to exceed ADIs

The ADI is the estimated amount per kg of body weight that a person can consume, on average, every day, over a lifetime without risk. ADIs are set 100 times lower than the smallest amount that may cause health concerns.
SOURCE: BRITISH SOFT DRINKS ASSOCIATION
https://www.britishsoftdrinks.com/media/js2lw4et/bsda_sweeteners_pamphlet.pdf

## Food Industry Recommendations

The food industry should:

- While acknowledging commercial sensitivities, disclose quantitative details of LNCS used in products and report sales data in a similar manner to sugar. LNCS should be included in metrics reporting for transparency initiatives like the Food Data Transparency Partnership.
- Continue efforts to reduce the quantity of free sugars in products, while exploring innovative and consumer-accepted approaches to improve nutrient density.
- Collaborate with academic researchers under transparent guidelines that mitigate bias and ensure full disclosure of funding sources and conflicts of interest.

## Healthcare Professionals (HCPs) Recommendations

**HCPs should be:**

- Equipped with training and resources to deliver up-to-date, evidence-based advice on LNCS consumption, tailored to individual dietary needs and mindful of both potential benefits and risks.
- Supported by transparent and clearly communicated research findings, with clarity on how evidence is selected and a balanced representation of different types of studies.
- Where appropriate, considering the inclusion of LNCS as a potential part of a stepwise approach to improving diet quality and reducing free sugar intake, while also promoting nutrient-dense food choices.

### *Applications to practice*

**For weight management (and supporting prevention of type 2 diabetes and cardiovascular disease):**

- LNCS should not be used as the primary dietary modification to support weight management. Instead, dietary interventions should focus on improving overall dietary quality by:
    - Reducing intakes of foods high in free sugars (e.g. cakes, pastries, sweet spreads, confectionery) and replacing them with alternatives such as fruits, vegetables, unsweetened dairy products e.g. plain yogurt, and unsalted nuts.
    - Encouraging the consumption of water or other unsweetened beverages, including tea and coffee, replacing sugar-sweetened beverages (SSBs). For regular SSB consumers, LNCBs may be a useful alternative, particularly for people at higher risk of type 2 diabetes.
- HCPs should encourage individuals to limit free sugar intake to less than 5% of total dietary energy and provide practical advice on how this should be achieved, whilst acknowledging the challenges posed by the current food environment, including the availability, accessibility and marketing of sugary foods and drinks.
- Infants and young children, especially those under 3 years old, should not be encouraged to consume products with LNCS.
- For children aged 5 years and older, LNCS may be an option to help reduce excess sugar and calorie intake based on individual dietary needs. Recommended drinks for children are water and milk (or unsweetened fortified milk alternatives). Unsweetened fruit/vegetable juices and smoothies should be limited to a maximum of one small glass (150ml) a day.
- HCPs should consider the diet quality of individuals choosing LNCS-containing products, to ensure no compensatory eating behaviours emerge (for example, consuming larger portions or choosing less healthy foods elsewhere in the diet under the assumption that LNCS “save calories”).

**For diabetes management:**

- Regular SSB consumers should be encouraged to replace these with water or other unsweetened drinks. LNCBs may be useful as part of a gradual approach to reducing free sugar intake.
- Replacing free sugars, including those found in SSBs, with LNCS and LNCBs can be an effective strategy for reducing carbohydrate intake and managing post-prandial blood glucose levels.

**Healthcare professionals should:**

- Encourage people living with diabetes to monitor how replacing free sugars with LNCS affects their diabetes management and body weight.
- Support individuals in understanding food and drink labels, to increase awareness of how product reformulation may impact their blood glucose levels and overall diabetes management.
- Help to show people living with diabetes how to improve their diets by following a dietary pattern rich in whole grains, fruits, vegetables, fish, pulses, nuts, seeds, and unsweetened dairy or fortified unsweetened dairy-alternatives, while limiting red and processed meats, salt, refined carbohydrates, and sugar-sweetened foods and drinks.
- Refer individuals to a dietitian for personalised dietary advice and support when needed and appropriate.

