Reviews of Scientific Evidence and Policies on Nutrition and Physical Activity

Objective Area B3: A comprehensive review of the scientific evidence and policies on the consumption, energy intake and impact of High Fructose syrups on overweight and obesity and health

Written by ICF Consulting Services Ltd

February 2018

EUROPEAN COMMISSION

Directorate-General for Health and Food Safety

Directorate C— Public health, country knowledge, crisis management

Unit C.4— Health Determinants and international relations

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February, 2018 EN

Luxembourg: Publications Office of the European Union, **2018**

ISBN 978-92-79-97428-1 DOI 10.2875/973476 EW-06-18-320-EN-N

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Preface

About this project

Overweight, obesity and their related diseases represent a leading cause of morbidity and mortality, and pose a major challenge for the sustainability of healthcare systems of EU Member States. The growing prevalence of overweight and obesity among all age groups across Europe constitutes a serious concern for policy makers. Tackling this issue requires a comprehensive response that reflects the multifactorial and complex nature of obesity and overweight. One particularly important area of focus has been on the development of preventative strategies which include nutritional and physical activity interventions.

The European Commission Directorate General for Health and Food Safety (DG SANTE) recognises the significant challenges policy makers face in developing effective and efficient policy interventions relating to diet and physical activity. One such challenge includes the complexity and breadth of the evidence base. By providing independent, accurate summaries of recent and relevant information and statistics on determinants of diet and physical activity and their impact on health, this project aims to support policy makers to continue to develop policy instruments which enable people to make healthier lifestyle choices. In particular, this project aims to support the development of healthier behaviours in vulnerable and/or at-risk subpopulations (including children, pregnant and lactating women, and older adults) and low socio-economic status groups (including low income and education).

About this series

This evidence review is one of eight reviews relating to different determinants of diet and physical activity.

Seven of the reviews are of the scientific evidence and policies in the following areas:

- Knowledge, attitudes and behaviours contributing to positive energy balance (objective area A1);
- Dietary and physical activity patterns in Europe (objective area B1);
- Consumption of fruit juices, artificially and sugar-sweetened beverages and its impact on weight status and health (objective area B2);
- Consumption of high-fructose syrup and its impact on weight status and health (objective area B3);
- Relationship between weight status and physical activity with school and work performance outcomes (objective area C);
- Early warning indicators of obesity and physical inactivity trends (objective area D);
- Nutrition and physical activity guidelines for specific population groups (objective area E).

Building on these seven reviews, the final review (objective area A2) examines specifically the evidence for effective and efficient policies and interventions in terms of promoting, supporting and improving nutritional and physical activity behaviours at both individual and population level.

All reviews, and their summaries, are available on the DG SANTE webpage here.

Approach and purpose

The reviews have been designed to provide policymakers with summaries of recent and relevant evidence in these key areas of interest. Given the broad scope of each of the reviews, it should be stressed that they are not intended to be rigorous systematic reviews of all literature published in this field. Rather, they are intended as pragmatic reviews combining a comprehensive search methodology with expert academic input,

facilitated through workshops, to provide a practical and accurate summary of key issues and tackling broad lines of enquiry, with the greater aim of supporting the development and improvement of policies in this area. Each of the project's eight methodologies and analyses was reviewed by DG SANTE and academic experts in these topics.

While the methods to conduct this comprehensive literature review are systematic, it is *not* a systematic review. This review does not systematically analyse literature to identify *all* relevant published data and/or appraise its quality. Methods to conduct the literature review consisted of five steps: (1) refining the research questions, (2) developing a search approach and databases, (3) conducting literature searches, (4) screening articles for inclusion; and (5) abstracting and synthesising relevant data.

To minimise bias, the literature search approach included identification of a priori search parameters (also considered first level inclusion and exclusion criteria), agreed with DG SANTE, to guide searches and inform screening and selection processes for data inclusion. Due to the immense number of literature search results at step 3, the application of quite limiting exclusion criteria at step 4 was deemed necessary. This may however have resulted in not screening all potentially relevant literature. All relevant articles that were found appropriate for inclusion were reviewed for relevance to each objective area, and the scope of the specific research questions. Furthermore, the inclusion of different types of scientific evidence (from systematic reviews and peer-reviewed original articles down to BSc theses) and the presentation of this scientific evidence next to grey literature information presented a challenge in terms of maintaining an understanding of the quality and weight of the evidence. The authors addressed this to some extent by structuring the document in such a way that peer-reviewed and grey literature are clearly identified. The full methodology and steps taken for each review is included in Annex of this document.

DG SANTE and the Joint Research Centre (JRC) provided input on all stages of the project and comments on the literature reviews. Expert workshops were organised to discuss findings, highlight additional relevant sources to fill gaps and improve the series of reviews. Experts were carefully selected from academic and policy-making fields, based on expertise of the specific topics addressed.

The methodology used across all eight reviews remained consistent, and within each review a detailed summary of the approach is provided, along with a full bibliography for further reading.

Glossary

The following definitions are common definitions that are used across all eight objective areas. Where a study uses a different definition, this will be highlighted on an individual basis in the review.

Table 1. Definitions of terms used across the reviews

Term	Definition	Source
Adult obesity	An abnormal or excessive fat accumulation that presents a risk to health, with a BMI of 30 or more.	World Health Organisation (WHO) (http://www.who.int/topics/obesity/en/)
Adult overweight	An abnormal or excessive fat accumulation that presents a risk to health, with a BMI equal to or more than 25.	WHO (http://www.who.int/topics/obesity/en/)
Alcopops	Pre-mixed beverages containing a spirit, wine or malt combined with a non-alcoholic drink.	1. Anderson, P., Suhrcke, M. and Brookes, C. (2012) An overview of the market for alcohol beverages of potentially particular appeal to minors. London: HAPI.
Artificially sweetened beverages (ASBs)	Beverages sweetened with low-calorie or zero-calories sweeteners such as sucralose, aspartame, saccharin, stevia or sugar alcohols.	ICF definition based on all literature identified in objective area B2 literature review
Body Mass Index	A person's weight (in kilograms) divided by the square of his or her height (in metres).	WHO (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)
Child/adolescent obesity	• There are different systems available to measure child or adolescent obesity for different ages. • Children under 5 obesity is weight-for-height greater than 3 standard deviations above WHO Child Growth Standards median;	WHO http://www.who.int/mediacentre/factsheets/fs311/en/ (Other definitions are available for different national and international systems).

Term	Definition	Source
	• Children aged 5-19 overweight is BMI-for-age greater than 2 standard deviation above the WHO Growth Reference median.	
Child/adolescent overweight	There are different systems available to measure child or adolescent overweight for different ages. • Children under 5 overweight is weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; • Children aged 5-19 overweight is BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median.	WHO http://www.who.int/mediacentre/factsheets/fs311/en/ (Other definitions are available for different national and international systems).
Exercise	Exercise, is a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective.	WHO (http://www.who.int/dietphysicalactivity/pa/en/)
Insufficient physical activity	Physical activity that does not meet WHO recommended levels of at least 60 minutes a day of moderate-vigorous activity for children and adolescents and at least 150 minutes of moderate-intensity aerobic physical activity throughout the week for	WHO http://www.who.int/mediacentre/factsheets/fs385/en/

Term	Definition	Source
	adults.	
Physical activity	Any bodily movement produced by skeletal muscles that requires energy expenditure.	WHO (http://www.who.int/topics/physical_activity/en/)
Physical inactivity	A lack of physical activity	WHO (http://www.who.int/dietphysicalactivity/pa/en/)
Sedentary behaviour	Any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting or reclining posture.	Tremblay, M. S., et al. (2017). Sedentary Behavior Research Network (SBRN) – Terminology Consensus Project process and outcome. *The International Journal of Behavioral Nutrition and Physical Activity*, *14*, 75. http://doi.org/10.1186/s12966-017-0525-8
Sugar sweetened beverages (SSBs)	Any beverage with added sugars. This includes soft drinks, soda, fruit drinks, punch, sports drinks, sweetened tea and coffee drinks, energy drinks and sweetened milk. These beverages may be sweetened with added sugars such as sucrose (table sugar) or high fructose corn syrup, which is what distinguishes them from 100% fruit juice and beverages with non-caloric sweeteners (e.g., aspartame, saccharin or sucralose).	US Department of Agriculture. 2010. *US Department of Health and Human Services. Dietary guidelines for Americans, 2010.* 7th edition, Washington (DC): US Government Printing Office

Objective B3: A comprehensive review of the scientific evidence and policies on the consumption, energy intake, and impact of high fructose syrups on overweight and obesity and health

This comprehensive review describes the findings from peer reviewed literature and grey literature on the scientific evidence on the consumption, energy intake, and, impact of high fructose syrups on overweight, obesity and health. This report synthesizes the findings of reviews of the peer-reviewed and grey literature on this topic. It has four sections:

- **Introduction,** describing the relevance of this topic, the scope of the reviews, and the principal research questions;
- **Methodology,** describing how the reviews were undertaken and relevant findings extracted;
- **Findings** from the peer-reviewed and grey literature, presented according to each research question; and
- **Conclusions** drawn from the reviews overall and an assessment of the current scientific evidence, including any gaps in the knowledge.

