Draft protocol for the Scientific Opinion on free sugars from all dietary sources

European Food Safety Authority

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1. Introduction and scope of the protocol

This document outlines the draft protocol for the Scientific Opinion on free sugars from all dietary sources of the EFSA Panel on Nutrition, Dietetic Products and Allergies (NDA Panel), supported by the ad-hoc Working Group (WG) on sugars. This draft protocol has been developed with the aim of defining as much as possible beforehand the strategy that will be applied for collecting data (i.e. which data to use for the assessment and how to identify and select them), appraising the relevant evidence, and analysing and integrating the evidence in order to draw conclusions that will form the basis for the Scientific Opinion.

The protocol has been developed following the principles and process illustrated in the EFSA PROMETHEUS project (PROmoting METHods for Evidence Use in Scientific assessments) (EFSA, 2015a).

2. Background and rationale of the mandate

In June 2016, the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway, and Sweden) sent a request to EFSA in order to provide a dietary reference value (DRV) for sugars, with particular attention to added sugars, on the basis of most recent scientific evidence. After discussing the mandate at its plenary meeting on 22-23 September 2016, the NDA Panel asked for some clarifications to the requestors, particularly regarding the type of DRV to be established, the exposure of interest, the target population, and the health outcomes to be considered. In February 2017, the requestors clarified that they were interested in a science-based cut-off value for a daily exposure to added sugars from all sources (i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing) which is not associated with adverse health effects. The target population for the assessment was defined as the general healthy population, including children, adolescents, adults and the elderly. The requestors also clarified that the request relates to an update of the EFSA's Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre (EFSA NDA Panel, 2010) in relation to the effects of added sugars on nutrient density, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type-2 diabetes, and dental caries in adults and children.

In the EFSA's 2010 opinion the term "added sugars" referred to sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup) and other isolated sugar preparations used as such or added during food preparation and manufacturing.

With regard to the effects of added sugar intake, the NDA Panel reached the following conclusions on the outcomes assessed:

- Micronutrient density of the diet: observed negative associations between added sugars intake and micronutrient density of the diet are mainly related to patterns of intake of the foods from which added sugars in the diet are derived rather than to the intake of added sugars *per se*. The available data are not sufficient to set an upper limit for (added) sugars intake.
- Glucose and insulin response: there are limited, and mainly short-term, data on the effects of high intakes of sugars on glucose and insulin response. Most studies do not find any adverse effects at intakes of predominantly added sugars up to 20 to 25% of total energy (E%), provided that body weight is maintained.
- Serum lipids: although there is some evidence that high intakes (>20 E%) of sugars may increase serum triglycerides and cholesterol concentrations, the available data are not sufficient to set an upper limit for (added) sugar intake.
- Body weight: the evidence relating high intake of sugars (mainly as added sugars), compared to high intakes of starch, to weight gain is inconsistent for solid foods. However, there is some evidence that high intakes of sugars in the form of sugar-sweetened beverages might contribute to weight gain. The available evidence is insufficient to set an upper limit for sugars based on their effects on body weight.
- Type 2 diabetes: controversial findings on the association between total sugars and/or specific types of sugars and diabetes risk were reported in large prospective cohort studies. However

positive associations were found between sugar-sweetened beverages and increased type 2 diabetes risk. The available evidence was found insufficient to set a Tolerable Upper Level of Intake (UL) for sugars based on their effects on type 2 diabetes risk.

- Dental caries: available data do not allow the setting of a UL for (added) sugars on the basis of a risk reduction for dental caries, as caries development related to consumption of sucrose and other cariogenic carbohydrates does not depend only on the amount of sugar consumed, but it is also influenced by oral hygiene, exposure to fluoride, frequency of consumption, and various other factors.

The NDA Panel concluded that the available data did not allow the setting of a UL for total or added sugars, neither an Adequate Intake (AI) nor a Reference Intake range (RI). However evidence on the relationship between patterns of consumption of sugar-containing foods and dental caries, weight gain and micronutrient intake should be considered when establishing nutrient goals for populations and recommendations for individuals and when developing food-based dietary guidelines (FBDG).