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## Appendix A: Abbreviations

| | |
|---|---|
| ADI | Acceptable daily intake |
| AOR | Adjusted odds ratio |
| BDA | British Dietetic Association |
| BMI | Body mass index |
| BNF | British Nutrition Foundation |
| CHD | Coronary Heart Disease |
| CI | Confidence interval |
| CoT | Committee on Toxicity of Chemicals in Food Consumer Products and the Environment |
| CRUK | Cancer Research UK |
| CVD | Cardiovascular disease |
| DC | Dihydrochalcone |
| DHSC | Department of Health and Social Care; *in the context of this document, the DHSC for England* |
| DNSG | The Diabetes and Nutrition Study Group |
| EASD | European Association for the Study of Diabetes |
| EC | European Commission |
| EFSA | European food safety authority |
| EU | European Union |
| FAO | Food and Agricultural Organisation |
| FDA | Food and Drug administration; *in the context of this document, the US FDA* |
| FDTP | Food Data Transparency Partnership |
| FSA | Food Safety Authority; *in the context of this document, the UK FSA* |
| GB | Great Britain |
| GI | Gastrointestinal |
| HbA1c | Hemoglobin A1C; *average blood glucose (sugar) levels* |
| HCP | Healthcare professionals |
| HEI | Healthy eating index |
| HR | Hazard ratio |
| IARC | International Agency for Research on Cancer |
| ISA | International Sweeteners Association |
| JECFA | Joint FAO/WHO Expert Committee on Food Additives |
| LNCBs | Low and no-calorie sweetened beverages |
| LNCS | Low and no-calorie sweeteners |
| MACE | Major Adverse Cardiovascular Events |
| MD | Mean Difference |
| NCDs | Non-communicable diseases |
| NDA | EFSA Panel on Nutrition, Novel Foods and Food Allergens |
| NDNS | National Diet and Nutrition Survey |
| NHANES | National Health and Nutrition Examination Survey |
| NHS | National Health Service; *in the context of this document, for the UK* |
| NI | Northern Ireland |
| NNS | Non-nutritive sweeteners |
| NSS | Non-sugar sweeteners |
| NTP | National Toxicology Program |
| OHID | Office for Health Improvement and Disparities |
| OR | Odds ratio |

| | |
|---|---|
| PHE | Public Health England |
| PKU | Phenylketonuria |
| RCT | Randomised control trial |
| RR | Risk ratio |
| SACN | Scientific Advisory Committee on Nutrition |
| SDIL | Soft Drinks Industry Levy |
| SMF | Social Market Foundation |
| SSBs | Sugar sweetened beverages |
| T2D | Type 2 diabetes |
| USDA | United States Department of Agriculture |
| WCRF | World Cancer Research Fund |
| WHO | World Health Organization |

## Appendix B: EFSA Updated Protocol on Hazard Identification and Characterisation of Sweeteners

A full systematic procedure will be applied to identify studies reporting on adverse health effects in humans and/or animals. For studies on genotoxicity and toxicokinetics, the approach is a narrative one.

Except for genotoxicity, information from *in vitro* studies will only be used, where appropriate, in order to inform on the mode(s) of action (MoA(s)) and biological plausibly, but not to establish a relationship (including any dose–response relationship) between the intake of sweeteners and apical[1] and non-apical[2] endpoints in humans.

[1] Definition of apical endpoint according to the Revised Guidance Document on Developing and Assessing Adverse Outcome Pathways (OECD, 2017): 'Apical endpoints are empirically verifiable outcomes of exposure, such as death, developmental anomalies, breeding behaviours, impaired reproduction, physical changes and alterations in the size and histopathology of organs, including clinical signs or pathologic states, that are indicative of a disease state (Krewski et al., 2011; Villeneuve and Garcia-Reyero, 2011). Note: Endpoints (outcomes) considered to be apical may differ if used as a surrogate for human health versus ecological health.'

[2] Intermediate (or non-apical) endpoints are events occurring at a step between the molecular initiating event and the apical outcome: they are toxicologically relevant to the apical outcome (a necessary element of the mode of action or a biomarker of effect (see e.g. OECD, 2013) and are experimentally quantifiable.