1 Introduction

1.1 Defining high fructose syrup

High fructose syrups are liquid fructose-glucose sweeteners, commonly derived via the hydrolisation of starch, alternative to common table sugar (sucrose). High fructose syrups are commonly known as either High Fructose Corn Syrup (HFCS), in the United States (US), or Isoglucose, in the European Union (EU). This review will refer to the most common variation used, HFCS, unless Isoglucose is the term presented in the literature reviewed. It must be noted that Isoglucose does not necessarily come from corn, yet acts in the same way as HFCS. HFCS is a sweetener that has been widely used by the food and beverage industry since the 1970s (Bray, Neilsen and Popkin, 2004), predominantly in soft drinks, fresh dairy products, and breakfast cereals (DG AGRI, 2015). HFCS gained popularity as a sugar replacement because of its price, intense sweet flavour, longer shelf-life, and, stability in solution when compared with sucrose (White, 2008).

From the literature reviewed, there is no common definition of what percentage of fructose constitutes the syrup being 'high fructose'. Different formulations of fructose concentration exist depending on the country regulation and the product that is being made. In the US for example, processed foods, cereals and baked goods are typically made up of a 42% fructose to 58% glucose formulation, where as soft drinks typically contain a 55% fructose to 45% glucose formulation (US Food and Drug Administration). About half (n=13) the peer reviewed sources in this review provided a definition of HFCS. Among the sources that did define HFCS, the definition used across sources was HFCS-55 – 55% fructose and 45% glucose (for example Ventura, Davis and Goran, 2011, and, Walker, Dumke, and Goran, 2015). Some sources also cited HFCS-42 - 42% fructose and 58% glucose. Additionally, two sources used "soft drinks" or drinks with "glucose-fructose syrup" as a proxy measure of the drink's content of HFCS (Brisbos et al., 2014, and, Boulton et al., 2016).

The lack of a defined composition of fructose in the term HFCS across industry and countries makes it difficult to assess the health impact of HFCS, as the health impact may vary with different molecule compositions. This limitation must be taken into consideration when using the information from this review. The intention of this review is not to define HFCS, rather to highlight definitions used in the wider literature. Where possible, the definition of HFCS from the literature has been given in the review, yet when a definition or formula composition of HFCS is not given, then it has been assumed that HFCS-55 is the composition being referred to. This review highlights a lack of common definition, presenting an opportunity for an industry wide recognition and consensus on what the term HFCS means in all products on a global scale, so that health impacts can be accurately measured.

1.2 Scope of the review

The abolition of the sugar quota in the EU in September 2017, which removes the production quota on HFCS, has led to uncertainty regarding the uptake of HFCS across the EU (JRC, 2014). Health concerns have been raised around what, if any, public health impact will occur from an increase in the consumption of HFCS, and, whether there needs to be an effective monitoring system in place to measure this.

Consequently, ICF have been commissioned to examine the scientific evidence and polices on the consumption, energy intake and impact of high fructose syrups on overweight, obesity, and, health. The intention of this review is not to investigate whether HFCS is safe or other issues addressed within the remit of European Food Safety Authority.

It is important to note that this review is linked to seven other comprehensive reviews on nutrition and physical activity, one of which looks at the effectiveness of policies and programmes in nutrition and physical activity (Objective A2), and, another which looks at the health impacts of other added sugars and artificial sweeteners (Objective B2). The focus of this review is on evidence in relation to the consumption, health impacts and monitoring of HFCS only, as the evidence on programmes and policies concerning HFCS is covered in Objective A2, and other evidence regarding sugar sweetened beverages is analysed in Objective B2.

1.3 Research questions for this review

The findings from the review are structured around the following research questions, which were outlined by DG SANTE when commissioning the research:

- **Who consumes** foods containing HFCS and how much?
- How much can that **market** be expected to change in the near future?
- What **consequences** related to overweight and obesity can be anticipated, if any?
- What feasible, effective and efficient **monitoring mechanisms** should be put in place to keep track of this issue?

The findings from the fifth research question (mentioned below) are included in Objective A2, as an overarching objective area report on existing policies in the broader thematic area of nutrition and physical activity:

- What policies are more effective and efficient in this area (information, advertising, taxation, reformulation, regulations, partnerships, etc.)?

1.4 Limitations to the review

This review is limited in the extent to which conclusive conclusions can be drawn, as there is a lack of literature and concrete evidence specifically on HFCS. The peer review literature searches predominantly found US based studies, and did not find any sources that looked at EU-level HFCS consumption, trends or changes in consumption patterns over time, or any systematic comparison of consumption patterns and drivers. Grey literature has been used to supplement the peer reviewed literature where possible.

The grey literature available on the topic is predominantly agricultural in focus; reflecting this, most data relates to the production of, and demand for, Isoglucose from an agricultural, perspective. The detail of this data is also relatively high-level, looking at overall patterns of consumption of Isoglucose, rather than particular products, age or other socio-economic or demographic groups. There was a lack of grey literature on the health impacts of HFCS.

2 Methodology

The review is based primarily on peer reviewed literature (which is prioritised), with grey literature used to supplement any gaps (but treated with caution and the strength of the evidence assessed). For each set of literature specific search terms and inclusion and exclusion criteria were used; and quality checks undertaken. The research questions and search terms were confirmed with DG SANTE at the start of, and then refined during a review point within, the process.

After the initial searching and extraction of literature, drafts were provided to DG SANTE and the Joint Research Centre (JRC) for review. Expert workshops (with experts from relevant academic and policy-making fields) were then held to discuss findings and highlight any additional sources to fill gaps, in order to improve the series of reviews. The final outputs of the study ('the reviews' as presented here for B3) were then reviewed by a topic expert at the University of Birmingham.

While the methods to conduct this comprehensive literature review are systematic it is not a systematic review. More information on the methodology can be found in the Annexes.

2.1 Peer review method

To search for and extract the most relevant peer reviewed literature the following steps were taken: refining the research questions; developing a search approach and databases; conducting literature searches; screening articles for inclusion; and abstracting and synthesizing relevant data.

A total of 8353 search hits of peer reviewed literature were initially retrieved using selected search terms per research question. A total of 2345 duplicates were found and removed from the search hits resulting in 5,999 search results for B3. From the 5,999 articles, the team aimed to screen 200 of the most recent titles and abstracts for each research question, to create a manageable amount of material within the resources for the study; and on the premise that the most recent material was most relevant science. Where there was a lack of relevant literature for a research question, more than 200 articles were screened. From the 1151 most recent titles and abstracts screened, 65 were deemed of potential relevance and reviewed as full texts. From the 65 deemed relevant and reviewed as full texts 19[1] publications were selected for inclusion, in this final review.

The full peer reviewed searching and extraction methodology is outlined in Annex 1.

2.2 Grey literature method

To search for and extract the most relevant grey literature the following steps were taken: searching for publications using agreed keywords and databases; screening of search results and exclusion of less relevant literature; and, extraction and review of remaining documents. The grey literature search process was a more fluid and dynamic process, where hand searching was also utilised to find the most relevant sources.

A total of 70398 search hits of grey literature were initially retrieved using selected search terms. A total of 3520 search results were retrieved and saved for B3. From the 3520 articles, the team excluded 3484 based on lack of relevance to the research questions. From the 86 results saved in the library, 71 were excluded based on the

[1] The full list of references included from the peer-reviewed literature can be found in Annex 3 and includes 4 publications recommended by the external expert review panel.

inclusion/exclusion criteria, quality of evidence and relevant to the research questions. From the 22 deemed relevant and reviewed as full texts, four publications were selected for inclusion, in this final review. The full grey literature searching and extraction methodology is outlined in Annex 4.