3. Terms of reference as provided by the mandate requestor

The request is for scientific assistance in line with Regulation (EC) No 178/2002 in assessing a dietary reference value for added sugars, which would benefit risk managers and substantially support their work with dietary guidelines and nutrient recommendations if they could base their advices on an up-to-date assessment by EFSA.

To this end, EFSA has been requested to update its Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre published in 2010 (EFSA NDA Panel, 2010), on the basis of the most recent scientific evidence, in order to derive a science-based cut-off value for a daily exposure to added sugars which is not associated with adverse health effects.

The mandate requestor clarified that the intake of interest is added sugars from all sources, i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing. The health outcomes of interest are those already addressed in the EFSA 2010 opinion, i.e. micronutrient density of the diet, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes, and dental caries in adults and children.

To address this mandate, EFSA is requested to consider published reports from national and international bodies/authorities addressing the health effects of added sugars, as well as systematic reviews and meta-analysis published since 2010 on this topic.

4. Interpretation of the Terms of Reference

4.1. Background information

To address this mandate EFSA is requested to consider, as background information and sources of data, published reports from national and international authorities/bodies addressing the health effects of sugars, as well as systematic reviews and meta-analysis published since 2010 on this topic.

An overview of the most recent existing dietary reference values and recommendations issued by other national and international authorities/bodies can be found in **Appendix A**. These publications will be used as sources of individual studies meeting the inclusion criteria for the present assessment through the scrutiny of their reference list.

A scoping literature search for systematic reviews and meta-analysis addressing the health effects of sugars or any of its dietary sources published in English since 2009 has also been performed. The list of the references identified and their main characteristics (e.g. exposure and endpoints of interest) can be found in **Appendix B**. These systematic reviews and meta-analysis will be used in two ways:

a) As sources of individual studies meeting the inclusion criteria for the present assessment through the scrutiny of their reference list;

b) As starting point for the literature searches to be carried out in the context of this assessment, whenever appropriate (see section 9.2).

4.2. Definition of the exposure

Different terms and definitions have been used by researches and risk managers for dietary sugars. Among these:

i) *Added sugars*, which include all sugars (mono- and disaccharides) used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table. This term was first used in the 2000 US Dietary Guidelines for Americans (2000, USDA & HHS), and then the IoM (2002), EFSA (2010), and some European countries (NNR, 2012).

ii) *Non-milk extrinsic (NME) sugars*, defined as sugars not located within the cellular structure of a food, such as those found in fruit juice, honey, and syrups, and those added to processed foods, excluding lactose in milk. The term originated from the UK Department of Health (UK Department of Health, 1989) as opposed to *intrinsic sugars*, which are those located within the cellular structure of a food (e.g. naturally found in fruits and vegetables).

iii) *Free sugars*, which include all monosaccharides (glucose, fructose, galactose) and disaccharides (sucrose, lactose, maltose, trehalose) added to foods by the manufacturer, cook, or consumer plus sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrates. This term has been used by the World Health Organization (WHO) (2003).

Following the first discussions among the WG experts, and in agreement with the mandate requestor, the term free sugars as defined by the WHO (definition iii) will be used for the purpose of this assessment.

The assessment concerns free sugars taken through the oral route only.

4.3. Objectives of the risk assessment

EFSA interprets this mandate as a request to provide scientific advice on a daily intake of free sugars from all dietary sources which, if consumed for long periods of time, is not associated with adverse health effects in the general healthy European population including children, adolescents, adults and elderly adults.

To explore possible adverse health effects of different types of free sugars (e.g. glucose vs. fructose vs. sucrose), or of different dietary sources of free sugars (e.g. sugar-sweetened beverages vs solid foods) is not a primary objective of the assessment. However, differences in the absorption, digestion and/or metabolism of different free sugars owing to their chemical structure and/or dietary source may be considered in the analysis, integration and interpretation of the scientific evidence.

The assessment also encompasses an estimation of the intake of free sugars from all dietary sources (foods and beverages) in the target population by age group (and sex group, if appropriate). The intake assessment will be compared with the level of intake of free sugars obtained, if any, for the characterisation of the risk.