**Table: Sub-questions to be addressed in the hazard identification and characterisation of 245 sweeteners**

| Number | Sub-question |
|---|---|
| 1a | What is the absorption, distribution, metabolism and excretion (ADME) of sweeteners in humans? |
| 1b | What is the ADME of sweeteners in mammalian animal species? |
| 1c | How do the human and animal ADME data correlate? |
| 1d | Are there any biomonitoring data that contribute to the assessment of ADME? |

| | |
|---|---|
| 2 | Do any of the substances included in the assessment show genotoxic potential? |
| 3a | Is there a dose–response relationship between the dietary exposure to sweeteners and adverse effects in humans (observational and interventional studies)? |
| 3b | Is there a dose–response relationship between exposure to sweeteners and adverse effects in experimental animal studies? |
| 4 | Which could be the potential mode(s) of action for the relationships found, if any, between sweetener intake and the adverse health outcomes? |

**Source:** [EFSA Protocol for the assessment of hazard identification and characterisation (europa.eu)]

## Appendix C: Acceptable daily intake of LNCS in the EU

| Sweetener | ADI mg/Kg/body weight/day |
|---|---|
| Advantame | 5 ( EFSA 2013a ) |
| Acesulfame K | 9 (EC 2000a) |
| Aspartame | 40 ( EFSA 2013b ) |
| Aspartame – Acesulfame K salt | As respective components |
| Cyclamate | 7 (EC 2000b) |
| Neotame | 2 ( EFSA 2007 ) |
| Neohesperidine DC | 5 (EC 1989) |
| Saccharin | 5 (EC 1995) |
| Steviol glycosides | 4 ( EFSA 2010b ) |
| Sucralose | 15 (EC 2000) |
| Thaumatin | Not specified ( EFSA 2015 ) |
| Polyols | Not specified ( EC 1985 ) |

Source: Acceptable daily intake of sweeteners in the EU | Knowledge for policy (europa.eu)

## Appendix D: Summary of the recent evidence on the association of individual LNCS and cancer

| LNCS | Study or review type | Outcome | Association between cancer and intake of LNCS | Study findings | Reference |
|---|---|---|---|---|---|
| **Stevia rebaudiana** | Narrative review | Anti-cancer effects | Negative association – higher consumption, lower cancer risk | Compounds like the flavonoids and fatty acids found in stevia leaves stimulate insulin production in people with diabetes, improve polycystic kidney disease, have chemotherapeutic action in cancer and possess powerful antibacterial, antioxidant and immunomodulating properties | Peteliuk et al. (2021) |
| **Stevia rebaudiana** | Narrative review | Anti-cancer effects | Negative association – higher consumption, lower cancer risk | Active compounds isolated from Stevia rebaudiana possess interesting medicinal activities, including antidiabetic, antihypertensive, anti-inflammatory, antioxidant, anticancer, and antidiarrheal activity. | Orellana-Paucar (2023) |
| **Acesulfame-K** | Systematic evaluation of mechanisms | Carcinogenic response in humans | No association | Found no association, based on animal exposure and mechanistic applications | Chappell et al., 2020 |

| | | | | | |
|---|---|---|---|---|---|
| **Aspartame and Acesulfame-K** | Cohort study | Overall cancer risk | Positive association | An above average exposure to LNCS, in particular aspartame and acesulfame-K, increased the risk of overall cancer, and in particular, breast cancer and obesity-related cancers | Debras et al., 2022 |
| **Aspartame and All LNCS** | Case control study | Overall cancer risk in diabetic patients | Positive association | Found an association between high consumption of aspartame and other LNCS and different cancer types among participants with diabetes. | Palomar-Cros et al. 2023 |
| **Aspartame, saccharin, or all LNCS** | Cross sectional study | Cancer mortality | No association | Using data from National Health and Nutrition Examination Surveys 1988-2018 (NHANES), found there was no indication that aspartame, saccharin, or all LNCS had any impact on overall cancer mortality | Fulgoni and Drewnowski., 2022 |
| **All LNCS** | Meta-analysis (4 prospective, 4 case-control studies) | Gastrointestinal (GI) cancer | Negative and no association | No significant association between LNCS intake and GI cancer risk overall, LNCS consumption was associated with a 19% reduction in risk of luminal GI cancer (OR 0.81, 95% CI:0.68-0.97). | Tepler et al. (2021) |
| **All LNCS** | Meta-analysis of observational studies | GI cancer | No association | No significant association between the consumption of LNCS sweetened soft drinks and the risk of GI cancer. | Jatho et al. (2021) |