3 Findings and discussion

3.1 Research Question 1: Who consumes foods containing HFCS and how much?

One study found that in comparison to the US, Europeans consume on average at least a third less of HFCS (kg/year per capita) and nearly half of countries within the EU do not use HFCS at all. Goran et al (2013) conducted an ecological study that examined the global use of HFCS in 43 countries. Using information obtained in a database on food availability, maintained by Food and Agriculture Organization of the United Nations, the authors calculated the number of kilograms of HFCS used per year, per capita. The results (Annex 6) showed that HFCS use varies by country with the highest in the US (24.78 kg/year per capita); 14 countries were found to not use HFCS at all, twelve of which were within the EU[2]. Of European countries that did consume HFCS, the five countries with the highest use (kilograms per year, per capita) were Hungary (16.85), Slovakia (9.82), Bulgaria (8.53), Belgium (8.32), and Turkey (4.20). All of these producers have increased their production of HFCS since 2005/2006 (EEIG Agrosynergie, 2011). The usage and production of HFCS is likely to change following the abolition of the EU sugar quota (see research question two), which may have been a main reason why the level of HFCS has been much lower in European than in the US until now.

The US is a good example of consumption of HFCS in an unrestricted market, where the availability and consumption of HFCS has increased over the past four decades. Precise data on when HFCS was introduced into the supply chain is not available, although the early 1980's are when large US soft drink manufacturers are cited as introducing it as a sweetener (Duffey and Popking 2008). Duffey and Popkin (2008) and Bray, Neilsen, and Popkin (2004) both report an increase in the US consumption of HFCS since its introduction, which coincides with an HFCS's increased use as a US caloric sweetener. Based on their estimates of HFCS caloric intake (estimated grams of HFCS per USDA food code), Duffey and Popking (2008) and Bray, Neilsen and Popkin (2004) suggested that:

- Soft drinks and fruit drinks provided most HFCS in the U.S. (Duffey and Popkin 2008). HFCS represents over 40% of caloric sweeteners added to foods and beverages and is the sole caloric sweetener in soft drinks in the U.S. (Bray, Neilsen and Popkin, 2004);
- The consumption of HFCS increased over 1000% between 1970 and 1990, which exceeded any other changes in USDA food consumption tables in this time period (Bray, Neilsen and Popkin , 2004);
- Between 1991 and 2000 there was a 120% increase in calories from HFCS. Since 2000, calories from HFCS have remained relatively stable (Duffey and Popkin2008);
- From 1989 to 2004, there was an estimated increase of HFCS for 67% in total energy and 57% of carbohydrates (Duffey and Popking 2008);
- There was a slight decrease in consumption of HFCS between 2000-2004 (Duffey and Popkin 2008).

Currently there is no direct way to measure total HFCS consumption (Duffey and Popkin 2008; Bray, Neilsen and Popkin, 2004). It is very difficult to tell how much HFCS is added to foods and beverages in the US, as studies and dietary surveys do not make a

[2] Slovenia, Latvia, Ireland, Lithuania, Sweden, Luxembourg, Czech Republic, Austria, Cyprus, Estonia, Malta and Denmark.

clear distinction between HFCS and other added sugars, for examples in food labels. Formulations vary in their fructose-glucose ratio and overall sugar content, so with no clear definition of what HFCS is, there is currently no accurate way of calculating consumption patterns.

3.2 Research Question 2: How much can the market for HFCS be expected to change in the near future?

There was no peer review literature on market changes for HFCS in Europe. The search strategy was broadened to include reasons for HFCS market trends in the US, but no explanations were found in the literature that was reviewed. The following information is taken from the grey literature only.

Following the abolition of the EU sugar quota, the Department of Agriculture and Rural Development (DG AGRI) in the European Commission estimated that the production of Isoglucode will increase from less than 4% to just below 10% of the sweetener market in 2026 across the EU (DG AGRI, 2016). This increase is based on a number of assumptions. Primarily, these projections assume a constant use of Isoglucose and sugar. That is, this assumption implies that an increase in EU Isoglucose production creates a decrease in sugar production. However, it is expected and desired is that EU farmers have opportunities to export more Isoglucose and/or beet sugar. This estimate also assumes that the current European consumption of Isoglucose has scope to increase; that the higher consumption in some countries indicates that it is acceptable to 'European taste palettes'; and, that there is therefore scope for the European food and beverage industry to increase its use (DG AGRI, 2015).

The extent to which this increase occurs is likely to vary by Member State, and is likely to be driven by a number of factors, including: manufacturers' willingness to switch to Isoglucose; consumer acceptance (Isoglucose has a different taste when compared to sugar); price (the average annual price of Isoglucose is between 70-84% of sugar); health concerns[3]; and, related policies to restrict demand due to obesity risks (EEIG Agrosynergie, 2011). For example, DG AGRI (2016) suggests that demand is likely to be highest in EU countries such as Romania, Bulgaria and Hungary, where both sugar prices and the level of consumption are high yet there is a deficit of sugar and an excess supply of cereals. Isoglucose could be seen as an attractive competitive alternative.

3.3 Research Question 3: What consequences related to overweight and obesity can be anticipated, if any?

In the peer-reviewed and grey literature, there is strong evidence that consumption of added sugars in general is linked to changes in metabolism, and increased risk of obesity, heart disease and diabetes. **The current literature explored here is inconclusive on whether consumption of HFCS specifically has health consequences related to overweight and obesity beyond those attributed to added/free sugars.** There is limited evidence of health consequences from HFCS as only a handful of scientific studies have been conducted in this area, specifically looking at HFCS. The studies highlighted below are the most relevant peer reviewed literature that was found in the searching process. It must be noted that only tentative statements can be made about the health consequences HFCS as the fructose content of HFCS is not always known with accuracy.

A nonrandomised double blind study implies that HFCS could be linked to increased risk in CVD. In a nonrandomized, double-blind study (n=85 adults),

[3] No further detail on what the health concerns might be, or their impact on Isoglucose consumption was provided.

Stanhope, et al. (2015) attempted to determine the dose-response effects of consuming beverages sweetened with HFCS at various proportions of energy requirements on risk factors for CVD, which could include overweight and obesity. Results indicated that the consumption of HFCS-sweetened beverages containing 10%, 17.5%, or 25% Ereq (energy requirements) produced dose-dependent increases of circulating lipid/protein risk factors for CVD and uric acid within two weeks. These results provide mechanistic support for the association between increased risk of CVD mortality and increased consumption of HCFS or added sugar, respectively.

A multi-stage, cross sectional study has shown that HFCS could be linked to increased insulin resistance and slower metabolism. In a multi-stage, cross-sectional study comprised of a random sample of Taiwanese adolescents (n=1454; aged 12-16 years), Lin, et al. (2016) investigated the association between SSB consumption and biomarkers (beta cell functioning and insulin sensitivity) of insulin resistance (IR) in adolescents. Results indicate that an increase in the consumption of fructose is related to increased IR (as estimated by measures of beta cell functioning and insulin sensitivity) and decreased insulin sensitivity in adolescents, implying that higher levels of fructose intake detrimentally impacts IR in children. The authors noted that the fructose component in HFCS is only slightly larger than it is in sucrose. The total sugar sweetened beverages (SSBs) included both types of sweetened beverages so the effect of sucrose-sweetened beverage intake on IR in children should not be discounted. The study also observed an increase in the two biomarkers of IR among obese adolescents consuming HFCS-sweetened SSBs, reflecting negative metabolic changes in research subjects.

Non-statistical temporal associations have been shown between increased availability and consumption of HFCS and increased obesity prevalence in the general US population. Two studies have shown correlations between HFCS and health impacts, yet caution must be taken in forming any conclusions from these studies, as correlations do not necessarily show causality. Bray, Neilsen and Popkin (2004) investigated the association between increased availability and consumption of HFCS with the obesity prevalence trends in the general US population across 40 years. Bray, Neilsen and Popkin (2004) found a non-statistical temporal association between HFCS availability, HFCS consumption, and non-stratified general US population trends in obesity. However, the measures of HFCS availability and consumption included *estimates* of HFCS consumption, because there are no measures of HFCS consumption among the general US population.

Goran et al. (2013)'s ecological study of the use of HFCS in 43 countries, highlighted a correlation between HFCS consumption and diabetes prevalence. The authors defined use of HFCS as a mean value of >0.5 kg per capita per year for 2000, 2004 and 2007. Countries classified as using HFCS[4] had approximately 20% higher diabetes prevalence compared to countries that do not use HFCS[5]. These differences in diabetes prevalence remained or were strengthened when adjusting for country-level estimates for body mass index.