It is out of the scope of this scientific assessment to address possible beneficial health effects of free sugars or of particular dietary sources of free sugars.

The outcome of the assessment is expected to assist Member States and health professionals in establishing nutrient goals for populations and recommendations for individuals, and when developing FBDG.

4.4. Target population

The scientific advice on a level of intake of free sugars will be provided for the general healthy European population, including children, adolescents, adults and elderly adults. Sub-populations with extreme and distinct vulnerabilities to the intake of free sugars due to genetic predisposition or other conditions (e.g. diseased individuals under medical care, individuals with inborn errors of carbohydrate metabolism, intense physical activity) are excluded from the assessment.

Variations according to age (and sex, if appropriate) will be considered. The choice of age groups is based upon differences in the type and amount of free sugars intake, and in their relative contribution to energy intake and their possible adverse health effects.

The following age groups will be considered *a priori*:

- Infants ≥ 4 to < 12 months
- Toddlers (young children) ≥ 1 to < 3 years
- Other children ≥ 3 to < 10 years
- Adolescents ≥ 10 to < 18 years
- Adults ≥ 18 to < 65 years
- Elderly adults ≥ 65 years

The age ranges may be modified by the NDA Panel depending on the available data, e.g. children may be further categorised according to the type of dentition (primary-milk, or secondary–permanent) in relation to dental caries endpoints.

Infants < 4 months of age will be excluded from the assessment on the assumption that they are exclusively fed with breastmilk or breastmilk substitutes (EFSA NDA Panel, 2009). Pregnant and lactating women will not be considered specifically.

Specific advice on a level of intake of free sugars from all dietary sources will not be provided for subgroups of the population on the basis of, for example, ethnicity, dietary habits (e.g. vegetarians, vegans), physical activity level (PAL) (e.g. for PALs > 2.0 corresponding to highly active lifestyles), disease conditions or nutritional status.

4.5. Adverse effects and endpoints

The assessment will focus on possible adverse effects of free sugars intake on several endpoints. These endpoints were selected based on the scope of the mandate, on previous assessments done by other bodies (Appendix A) and on the systematic reviews available (Appendix B). They include indicators of micronutrient status, including biochemical markers and the micronutrient density of the diet; indicators of body fatness and risk of developing obesity; indicators of glucose homeostasis and risk of developing type 2 diabetes mellitus (T2DM); serum lipids, blood pressure and risk of cardiovascular events; risk of developing dental caries. Possible adverse effects of free sugars intake on indicators of liver function will also be addressed, the liver being a key organ in the regulation of glucose and lipid metabolism.

Both disease endpoints and surrogate endpoints will be considered for the assessment. Disease endpoints are considered to be the most direct, or applicable, to the assessment, e.g. incidence of micronutrient deficiency, obesity, T2DM, cardiovascular disease and dental caries. Surrogate endpoints are relevant but less direct, and can include upstream indicators, risk factors, intermediate endpoints or measures related to the final endpoints, e.g. body weight/BMI, insulin sensitivity, blood lipids. Adverse effects (disease and surrogate endpoints) for human studies which have been identified by the EFSA WG on sugars after internal discussion are illustrated in Table 1.

Table 1: Adverse effects (disease and surrogate endpoints) for human studies

Target	Disease endpoints	Surrogate endpoints
Micronutrient status	Clinical signs/symptoms of micronutrient deficiency	Biomarkers of micronutrient status Micronutrient intakes Micronutrient density of the diet (micronutrient intake/energy unit)
Teeth	Dental caries incidence/severity	None
Chronic metabolic diseases		
Adipose tissue	Obesity incidence	Body weight, BMI Body composition (body fat, lean body mass) Waist circumference Ectopic fat deposition (muscle, VAT)

Glucose homeostasis	T2DM incidence	Insulin sensitivity Beta-cell function Blood glucose control
Cardiovascular system	CVD incidence/mortality	Blood pressure Blood lipids
Liver function	Liver fibrosis/cirrhosis incidence/ mortality	Liver fat accumulation NAFLD/NASH activity score