| | | | | | |
|---|---|---|---|---|---|
| **All LNCS** | Meta-analysis of observational studies | GI cancer | Insignificant positive associations | Although the statistically significant threshold was not reached, a positive association was observed between LNCS sweetened beverages and pancreatic cancer risk. | Llaha et al. (2021) |
| **All LNCS** | Meta-analysis of case-control studies | Risk of all cancers | Negative association | In women the use of LNCS was inversely related to urinary system cancer risk. | Liu et al., (2021) |
| **All LNCS** | Retrospective observational | Thyroid cancer risk | Positive association | Showed LNCS consumption to be a potential risk factor for well-differentiated thyroid cancer. | Singh et al. (2020) |
| **All LNCS** | Systematic review and meta-analysis of observational studies | Breast Cancer risk | Negative association | 2 case control studies and 3 cohort studies showed that consumption of LNCS was not associated with risk of breast cancer (OR 0.98, 95% CI:0.93-1.02). | Ye et al. (2023) |

## Appendix E: Summary of Rios-Leyvraz and Montez systematic review and meta-analysis (2022)

This review updated the 2019 systematic review on intake of non-sugar sweeteners LNCS (referred to in the document as NSS) in adults and children, but also included studies in which LNCS were not specified by name and studies of effects of LNCS on pregnant women published through July 2021. A total of 283 studies were included. Meta-analyses focused on randomised controlled trials, prospective cohort studies and case–control studies assessing cancer. Certainty in results was assessed via GRADE (Grading of Recommendations Assessment, Development and Evaluation). The results (*figure D1*), and specifically cancer outcomes (*figure D2*), are summarised below.

***Figure D1: Results for key outcomes in adults (including pregnant women)***

| Randomised Control | Cohort/case-control studies |
|---|---|
| **Adiposity**<br>↓ Body weight: MD -0.71 kg (95% CI -1.13, 0.28) (low) – mostly in LNCS -> sugars<br>↓ BMI: MD -0.14 kg/m$^2$ (95% CI -0.30, 0.02) (low) – mostly in LNCS -> sugars<br>Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass) | **Adiposity**<br>↑ Incident obesity: HR 1.76 (95% CI 1.25, 2.49) (low)<br>↑ BMI: MD +0.14 kg/m$^2$ (95% CI 0.03, 0.25) (very low)<br>Ø Other measures |
| **Type 2 diabetes**<br>Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c) | **Type 2 Diabetes**<br>↑ Disease (beverage): HR 1.23 (95% CI 1.14, 1.32) (low)<br>↑ Disease (tabletop): HR 1.34 (95% CI 1.21, 1.48) (low)<br>↑ High fasting glucose: HR 1.21 (95% CI 1.01, 1.45) (low)<br>Ø Other measures |
| **All-cause mortality**<br>No data | **All-cause mortality**<br>↑ Mortality HR 1.12 (95% CI 1.05, 1.19) (low) |
| **Cardiovascular diseases**<br>↑ Total:HDL cholesterol: MD +0.09 (95% CI 0.02, 0.16) (moderate)<br>Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides | **Cardiovascular diseases**<br>↑ CVD mortality: HR 1.19 (95% CI 1.07, 1.32) (low)<br>↑ CV events: HR 1.32 (95% CI 1.17, 1.50) (low)<br>Ø Other measures<br>↑ Stroke: HR 1.19 (95% CI 1.09, 1.29) (low)<br>↑ Hypertension: HR 1.13 (95% CI 1.09, 1.17) (low) |
| **Cancer**<br>No data | **Cancer**<br>Ø Mortality (very low)<br>Ø Incidence: any type (very low)<br>↑ Bladder cancer: OR 1.31 (95% CI 1.06, 1.62) (very low) – mostly in saccharin |
| **Total energy intake (kJ/day)**<br>↓ Energy intake: MD -569 (95% CI -859, -278) (low) – mostly in LNCS -> sugars | **Total energy intake (kJ/day)**<br>No data |
| **Sugars intake (g/day)** | **Sugars intake (g/day)** |