Non-systematic reviews of peer-reviewed research indicate inconsistent findings regarding association between HFCS consumption with weight gain and obesity. In a non-systematic review of published literature, Stanhope (2016) found that metabolic changes associated with consumption of added sugar (i.e., not solely HFCS, but including HFCS and other added sugars) are independent of body weight gain. From

[4] Germany, Poland, Thailand, Greece, Portugal, Malaysia, Egypt, Spain, Finland, Serbia, Turkey, Mexico, Japan, Republic of Korea, Argentina, Belgium, Bulgaria, Canada, Slovakia, Hungary and U.S

[5] India, Slovenia, Latvia, Uruguay, Ireland, Lithuania, Sweden, Luxembourg, Czech Republic, Austria, Cyprus, Estonia, Malta, Denmark, Indonesia, France, China, Australia, United Kingdom, Romania, Italy and Netherlands

this, Stanhope concludes that there is "strong evidence for an indirect causal/contributory role mediated by sugar consumption promoting body weight and fat gain." In regards to specific populations, Tappy and Le (2010) identified inconsistent findings among cross-sectional child and adolescent studies that assessed weight gain and HFCS consumption. Here, as in other studies cited in this report, sugar-sweetened beverages served as a proxy for HFCS. The challenges in measuring HFCS in diets, as well as the reported inconsistent findings contribute to the uncertainty of the causal relationship between HFCS and obesity. No randomised controlled trials (RCTs) were found in the included peer-reviewed literature, and within the reviews cited, no specific strengths/weakness of research designs of reviewed studies were highlighted.

Multiple research gaps exist. Further research needs to be conducted before it can be determined whether HFCS has any consequences related to overweight and obesity. The impact of HFCS in comparison to other sugars and sweeteners, and, the impact of HFCS on the consumption of excess sugar needs to be further explored. This leads to the overall conclusion that unless new evidence appears, efforts should be targeted at decreasing total (added) sugar/sweetener consumption rather than specific types of sugar.

3.4 Research Question 4: What feasible, effective and efficient monitoring mechanisms should be put in place to keep track of this issue?

The review did not uncover literature that dealt specifically with monitoring industry use of HFCS or effective monitoring of HFCS consumption. The monitoring mechanisms below are not specific to HFCS yet are presented to provide sample methodology for monitoring the use of HFCS by industry and consumer behaviours changes overtime:

- **Estimating HFCS composition in food using food composition surveys.** Bray, Neilsen and Popkin (2004) identified a method to estimate HFCS intake in the general US population based on estimates created by the US Food and Drug Administration from the 1977-1978 US Nationwide Food Consumption Survey. This estimate is formed by an assessment of the food category-wide estimate of the proportion of caloric sweeteners that is HFCS. Bray, Neilsen and Popkin (2004) identify that the availability of HFCS increased from 27.3 $g \cdot person^{-1} \cdot d^{-1}$ in 1980 to 64.7 6 $g \cdot person^{-1} \cdot d^{-1}$ in 1985 to 91.6 $g \cdot person^{-1} \cdot d^{-1}$ in 2000 for all Americans aged ≥2 years.
- **Estimating HFCS composition in food and beverages using nationwide Nutrient Database Systems (NDS).** A more recent estimate of amount of added sugar in food and beverages that is HFCS is offered by Duffey and Popkin (2008). Using data from the US Nutrient Database System (NDS) sugars file and the USDA's food composition table, the authors estimated the proportion of added sugar that is fructose (P_f) and multiplied this number by the amount of added sugar in each food as reported by the USDA. This then resulted in an estimate of the gram amount of HFCS per food code in USDA food composition table. Additionally, Duffey and Popkin's (2008) primary assumption is that HFCS is 100% of the added sugar for soda and fruit drinks. This assumption parallels research cited in this review where sweeteners in soft drinks (SSBs) are a proxy for HFCS, and is therefore limited in its accuracy: it is particularly limited in accuracy in countries where HFCS is not routinely used in SSB's, or may have mixed use.
- **Example monitoring mechanism of the nutritional make up of fast food products.** The Food Monitoring Group (2012), an international group of academics and public-health stakeholders, developed a protocol for monitoring the nutritional makeup of fast food products across countries. It relies on annual surveys

obtaining nutritional information directly from fast food companies, product information available online and on packaging, and, direct chemical analysis where nutritional information is unavailable. The protocol is scalable, anticipating initial limits on the number of participating countries, targeting fast food chains with the largest presence in each country, and noting that cases that require chemical analysis will further limit the scale of research. The group developed a typology of fast foods to facilitate reporting of aggregate data, but has no data for specific food items.

- **Using market research data on consumer purchasing behaviour**. Mathias et al. (2015) conducted a regression analysis of Nutrition Facts Panel data (nutritional values listed on products) and market-research data on consumer purchasing behaviour to find changes in the nutritional composition of ready-to-eat grain-based desserts over time. The dataset was produced by Nielsen, a consumer and market research firm, through a longitudinal study, in which a convenience sample of 134,128 households recruited by direct mailing and online advertising were given Universal Product Code scanners to document their purchases between 2005 and 2012.
- **Limitations in using self-reported data of dietary behaviour.** The reliability of self-reported data for the study of dietary behaviour has come under question. Schoeller et al. (2013) found noteworthy errors in self-reported energy intake data from the National Health and Nutrition Examination Survey. They propose that underreporting of consumption of high-sugar and high-fat foods has increased in recent years as health messages about fighting obesity and managing food intake become more common, attaching greater stigma to unhealthy eating (i.e., social desirability bias).
- **The possibility of using biomarker-based methods to monitor molecule consumption.** Although Biomarker-based methods, are not subject to social desirability bias as in self-reporting methods, biomarker measurement is not currently used for monitoring HFCS consumption. Jahren et al. (2006) tested a measurement method based on the relative abundance of carbon isotopes and found that it could distinguish foods containing corn- and cane-based sugars from a variety of other plant-based foods; however, this method was tested for off-the-shelf food products and not as part of a participant-based research design (e.g., measuring food consumption among a sample of subjects). Tasevska et al. (2014) and Davy and Jahren (2016) have employed carbon-isotype and urinary sugar excretion in research on human subjects. These were conducted to mitigate misreporting of sugar consumptions and to establish a "modest" association between the abundance of both biomarkers and sugar intake. However, biomarker-based methods for measuring the intake of HFCS or other forms of sugar are not yet feasible for use in public health research. According to Davy and Jahren (2016) the relationship between measurements of sugar biomarkers and actual sugar intake is indirect and influenced by other undetermined factors. They conclude that more robust studies are needed in order to model this relationship.

Mandatory, accurate nutritional information and reporting by EU food manufacturers has been implemented and can be used to establish a monitoring system for HFCS. Without such measures, it is challenging to accurately monitor HFCS availability and consumption. In the EU, regulation EU 1169/2011 on food information to consumers requires manufacturers to provide information (in a descending order of quantity) on the use of sucrose, fructose-glucose syrup, and glucose-fructose syrup in the ingredient list. Since 2016 in the EU, the nutrition information is mandatory and includes 'sugars'.

In the U.S., however, there is little publicly available data on HFCS use by food and beverage manufacturers. This is primarily due to a lack of nutritional information for consumers on food and beverage products and challenges of developing tests that can examine the chemical composition of food and beverages to determine the presence of HFCS. Consequently, proxy measures (e.g., soft drink consumption) or conservative estimates of HFCS content in foods are used to monitor consumption of HFCS in the U.S. (Bray et al., 2004). U.S. industry need to be clearer about the HFCS content in their products so that availability and consumption patterns can be assessed accurately.

4 Conclusion

More precise information on the formula for HFCS used in various foods and beverages, and available data on production of products containing HFCS, is needed before progress is made in monitoring its production and consumption, and the subsequent consequences, if any, on overweight, obesity and health.

The findings from the peer reviewed and grey literature reviewed show that there are significant gaps in our knowledge and understanding of HFCS, its consumption, and, health impact. Studies so far have mostly been carried out in the US, where use and consumption of HFCS is substantially higher than in Europe. In general, evidence supports that consumption of excess sugar increases risks of type 2 diabetes and cardiovascular disease, which are both strongly associated with the presence of overweight and obesity (Stanhope 2016). However, there is much less evidence concerning the unique contribution of HFCS to such health impacts (Stanhope 2016). HFCS is used alongside other added sugars in different ways and so studies have tended to focus on measuring the health impact of sugar sweetened foods and beverages as a whole. In the research found, there is very limited or weak evidence addressing this issue. Additionally, within the limitations of this research, there are discrepancies in whether HFCS in particular is more harmful than other sweeteners, such as fructose and sucrose.

Whilst we know that production of HFCS in the EU is currently low in comparison to the US, there is no detailed information about HFCS use by industry and consumption in European countries. Earlier studies have shown variation in the production and use of HFCS among EU MS; and price, consumer acceptance, and the evolution of policy addressing the use of sugar in food and drink more generally are all likely to play a role in how the use of HFCS across the EU develops over time, making changes in the future difficult to predict. There is no firm evidence on which to base projections of how EU markets may respond to an increased supply of HFCS post the abolition of the EU sugar quota in 2017.