BMI = body mass index; CVD = cardiovascular disease; NAFLD = non-alcoholic fatty liver diseases; NASH = non-alcoholic steato-hepatitis; T2DM = type 2 diabetes mellitus; VAT = visceral adipose tissue

5. Identification of the assessment sub-questions

In setting a level of intake for free sugars, the selection of the criteria (adverse effects) on which to base such scientific advice is an important step. The purpose of the assessment is to identify the adverse effect(s) (disease and surrogate endpoints, see Table 1) which is(are) the most appropriate to derive a level of intake for free sugars. Adverse effects will be considered first within a given target (see Table 1), and then across targets related to chronic metabolic diseases. Adverse effects related to micronutrient status, teeth and chronic metabolic diseases will, in principle, not be combined to derive a level of intake for free sugars.

The suitability of each adverse effect will be assessed on the basis of the quality of the available evidence, taking into account the related uncertainties, and of the possibility to derive quantitative estimates. If more than one adverse effect is found to be suitable and the level of intake of free sugars that can be derived from each of them differs, scientific advice will be provided for each adverse effect separately. If the available evidence does not allow setting a level of intake for free sugars on the basis of one or more adverse effects, data gaps will be identified and reported in the Scientific Opinion.

Basic research in animal models can produce valuable knowledge on mechanisms and/or dose–response relationships, for instance in relation to the physiology and metabolism of sugars. However, due to inter-species differences, extrapolation from animal models to humans is subject to considerable uncertainties and data from animal models are rarely used in the setting of reference values for nutrients (EFSA NDA Panel, 2010). Existing recommendations on sugar intake set by other bodies have been primarily based on a large number of human studies (Appendix A). The Panel considers that the assessment of the criteria (disease/surrogate endpoints) on which to base a level of intake of free sugars should rely on the human studies available. Information from animal and/or *in vitro* studies will only be used, where appropriate, as background knowledge on mode(s) of action and biological plausibly, but not to establish a relationship (including any dose-response relationship) between the intake of free sugars and disease/surrogate endpoints in humans.

The question raised in the ToR (section 4.3) can be broken down into a series of sub-questions that will be addressed and combined in the assessment (Table 2).

The objective of the assessment is to establish if there is a relationship between the intake of free sugars from all dietary sources and the relevant adverse effects listed in Table 1 in population subgroups which are considered relevant for the target population. For that purpose, a qualitative and, if possible, a quantitative description of the relationship with the endpoints of interest for this assessment will be performed, including an assessment of a dose–response relationship and an evaluation of possible uncertainties; for example, those derived from the extrapolation of a type of free sugar (e.g. fructose, glucose, sucrose) from a particular source (e.g. sugar-sweetened beverages, sweets and candies) to free sugars in general from all dietary sources. The aim of the dose–response assessment is the identification of a level of intake of free sugars at which (and below which) no adverse health effects are observed. Background information on the digestion, absorption and metabolism of different types of sugars from different food matrices in humans and data on potential mode(s) of action (depending on the relationships(s) found between free sugars intake and the endpoints considered) will be gathered to help the interpretation of the results obtained.

The assessment also encompasses, from occurrence data and food consumption data, an estimation of the intake of free sugars from all dietary sources (foods and beverages) in the target population by

age group (and sex group, if appropriate). The intake assessment will be compared with the level of intake of free sugars obtained, if any, for the characterisation of the risk.

Table 2: Assessment sub-questions to be answered

Number	Sub-question
1	What are the levels of free sugars in foods and beverages in Europe?
2	What is the distribution of intakes of free sugars from all dietary sources (and by food source) in the target population?
3	What are the digestion, absorption and metabolism of different types of free sugars from different food matrices in humans?
4	What is the relationship between the intake of free sugars from all dietary sources and micronutrient status (disease and/or surrogate endpoints)?
5	What is the relationship between the intake of free sugars from all dietary sources and chronic metabolic diseases (disease and/or surrogate endpoints) in the target population?
6	What is the relationship between the intake of free sugars from all dietary sources and dental caries in the target population?
7	Which could be the potential mode(s) of action for the relationships found, if any, between free sugars intake and chronic metabolic diseases (disease and/or surrogate endpoints)? (a)

(a): The mode of action by which sugars can contribute to the development of dental caries (sub-question 6) is considered to be well-known.