| | |
|---|---|
| ↓ Sugars intake: MD -38.4 (95% CI -57.8, -19.1) (low) | No data |
| **Pregnancy**<br>No data | **Pregnancy**<br>↑ Preterm birth: HR 1.25 (95% CI 1.07, 1.46) (low) |
| BMI: body mass index; CHD: coronary heart disease; CV cardiovascular; CVD: cardiovascular disease; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HR: hazard ratio; LDL: low-density lipoprotein; OR: odds ratio; tabletop = NSS added to foods or beverages by the consumer. | |

| Cancer site | No. of studies/cohorts | Effect estimate (95% CI) | $I^2$ (%) | Figure |
|---|---|---|---|---|
| Cancer mortality | 4 cohorts | HR 1.02 (0.92, 1.13) | 50 | 25 |
| Any type | 7 cohorts | HR 1.02 (0.95, 1.09) | 37 | 26 |
| Bladder | 26 case–controls | **OR 1.31 (1.06, 1.62)** | 92 | 27 |
| Brain | 2 case–controls<br>1 cohort | OR 1.13 (0.76, 1.69)<br>RR 0.73 (0.46, 1.15) | 0<br>NA | A9.37<br>NA |
| Breast | 3 case–controls<br>4 cohorts | OR 0.83 (0.64, 1.08)<br>HR 0.98 (0.89, 1.09) | 47<br>55 | A9.38<br>A9.39 |
| Colorectum | 3 case–controls<br>3 cohorts | OR 0.85 (0.68, 1.07)<br>HR 0.80 (0.63, 1.01) | 0<br>0 | A9.40<br>A9.41 |
| Endometrium | 1 case–control<br>1 cohort | OR 0.96 (0.66, 1.39)<br>HR 0.81 (0.42, 1.56) | NA<br>NA | NA<br>NA |
| Kidney | 4 case–controls<br>1 cohort | OR 1.25 (0.94, 1.65)<br>HR 0.92 (0.46, 1.84) | 61<br>NA | A9.42<br>NA |
| Larynx | 1 case–control | **OR 2.34 (1.20, 4.56)** | NA | NA |
| Lung | 2 case–controls | **OR 0.40 (0.26, 0.61)** | 0 | A9.43 |
| Oesophagus | 1 case–control | OR 1.24 (0.54, 2.83) | NA | NA |
| Oral cavity and pharynx | 1 case–control | OR 0.77 (0.36, 1.64) | NA | NA |
| Ovary | 1 case–control<br>1 cohort | **OR 0.56 (0.38, 0.82)**<br>HR 1.37 (0.72, 2.61) | NA<br>NA | NA<br>NA |
| Pancreas | 4 case–controls<br>3 cohort | OR 0.88 (0.51, 1.50)<br>RR 1.06 (0.88, 1.28) | 83<br>0 | A9.44<br>A9.45 |
| Prostate | 2 case–controls<br>2 cohorts | OR 0.88 (0.30, 2.62)<br>HR 1.09 (0.67, 1.75) | 40<br>66 | A9.46<br>A9.47 |
| Stomach | 2 case–controls<br>1 cohort | OR 0.79 (0.50, 1.26)<br>HR 1.03 (0.53, 1.99) | 0<br>NA | A9.48<br>NA |
| Leukaemia | 3 cohorts | RR 1.24 (0.92, 1.69) | 0 | A9.49 |
| Multiple myeloma | 4 cohorts | RR 1.05 (0.70, 1.59) | 70 | A9.50 |
| Hodgkin lymphoma | 1 cohort | RR 0.77 (0.44, 1.33) | NA | NA |
| Non-Hodgkin lymphoma | 4 cohorts | RR 1.08 (0.87, 1.34) | 64 | A9.51 |
| All cancers | 1 case–control<br>1 cohort | RR: 0.90 (0.67, 1.23)<br>HR : 1.00 (0.84, 1.19) | NA<br>NA | NA<br>NA |
| Cancers not related to obesity | 1 cohort | **HR: 1.23 (1.02, 1.48)** | NA | NA |
| Cancers related to obesity[a] | 1 cohort | HR: 1.00 (0.79, 1,27) | NA | NA |