The peer reviewed literature showed that there are limitations in monitoring industry use of HFCS in the U.S. Current studies in the U.S. have shown that it is not possible to accurately identify how much HFCS was added when food and beverages are analysed, nor is this reported in nutritional information shared with the public.

The changing formulation of foods and beverages and the use of HFCS in combination with other sugars makes it difficult to measure changes in U.S. consumption patterns. However, in the EU FIC regulation 1169/2011 has made it possible to inform the consumer whether fructose-glucose/glucose-fructose syrups or sucrose are used. With these mandatory regulations consumers have the opportunity to monitor which ingredients contribute to the sugars in a food product. Research is necessary to assess whether these distinctions and acknowledgement of sugar content is adequate for consumer in their decision-making.

Annex 1 Peer-reviewed literature review methodology

This sub-section describes the approach taken to gather and synthesise the evidence.

A1.1 Research questions for this review

In this comprehensive review, current literature was gathered and synthesised to address Objective B3. This literature review provides a review of relevant, recent studies using the methodology presented below to summarise this topic. While the methods to conduct this comprehensive literature review are systematic it is not a systematic review. Note that unlike a systematic review, this review does not systematically analyse literature to identify *all* relevant published data and/or appraise its quality

To explore this area,, the literature review was conducted around the following agreed upon questions:

- Who consumes foods containing HFCS and how much?
- How much can that market be expected to change in the near future?
- What consequences related to overweight and obesity can be anticipated, if any?
- What feasible, effective and efficient monitoring mechanisms should be put in place to keep track of this issue?

The findings from the fifth research question (mentioned below) are included in Objective A2, as an overarching objective area report on existing policies in the broader thematic area of nutrition and physical activity.

- What policies are more effective and efficient in this area (information, advertising, taxation, reformulation, regulations, partnerships, etc.)?

The methodology for the peer-reviewed literature is described below, with greater detail on search terms provided in other Annexes.

A1.2 Peer-Reviewed Literature

Methods to conduct the literature review consisted of five steps: (1) refining the research questions, (2) developing a search approach and databases, (3) conducting literature searches (Stage 1 below), (4) screening articles for inclusion (Stage 2 below); and (5) abstracting and synthesizing relevant data (Stage 3 below).

In Step 1, in partnership with DG SANTE the research questions above were confirmed. In Step 2, the 3 stage approach noted below and databases were confirmed. To minimise bias, the literature search approach included identification of a priori search parameters (also considered first level inclusion and exclusion criteria) to guide searches and inform screening and selection processes for data inclusion. Steps 3, 4 and 5 followed the process below:

- Conduct searches and document results (Stage 1)
- Screening search results (title and abstract) for relevance (Stage 2)
- Review full publication and abstract key characteristics and study findings (Stage 3)

Searches were conducted in multiple databases and screened following the procedures below. Following the literature review pilot, it was agreed to merge Stages 1 and 2.

A1.2.1 Stage 1: Conduct Searches and Document Results

In Stage 1, searches were conducted using search terms and criteria agreed with DG SANTE, with filters set for databases to ensure accurate inclusion and exclusion of literature, as shown in tables below. The search terms used were specific to each of the five research questions. Literature searches were conducted in PubMed, EBSCO (CINAHL, ERIC, PsycInfo) and Embase. The reviewers used title and abstract [tiab] key word searches in EBSCO, PubMed and Embase. Medical Subject Heading (MeSH) terms were also used in PubMed and Embase searches. Searches included publications with all availability types (i.e. free full text and pay/subscription access).

Table 2. Inclusion and Exclusion Criteria Applied at Stage 1

Set Database Filter to Include:	Set Database filters to exclude:
Published between 1/1/2005-5/31/2016	Articles published before 1/1/2005
Peer-reviewed scientific publications	Editorial comments/commentaries
Original research	Dissertations
Systematic reviews	Theses
Meta-analyses	Opinion articles
Article published in English, French, German, Italian Polish and/or Spanish	Article not published in English, French, German, Italian Polish and/or Spanish

In addition to reviewing studies in databases noted above, in order to help ensure inclusion of high quality literature (e.g., literature having gone through more formal quality assessments) systematic reviews and meta-analyses were reviewed for inclusion in the literature review. Searches for systematic reviews were conducted in Cochrane Review and healthevidence.org.

As noted a separate search was carried out for each research question, resulting in five groups of publications for screening for B3. After the searches, the results were reviewed to ensure they accurately met search parameters and duplicates were removed for screening in Stage 2.

A1.2.2 Stage 2: Screening search results (title and abstract) for relevance

At Stage 2, two screening levels were used: Level 1 quality check and Level 2 screening. Stage 2 screenings were done simultaneously. These screening inclusion and exclusion criteria are shown below.

A1.2.2.1 Stage 2 Level 1 Initial Screening (Quality check)

Search hits from all databases searched in Stage 1 were grouped by the five research questions and search terms to which they were related. Duplicate hits were deleted, and search hits by research question were organised from the most recent publications in 2017 going back in time to 2005, saved in an Excel file for that specific research question, and provided to reviewers for screening. These date parameters were agreed with DG SANTE as part of the pragmatic approach to managing the review material.

Using screening criteria in Table 2 reviewers screened the title and abstract of up to the first 200 hits per research question in each Excel file to identify literature to move

forward for review.[6] This was done to ensure the screening process was manageable given project timelines yet captured the most recent and relevant literature.[7]

A1.2.2.2 Stage 2 Level 2 Subsequent Screening

Simultaneous with the Level 1 initial screening check, more detailed overall inclusion and exclusion criteria were applied by the reviewers to the title and abstract to screen publications. These criteria, are shown in Table 4 below under Level 2.

Table 3. Stage 2 Inclusion/Exclusion Criteria: Levels 1 and 2 Screening

Stage 2 – Level 1		
Category	**Inclusion Criteria**	**Exclusion Criteria**
Date	Published between 1/1/2005-5/31/2016[8]	Articles published before 1/1/2005
Publication Type	Peer-reviewed scientific publications Original research Systematic reviews Meta-analyses	Editorial comments/commentaries Dissertations Theses Opinion articles Non-academic journal
Language	Article published in English, French, German, Italian Polish and/or Spanish	Articles in all other languages

Table 4. Overall screening criteria for Stage 2

Stage 2 – Level 2		
Category	**Inclusion Criteria**	**Exclusion Criteria**
Geography	Studies conducted in America, Australia, Canada, European Countries, Mexico or Brazil[9]	Studies in all other countries
Human subject	Human-focused research	Animal-focused research
Behavior/ Outcome	Studies specific to how a behaviour (e.g., consumption	Studies specific to sugar sweetened beverages without

[6] As there was a lack of relevant literature for B3, for some research questions more than 200 relevant hits were looked at.

[7] Results for each research question were screened separately, however, as screening took place, team members considered if articles might be relevant to other research questions, and if so, coded the article as such.

[8] During screening, publications prior to 2005, and publications such as commentaries, dissertations or editorials were screened out, as were publications focusing on animals (rather than humans). Articles prior to 2005 and post 2016 were included only if they had been suggested by the experts from the expert workshop.

[9] Note that systematic reviews could have references including other countries. Also ad hoc searches conducted post screening to supplement screened literature may have included other countries.

Stage 2 – Level 2		
	of high fructose corn syrup)) contributes to energy balance or healthy weight; OR Studies specific to an outcome of interest overweight/obesity in relation to HFCS consumption. Studies specific to ways in which consumption and/or use of HFCS can be.	specifying HFCS). Studies specific to an outcome of overweight/obesity in relation to sugar sweetened beverages or other sweeteners. Specific to methods for assessing outcomes (e.g. reliability and/ or validity of overweight/obesity measures) or whose goal is to improve methodology.
General population	Studies where the population of focus includes children, adults or older adults in the general population.	Studies where the population of focus is a narrow population such as critically ill, hospitalized patients, people with a chronic condition or terminal illness, those incarcerated, etc.
Weight Status/ BMI	Studies that examine the association of behavior with weight status or BMI[10].	Studies that examine the association of behavior with metabolic indicators (adiponectin, ghrelin, LDL, etc.), environment or genetics.

Stage 2 – Level 3 Objective Area Specific Final Screening		
Objective Area Specific Screening Criteria for B3		
Although not specified in the original methodology, in order to secure data relevant to the objective area, reviewers applied criteria specific to objective search terms at stage 2. Articles meeting two primary inclusion criteria listed here were coded as "include". Any publication with one	Primary B3 inclusion/exclusion criteria	
	Studies specific to HFCS.	Studies specific to "sugar sweetened beverages" without mention of HFCS.
	Studies focused on individuals as the unit of analysis.	Studies specific to cellular metabolism as the unit of analysis.
	Secondary B3 inclusion/exclusion criteria	
	Studies specific to ways to monitor use and intake of HFCS.	Studies specific to ways to monitor use and intake of HFCS.