6. Methods to answer sub-questions 1 and 2

6.1. Levels of free sugars in foods and beverages in Europe

A European food composition database for free sugars in foods and beverages will be developed taking into account the 10-step methodology described by Louie et al. (2015) for added sugars and adapted by FSANZ[1] to determine the amount of free sugars in foods in the AUSNUT 2010-2013 food nutrient database. Although the definition of added sugars (a component of free sugars) in the Australian code includes maltodextrin and similar products, a decision was made by FSANZ not to capture these ingredients in the dataset of added sugars (and therefore neither in the dataset of free sugars) to maintain consistency with the definition of sugars used in nutrition labelling and with international food composition database practice where total sugars have been defined as being only mono- and di-saccharides. The same approach will be followed by EFSA for the same reasons.

Since only total sugars are subject to mandatory labelling in Europe and there are no analytical methods to distinguish between free sugars and other sugars present in foods, available data on total sugars will be used as starting point to estimate the levels of free sugars in foods and beverages. To that end, a food composition database for total sugars will be developed first.

6.1.1. Development of a food composition database for total sugars

Data on total sugars will be extracted from the EFSA's food composition database, which was compiled as a deliverable of the procurement project "Updated food composition database for nutrient intake" (Roe et al., 2013). The aim of the project was to provide EFSA with an updated food composition database covering approximately 1750 food entries in the EFSA FoodEx2 classification system[2] with additional FoodEx2 facet descriptors, and to expand the dataset to include harmonised information on the most common composite recipes of European countries and harmonised information on food supplements. Fourteen national food database compiler organisations participated in this data collation project, providing information from national food composition databases up to 2012. In case no country-specific data were available for certain food codes, data compilers borrowed

[1] http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/foodnutrient/Pages/Determining-the-amount-of-added-sugars-and-free-sugars-in-foods-listed-in-the-AUSNUT-201113-dataset.aspx

[2] https://www.efsa.europa.eu/en/data/data-standardisation

compatible data from other countries and/or from similar foods. Within the EFSA's food composition database, 12 countries provided data on total sugars covering about 1290 FoodEx2 codes.

For the purpose of this Scientific Opinion, a single European food composition database for total sugars will be developed from the information available in the national food composition databases. To that end, an outlier analysis will be performed to identify any value which deviates from the others for a given food code (e.g. more than a 10-fold difference between any two values available). For food codes for which no outliers can be identified, the mean will be taken as a unique value. Whenever outliers are identified for a given food code, highest and lowest values will be compared with values published after 2012 for the same/similar food and the same/similar country to understand which are the real outliers. For this purpose, national food composition data published after 2012 will be retrieved through a questionnaire to the National Competent Authorities of European countries (section 8.1). The Mintel Global New Products Database (GNPD)[3], an online database which monitors product introductions in consumer markets of packaged goods worldwide, will be used to check whether differences among countries might be explained by differences in product formulations being available in different European countries. If so, different values for different countries might be used. If differences between countries regarding the total sugar content cannot be explained by differences in product formulations, different scenarios will be considered, e.g. two extreme values (lowest and highest) will be assigned to that food code to evaluate the impact of this variability in the content of total sugars. The outlier assessment will prioritise foods with a high content of total sugars and foods largely consumed by one or more population subgroups.

6.1.2. Development of a food composition database for free sugars

A food composition database for free sugars will also be developed for all FoodEx2 codes for which a consumption has been reported in the EFSA Comprehensive Food Consumption Database (see section 6.2.1) in combination with the relevant FoodEx2 facet descriptors included in the EFSA FoodEx2 classification system (e.g. sugar free facet), using as starting point the food composition database for total sugars (section 6.1.1.). All foods will be classified in four groups following a step-wise approach adapted from Louie et al. (2015) and FSANZ:

1. **Foods containing no sugars.**

The value for free sugars will be 0.