NA: not applicable.
[a] Defined as liver cancer, aggressive prostate cancer, ovarian cancer, gallbladder cancer, kidney cancer, colorectal cancer, oesophageal cancer, postmenopausal breast cancer, pancreatic cancer, endometrial cancer and gastric cardia cancer *(165)*.
*Note:* Bold font indicates a statistically significant effect.

***Figure D2: Summary of results for LNCS intake and cancer***
Source: Rios-Leyvraz and Montez, 2022

## Appendix F: Use of non-sugar sweeteners: WHO guideline

A recent guideline, published by WHO (2023), recommended against the use of LNCS (referred to as NSS in the original document) to control body weight or reduce the risk of non-communicable diseases (NCDs). The systematic review that this was based upon (Rios-Leyvraz & Montez 2022) reported that, though short term RCTs have shown benefits of LNCS in weight loss, there is a lack of evidence to suggest LNCS benefit weight loss in the long term and as such did not recommend their use for weight control. The recommendation is classed as 'conditional' (as opposed to 'strong') because of uncertainty over the balance of risk and benefits of LNCS, and it is based on evidence that WHO classified as 'low certainty' overall. The methodological limitations of the review, reported by Khan et al. (2023), include greater weight given to observational studies, where causality cannot be established, and omitting studies that addressed bias.

The guideline also states that they may not be applicable or relevant to individuals living with diabetes whose intake may be higher. The guidance focused on the prevention of unhealthy weight gain and diet-related NCDs, meaning the management of diabetes in individuals with pre-existing diabetes was beyond the scope of this guideline.

The WHO recommendation is intended to be considered in the context of wider dietary recommendations to reduce free sugars intake and other guidance promoting healthy diets, including guidelines on carbohydrates, total fat, saturated and trans-fatty acids, polyunsaturated fatty acids, sodium and potassium.

It is at the discretion of the individual WHO European Region member companies, as to how they address, and either action or disregard, these guidelines. In the UK, SACN is currently reviewing the evidence supporting the WHO guideline in the UK national context, in order to consider the appropriateness of the WHO conditional recommendation for the UK.

# Appendix G: Hierarchy of evidence and common limitations

Source: https://scientific-publishing.webshop.elsevier.com/research-process/levels-of-evidence-in-research/