[10] The team agreed that as a proxy for BMI articles with other measures of BMI, such as respiratory factors, heart rate, or skin fold measures could have been included as well.

or more exclusion criteria was coded as "exclude".	Publications documenting food/beverage industry response to the obesity epidemic or HFCS concern (self-regulation, partnership etc.).	Publications without historical facts/figures regarding industry response to the obesity epidemic or HFCS concern – primarily commentary or opinion.

From 1151 publications screened in Stage 2, 65 publications were deemed of potential relevance, coded as "Include" and selected for full article review after stage 2 screening. Thirty (30) publications were then excluded based on assessed relevance to Objective B3 research questions.

A1.2.3 Stage 3: Full Article Review and Synthesis

65 publications were exported for review of full text in this B3 literature review. After reading the full text, if the article was still deemed relevant for inclusion (based on consideration of the objective and if the article helped answer research questions), it was saved for use and reference in the bibliography. Following reading articles full text in this stage, 19 publications were selected for inclusion.

At each stage in this process, the team met to discuss successful strategies, challenges, and recommendations to improve the literature review processes. Note that although this is a comprehensive literature review and does not include a formal quality assessment process commonly conducted in systematic reviews, the team documented study designs (e.g., cross sectional, experimental) and the articles were checked by reviewers for signs of bias and poor quality research design. Further, the lead reviewer for each objective area conducted blind quality assurance checks for up to 10% of the coded articles. Any disagreements were discussed as a group and resolved with the review task lead.

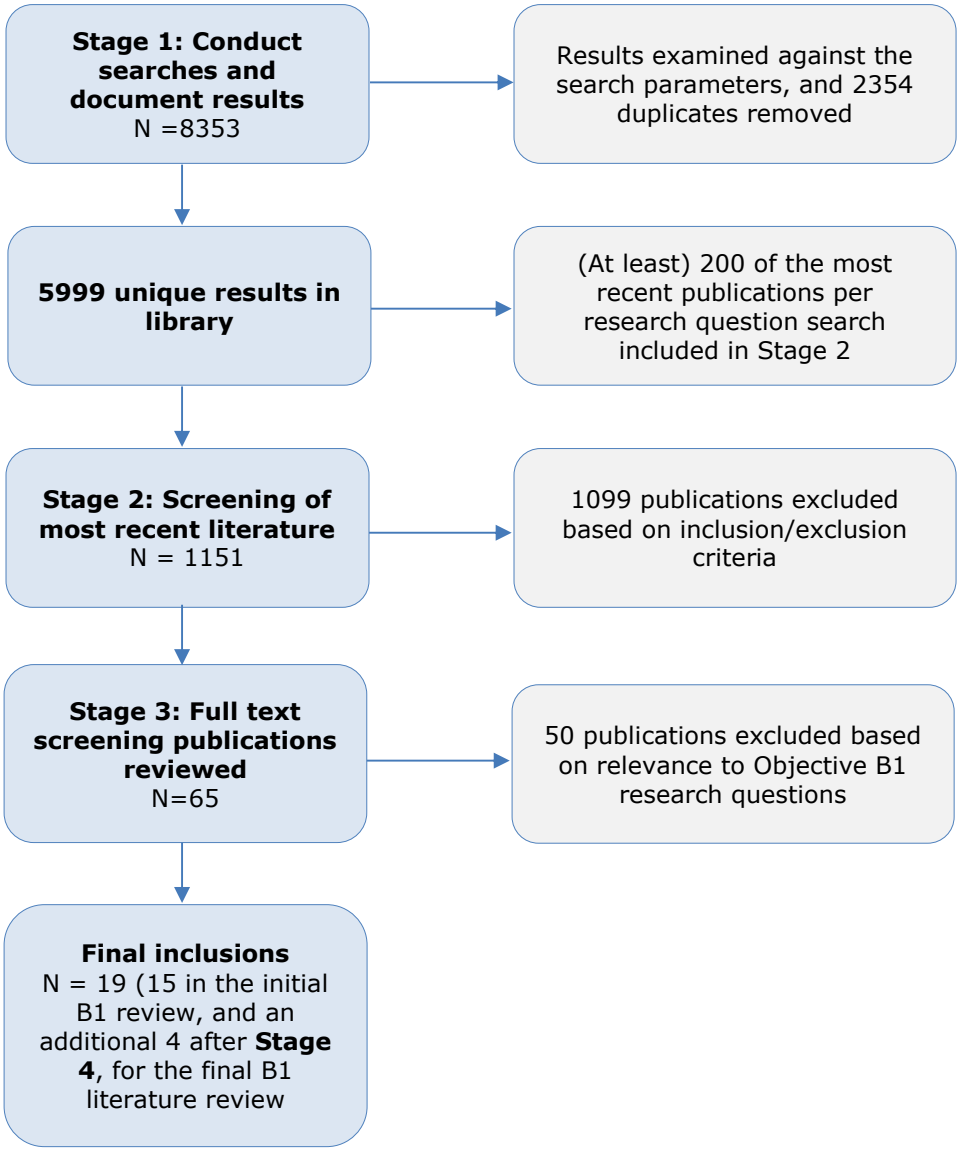
A1.2.4 External expert reviews and input

Upon completion of the draft set of comprehensive literature reviews, subsequent to review by DG SANTE and the Joint Research Centre (JRC), expert workshops were organised to discuss findings, highlight additional relevant sources to fill gaps and improve the series of reviews. Experts were carefully selected from academic and policy-making fields, based on expertise of the specific topics addressed. As a result of this exercise, four additional references were screened and incorporated into these reviews.

A1.2.5 Number of included and excluded publications

Figure 1 below shows the number of articles identified in peer reviewed literature searches, and the filtering out of literature at successive stages to arrive at the final number of 19 publications whose full text was reviewed and summarised for this review. The diagram also includes additional relevant references proposed by external experts, and incorporated into this final comprehensive review.

Figure 1. Diagram showing number of included and excluded publications at each stage – peer reviewed literature



**As there was a lack of relevant literature for B3, for some research questions more than 200 relevant hits were looked at.*

As shown in Figure 1**,** a total of 8353 search hits were retrieved. A total of 2345 duplicates were found and removed from the search hits resulting in 5,999 search results for B3. From the 5,999 articles, the team screened 200 of the most recent titles and abstracts (200 for each of five research questions[11]). From the 1151 most recent titles and abstracts screened, 65 were deemed of potential relevance and reviewed as full texts. From the 65 deemed relevant and reviewed as full texts, 19 publications were selected for inclusion, in this final review (with four articles included in Stage 4).

[11] As there was a lack of relevant literature for B3, for some research questions more than 200 relevant hits were looked at.

Annex 2 Peer-reviewed literature search terms

Objective B3 Search Terms Per the B3 Research Questions

1.: Who consumes foods (and beverages) containing high fructose corn syrup and how much?

Primary Term		Combined With	
"Added sugar"	[tiab]	"Consumption"	[tiab]
"Sugar sweetened beverage"	[tiab]	"Consume"	[tiab]
"Dietary sucrose"	[mh]	"Intake"	[tiab]
"Sweetening agents"	[mh]	"Prevalence"	[mh]
"High fructose corn syrup"	[mh]	"Diet"	[mh]
"Sweetening agents"	[tiab]	"Diet"	[tiab]
"Dietary sucrose"	[tiab]		

2. How much can that market be expected to change in the near future?

Primary Term		Combined with:	
"Food industry"	[tiab]	"Public health"	[mh]
"Beverage industry"	[tiab]	"Obesity"	[mh]
"Fast foods"	[mh]	"Public health"	[tiab]
fast-food*	[tiab]	"Obesity"	[tiab]
		"Obese"	[tiab]

3. What consequences related to overweight and obesity can be anticipated, if any?

Primary Term		Combined with:	
"Added sugar"	[tiab]	"Metabolic syndrome"	[tiab]
"Sugar sweetened beverage"	[tiab]	"Health outcome"	[tiab]
"Dietary sucrose"	[tiab]	"Risk factor"	[tiab]
"Sweetening agents"	[tiab]	"Consequence"	[tiab]
"High fructose corn syrup"	[tiab]	"Adverse effect"	[tiab]
"Sweetening agents"	[mh]	"Obese"	[tiab]
		"Obesity"	[tiab]
		"Metabolism"	[mh]
		"Metabolic disease"	[mh]
		"Risk factors"	[mh]

Objective B3 Search Terms Per the B3 Research Questions			
4. What feasible, effective and efficient monitoring mechanisms should be put into place to track this issue?			
Primary Term		Combined with:	
"Added sugar"	[tiab]	"Data"	[tiab]
"Sugar sweetened beverage"	[tiab]	"Analysis"	[tiab]
"Dietary sucrose"	[tiab]	"Self regulation"	[tiab]
"Fructose"	[tiab]	"Monitoring"	[tiab]
"Sweetening agents"	[tiab]		
"High fructose corn syrup"	[tiab]		
"Sweetening agents"	[mh]		
"Fructose"	[mh]		

Annex 3 Peer-reviewed literature bibliography

Boulton, J., Hashem, K.W., Jenner, K.H., Lloyd-Williams, F., Bromley, H., Capewell, S. (2016). How much sugar is hidden in drinks marketed to children? A survey of fruit juices, juice drinks and smoothies. BMJ Open, 6: 1-5. doi:10.1136/bmjopen-2015-010330

Bray, G. A., Nielsen, S. J., & Popkin, B. M. (2004). Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. The American journal of clinical nutrition, 79(4), 537-543.

Brisbois, T.D., Marsde, S.L., Anderson, G.H., Sievenpiper, J.L. (2014). Estimated intakes and sources of total and added sugars in the Canadian diet. Nutrients, 6: 1899-1912. doi:10.3390/nu6051899

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Stanhope, K. L., Medici, V., Bremer, A. A., Lee, V. Lam, H. D., Nunez, M. V., Havel, P. J. (2015). A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. The American Journal of Clinical Nutrition, 101(6), 1144-1154. doi:10.3945/ajcn.114.100461.

Tappy, L., & Lê, K. A. (2010Metabolic effects of fructose and the worldwide increase in obesity. Physiological reviews, 90(1), 23-46.

Tasevska, N., Midthune, D., Tinker, L. F., Potischman, N., Lampe, J. W., Neuhouser, M. L., … Kipnis, V. (2014). Use of a urinary sugars biomarker to assess measurement error in self-reported sugars intake in the Nutrition and Physical Activity Assessment Study (NPAAS). Cancer Epidemiology, Biomarkers & Prevention, 23(12), 2874–2883. https://doi.org/10.1158/1055-9965.EPI-14-0594

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http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm324856.htm. Accessed on November 4, 2016.

Ventura, E.E., Davis, J.N., Goran, M.I. (2011). Sugar content of popular sweetened beverages based on objective laboratory analysis: focus on fructose content. Obesity, 19(4): 868-874. doi: 10.1038/oby.2010.255

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White, J.S (2013). Challenging the Fructose Hypothesis: New Perspectives on Fructose Consumption and Metabolism. *Am Soc Nutr*, 4: 246-256.

Annex 4 Grey literature review methodology

A4.1 Detailed search and review methodology

The review followed a process with five main stages:

- Searching for publications using set keywords and databases;
- Screening of search results for relevance;
- Screen results against inclusion/exclusion criteria, quality and relevance;
- Extraction of full texts and final screening process; and
- External expert reviews and input.

A4.2 Stage 1: Conducting searches and documenting results

A4.2.1 Searching for grey literature

The search terms initially used were agreed upon in the inception phase (Table 5). The main key words were either specific to the objective or broader thematic terms; for objective B3 the main key words included both 'High fructose corn syrup' and 'calorie intake'. A second list of search terms was also used – these combination words were used to guide the search and produce the most relevant results; for objective B3, the key word 'Isoglucose' would be combined with the broader term 'consumption'.

Table 5. Search terms used for objective B3 grey literature review

Suggested Search Parameters	
Parameters	
Scientific evidence and policies of EU Member State initiatives Published in English, French, German, Italian, Polish and/or Spanish Date range (1995 – 2017)	
Key Words and Suggested Combinations of Search Terms	
Key Words	Combined With
High fructose syrup food	Consumption
High fructose corn syrup (HFCS*)	Trends
Corn syrup	Patterns
Glucose-fructose syrup (GFS)	Health consequences: overweight, obesity
Fructose-glucose syrup (FGS)	Prevention programs (programmes)
Isoglucose	Prevention policies
Soft drink	Policies
Industry	Regulation
Calorie intake	Reformulation
	Monitoring
	Health*
	Health determinants

	Health outcomes Metabolic anomalies Metabolic diseases Diabetes Obesity Body Mass Index (BMI) Physical Activity Public health Health monitoring systems Member States (of the EU) / Country (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom)

A4.2.2 Using set key words in databases, search engines and websites

In order to appropriately link and define the relationship between the key and combination search terms, the Boolean operators 'AND', 'NOT' and 'OR' were used in the search engines. In particular, the use of 'AND' helped to narrow the number of hits to ensure that only documents which included all the search terms showed up. Further, if a search led to a high number of irrelevant hits, a repeat search was conducted and key words which were separated by spaces or other characters (e.g. high fructose corn syrup) were enclosed in quotation marks (e.g. "high fructose corn syrup") to return only those documents that matched the search terms exactly.

The set key words and combination words were used to generate results in databases, search engines and websites recommend by the pilot review:

- Search Europa
- European Sources
- Eurostat
- NICE
- Opengrey
- WHO websites

The European Commission and WHO yielded the most results for Objective B3. The grey literature search was a fluid and dynamic process. Suggestions of other combination words were made, by the grey literature review team after the initial key word searches for objective B3. As a result, the word 'health' was included in supplementary searches. Additional hand searching was used to supplement the key and combination word searches (see section below).

A4.3 Stage 2: Screen Search Results for Relevance

Most databases, search engines and websites offered the use of a relevancy filter[12] which automatically sorts results in order of their applicability to the key terms in the search engine. When a relevancy filter was not available, the links were manually screened by the appearance of the key search terms in the title of the source and the abstract (where available). For database and search engines, initially the top 50 most relevant search results were looked at per search string. If there were less than 50 results, all were looked at. For example, for objective B3, when the search terms 'HFCS' and 'Health' were used in the WHO website there were seven hits, so all the results were looked at. The titles and abstracts were then examined for key search terms in the grey literature and relevance to the research questions.

Extra hand searching was conducted when search strings did not produce enough relevant information, and/or, when the top 50 results did not produce the most relevant literature. Hand searching involved extending the basic key word searches by using additional, contextual information. For example, in objective B3, phrases such as "forecasting the use of HFCS" were used to find more relevant results relating to future trends of HFCS. This process ensured that highly-focused and relevant search results were generated for the original key words, in this case, "HFCS" and "monitoring". All hand searches for this objective were completed on Google.

Following the expert workshop (see stage 5 below), experts recommended further sources which were reviewed in the final redraft of the review.

Overall 86 results from the searching for objective B3 were saved into a library.

A4.4 Stage 3: Screen results against inclusion/exclusion criteria, quality and relevance

Results were then screened against agreed inclusion and exclusion criteria detailed in Table 6 below.

Table 6. Grey literature inclusion and exclusion criteria

Inclusion	Exclusion
Published between 1995-2017	Published or enacted prior to 1995
Government reports from European Commission, European Parliament and EU Member States.	Non-nutrition and physical activity themed/focused
Think tank reports/publications	Industry-produced publications
Academic papers, conference papers and abstracts	Industry-produced project evaluation reports
Bibliographies	Industry-produced good practice reports
Programme evaluation reports[13]	Publications focusing on animal

[12] 'Sorting by relevance' on databases and search engines enables a connection to be established between the information in the database, the search string entered and any search filters chosen. If the keywords appear in a Title or Author field, the system shows these results first in the list of search returns. Less relevant articles e.g. ones where the keyword appears less often or may only appear in the actual content, appear later in the list of search results.

[13] For example: Hallsworth M, Ling T. (2007) *The EU platform on diet, physical activity, and health: second monitoring progress report. Cambridge: RAND Corporation*, http://www.rand.org/content/dam/rand/pubs/technical_reports/2008/RAND_TR609.pdf

Standard/best practices documents Policy initiatives at European and/or national level- run by governments, not-for profit organisations Industry funded publications (As regards the grey literature reviews, particular care will be exerted in assessing any inclusion of industry-funded literature. These will be justified and discussed with the client). Primary theme/focus is human nutrition and physical activity Publication available via accessible databases Published in English, French, German, Italian, Polish and/or Spanish Theses and dissertations (post-2010 only)	nutrition and physical activity Blog or personal think thought pieces Newsletters or news articles Theses and dissertations (2010 and older)

Due to the large number of results still returned after this screening the data parameters were further refined to only include those reports published 2005-2017.