| Strength of evidence | Type of study | Study design | Description | Strengths of study design if conducted properly | Limitations |
|---|---|---|---|---|---|
| High<br>^<br>\|<br>\|<br>\| | Review | Meta-analysis | Statistical summary of the effect of an intervention across multiple studies. These are often combined with systematic reviews, using a similar review methodology to search and synthesise the literature. | • Rigorous literature search of published and unpublished literature<br>• Appraisal of each included article for bias and quality<br>• Highest quality evidence available | • Studies with biased results may lead to inaccurate qualitative or quantitatively synthesis of results.<br>• Quality of review can be dependent on the quality of studies assessed.<br>• Quantitative synthesis of results from heterogeneous studies may lead to biased results |
| | | Systematic review | Produce an answer to a clinical question on the basis of the synthesis of available evidence evaluated from multiple studies, usually presenting results in a forest plot. | | |
| \|<br>\|<br>\| | Intervention / experimental study | Randomised control trials (RCT) | This design assigns individuals randomly to two or more groups, where one group receives the intervention under investigation and the other(s) receives no treatment, a placebo, or a standard intervention.<br><br>In some RCTs, participants and/ or study personnel may be blinded to the assigned group. | • A large Double Blinded RCT is the most reliable "test" or study design and provides the strongest support of a cause and effect relationship.<br>• Randomization can lead to equal distribution of confounding factors in each group.<br>• Allocation concealment can help prevent the research team from knowing the next potential participant's assignment and reduce selection bias.<br>• Blinding can help address observation bias | • Resource-intensive and time-consuming<br>• Limits to generalisability if low consent rate or numerous exclusion criteria<br>• Attrition bias may occur if loss to follow-up or drop-out rates are unbalanced between arms.<br>• Expensive<br>• Ethically problematic depending on the intervention |
| \|<br>\|<br>\| | Observational study | Cohort study | Retrospective and prospective cohort studies identify a specific patient population in which a subset of individuals has experienced a particular exposure and compare the rates of disease development in exposed to unexposed individuals, over time. | • Feasible design for rare exposures because groups defined by exposure status.<br>• Appropriate design for common outcomes<br>• Multiple outcomes can be measured.<br>• Able to ascertain time course of exposure and outcome to build evidence toward causality.<br>• Can report incidence and relative risk, absolute risk reduction, and number needed to treat | • Prone to confounding bias given.<br>• Measured confounders can be addressed statistically but unmeasured confounders may exist.<br>• Prospective cohorts may be time-consuming and expensive.<br>• Loss to follow-up could lead to attrition bias. |

| | | | | | |
|---|---|---|---|---|---|
| \| | | | | | • Surveillance bias as diseases are more likely to be identified than in the general population because of increased monitoring. |
| \| | | Case control studies | Two existing groups, with or without a disease, are compared, to identify disease risk factors. | • Use existing data, which could be cheaper and easier.<br>• Operate with fewer participants compared to other designs.<br>• Efficient and takes less time to perform.<br>• Feasible design for rare outcomes or diseases<br>• Matching of cases and controls by certain research participant characteristics is often used to address confounding factors | • Potential for confounding factors and biases<br>• Potential challenges accessing pre-existing data.<br>• Cannot draw cause and effects conclusions as participants are not randomly selected.<br>• Selection bias can occur if control group is selected from a different population than cases.<br>• Recall bias may occur if cases are more likely to remember an exposure than controls or vice versa.<br>• Results are limited to odds ratios. Risk difference cannot be measured. |
| \|<br>v<br>Low | | Cross-sectional | Population data are collected at a specific point in time, with simultaneous measurement of the exposure and outcome. This study design is often used for survey-based studies | • Low cost and time<br>• Suitable design for diagnostic accuracy studies because investigational test and reference standard obtained at same point in time.<br>• Can report prevalence (%) of diseases or outcomes | • Cannot ascertain causality since exposure and outcome occur at 1 point in time.<br>• Survey-based research can be prone to missing data or nonresponse bias |

## Appendix H Scientific Advisory Committee on Nutrition (SACN) Recommendations

SACN’s recommendations on NSS are precautionary. This is because evidence on NSS and health outcomes is inconsistent.
SACN reiterates its recommendation that average population intake of free sugars should not exceed 5% of energy.
SACN recommends that intake of NSS be minimised.
For younger children, SACN recommends:

- not giving them drinks sweetened with sugar or NSS
- giving them unsweetened food (not sweetened with either sugar or NSS)

For older children and adults, SACN recommends:

- swapping sugars for NSS may help reduce sugar intake from foods and drinks (and so reduce energy intake), at least in the short term - the long-term goal is to limit both sugar and NSS intake

It is recommended that government:

- monitors the NSS content of food and drinks in the UK diet and their consumption, including trends, particularly among high consuming and vulnerable groups
- evaluates the impact of policies to reduce energy and sugar intakes on intakes of NSS, particularly among high consuming and vulnerable groups
- compels industry to make publicly available data on the amounts of individual NSS within foods to enable monitoring and further research on associations with health outcomes

SACN also made a range of research recommendations. This includes conducting research that:

- addresses concerns relating to confounding between NSS and health outcomes
- considers vulnerable groups (including high consumers, young children and pregnant or lactating women)
- explores innovative ways to reliably monitor exposure to NSS