Following this criteria screening and exclusion of search results, the remaining results were checked for quality and relevance.

A4.4.1 Exclusion based on quality checklist

The quality check was based on the AACODS checklist (AACODS)[14] which included:

- Authority

Is the author credible?

- Accuracy

Is the document supported by documented and authoritative references?

Is there a clearly stated methodology?

Is the document representative of work in the field?

- Coverage

Have limitations been imposed and are they clearly stated?

- Objectivity

Can bias be detected (if so the bias was clearly stated in the extraction form)?

- Date

Does the document have a clearly stated date relating to the content?

[14] Please see the full outline of the AACODS checklist here: https://dspace.flinders.edu.au/jspui/bitstream/2328/3326/4/AACODS_Checklist.pdf

- Significance

Is the document relevant?

Would the document enrich the findings?

The remaining grey literature was examined further so that only results most relevant to the objective were extracted. In particular, each article was examined for text relating to the key terms and questions under the objective. For example, in objective B3, the text was examined for reference to the research *question* 'Who consumes foods containing High Fructose Syrups and how much?'.

A4.5 Stage 4: Review and extraction of full texts

A data extraction template in Excel was used to capture the following categories of information: 1) identifying information for each publication, 2) study design characteristics, 3) sample characteristics, 4) intervention characteristics, 5) content (behaviour/outcome) focus, 6) description of results, 7) assessment of rigour/bias and 8) objective specific information. In total 22 results were extracted.

After extraction, the review author read through all of the extracted data and a final screening process excluded more results due to quality or a lack of enough relevant information, now made obvious after extraction. Sources were also excluded from the grey literature where this was superseded by, either more rigorous peer reviewed research on the same theme, or more recent statistics. In total, 20 results were excluded.

A thematic analysis was applied to the remaining extracted data and their findings synthesised with those of the peer reviewed literature. Any identified bias in sources which passed the inclusion criteria is highlighted in the analysis.

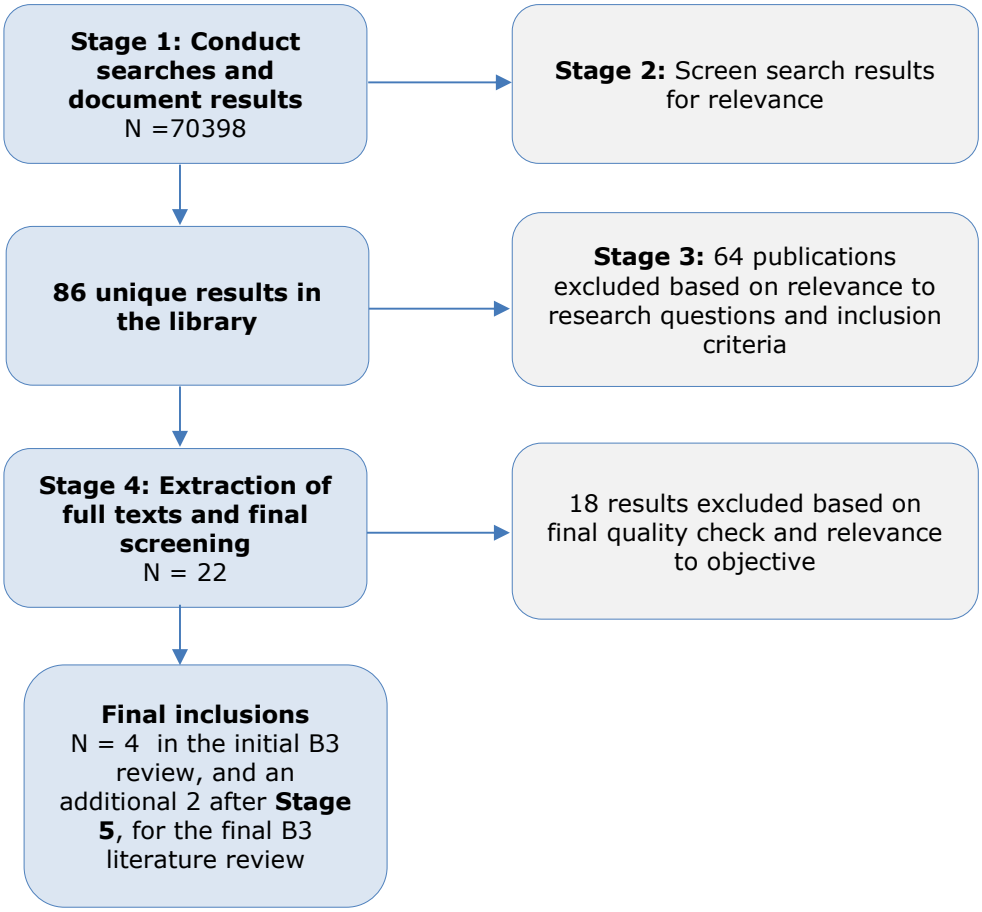
A4.6 Stage 5: External expert reviews and input

Upon completion of the draft set of comprehensive literature reviews, expert workshops were organised to discuss findings, highlight additional relevant sources to fill gaps and improve the series of reviews. Experts were carefully selected from academic and policy-making fields, based on expertise of the specific topics addressed. As a result of this exercise, two additional references were screened and incorporated into these reviews.

A4.7 Number of included and excluded references

The diagram in Figure 2 below shows the number of articles identified in grey literature searches, and the filtering out of literature at successive stages to arrive at the final number of four publications whose full text was reviewed and summarised for this review. The diagram also includes additional relevant references proposed by external experts, and incorporated into this final comprehensive review.

Figure 2. Diagram showing number of included and excluded publications at each stage – grey literature



As shown in Figure 2, a total of 70,398 search hits were retrieved. From the 86 results saved in the library, 64 were excluded based on the relevance to Objective B3 research questions. Following this, 22 results were extracted fully. An additional 18 publications were then excluded based on inclusion/exclusion criteria, quality of evidence and relevance to the research questions. In Stage 5, supplementary searches were conducted and/or articles recommended by experts during the workshops were looked at and another 2 grey literature sources were included in the final review.

Annex 5 Grey literature bibliography

DG AGRI (DG Agriculture and Rural Development), European Commission. (2015). *EU Agricultural Outlook: Prospects for EU agricultural markets and income 2015-2025*. [ONLINE] Available at: http://ec.europa.eu/agriculture/markets-and-prices/medium-term-outlook/2015/fullrep_en.pdf (Accessed 14th June 2016)

DG AGRI (DG Agriculture and Rural Development), European Commission. (2015). *EU Agricultural Outlook: Prospects for EU agricultural markets and income 2016-2026*. [ONLINE] Available at: https://ec.europa.eu/agriculture/sites/agriculture/files/markets-and-prices/medium-term-outlook/2016/2016-fullrep_en.pdf (Accessed on 21st November 2017)

EEIG Agrosynergie. (2011). *Evaluation of CAP Measures Applied to the Sugar Sector*. [ONLINE] Available at: https://ec.europa.eu/agriculture/sites/agriculture/files/evaluation/market-and-income-reports/2011/sugar-2011/fulltext_en.pdf (Accessed 14th June 2016)

Joint Research Centre (JRC), European Commission. (2014). *EU sugar policy: A sweet transition after 2015?* [ONLINE] Available at: http://publications.jrc.ec.europa.eu/repository/bitstream/JRC76619/jrc%20tr%20sugar_study_pubsy_v6.pdf (Accessed on 20th November 2017)

Annex 6 HFCS use by country

Country	HFCS (kg/year per capita)	Country	HFCS (kg/year per capita)
Indonesia	0.14	Spain	1.78
France	0.15	Finland	1.81
China	0.25	Serbia	2.79
Australia	0.35	Turkey	4.20
United Kingdom	0.38	Mexico	5.83
Romania	0.40	Japan	6.19
Italy	0.41	Republic of Korea	6.75
Netherlands	0.46	Argentina	7.67
Germany	0.54	Belgium	8.32
Poland	0.87	Bulgaria	8.53
Thailand	0.91	Canada	9.13
Greece	0.96	Slovakia	9.82
Portugal	1.10	Hungary	16.85
Malaysia	1.13	United States	24.78
Egypt	1.36		

*Data for this table taken from Goran, Ulijaszek and Ventura, 2013.

For India, Slovenia, Latvia, Uruguay, Ireland, Lithuania, Sweden, Luxembourg, Czech Republic, Austria, Cyprus, Estonia, Malta, and Denmark the HFCS se indicator (kg/year per capita) equalled “0”.

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ISBN: 978-92-79-97428-1

doi:10.2875/973476