2. **Foods containing only intrinsic sugars and/or lactose in milk.**

The value for free sugars will be 0, even if the content of total sugars is >0. These include fruits, vegetables and dairy products with no sugars added.

3. **Foods containing free sugars only.**

The value(s) for free sugars will be equal to the value(s) for total sugars. These are foods with a content of total sugars >0 which do not contain intrinsic sugars or lactose in milk, such as:

- Sucrose (table sugar), including white, brown, flavoured, and icing sugar.
- Syrups and molasses.
- Honey.
- Fruit and vegetable juices and nectars (including concentrates), either commercial or homemade.
- Alcoholic beverages.
- Confectionery with no dried fruit or milk sugars.

[3] The Mintel GNPD contains information on over two million food and beverage products, of which more than 800,000 are or have been available on the European food market. Mintel started covering European Union's food markets in 1996. Twenty out of the 28 EU member countries and Norway are present in the Mintel GNPD. The database provides the compulsory ingredient information presented in the labelling of products and the nutritional facts when available on the labels, which provide information about the use of sugars as ingredients and about the total sugar content of foods. http://www.mintel.com/global-new-products-database

- Water-based beverages (including soft drinks, energy drinks and sport drinks) and beverage concentrates.

4. Foods containing free sugars and intrinsic sugars and/or lactose in milk.

For foods which contain a combination of free and intrinsic sugars and/or lactose in milk, attributing a value for free sugars may be more challenging. For these foods, the following step-wise approach will be considered:

4.1. If a comparable unsweetened variety of the food exists, the content of free sugars will be calculated on the unsweetened variety method as described by Louie et al. (2015) for added sugars.

4.2. If the condition for step 4.1 is not met but the free sugars content of all ingredients in the standard recipe is known, the content of free sugars will be calculated on proportioning method as described by Louie et al. (2015) for added sugars.

4.3. If the conditions for steps 4.1 and 4.2 are not met, a value will be borrowed from a similar product from this database or from another database (possibly from the EU, otherwise from abroad).

4.4. If the conditions for steps 4.1 - 4.3 are not met, it will be assumed that 50% of total sugars are free sugars.

Efforts will be made to avoid using the subjective steps 4.3 and 4.4 as much as possible.

The food composition database for free sugars will be published together with the draft Scientific Opinion for public consultation.

6.2. Estimates of intake of free sugars from all dietary sources

Estimates of intake of free sugars from all dietary sources will be obtained using data from the EFSA Comprehensive Food Consumption Database in combination with the food composition database for free sugars (section 6.1.2).

6.2.1. The EFSA Comprehensive Food Consumption Database

Food consumption data from the EFSA Comprehensive Food Consumption Database (hereinafter referred as Comprehensive Database) will be used in order to assess the intake of free sugars. The Comprehensive Database provides a compilation of existing national information on food consumption at individual level. It was first established in 2010 (EFSA, 2011a; Huybrechts et al., 2011; Merten et al., 2011). The latest version of the Comprehensive Database, updated in 2015, contains results from 51 different dietary surveys carried out in 23 different Member States, covering 94,532 individuals.

Within the dietary surveys, subjects are classified in different age groups as follows:

1) Infants: 1-11 months old
2) Toddlers: ≥ 1 year to < 3 years old
3) Other children: ≥ 3 years to < 10 years old
4) Adolescents: ≥ 10 years to < 18 years old
5) Adults: ≥ 18 years to < 65 years old
6) Elderly: ≥ 65 years to < 75 years old
7) Very elderly: ≥ 75 years old

Two additional surveys which provided information on specific population groups that are not the target population for this assessment (pregnant women and lactating women) will not be considered for this opinion. Only data from infants 4 to 11 months old will be considered in this assessment.

Overall, the Comprehensive Database is the most complete and detailed collection of food consumption data currently available in the EU. Consumption data were collected using single or repeated 24- or 48-hour dietary recalls or dietary records covering from three to seven days per

subject. Surveys with only one observation day per subject, or which used food frequency questionnaires (FFQ) for data collection, were excluded. Owing to the differences in the methods used for data collection, direct country-to-country comparisons can be misleading. Detailed information on the different dietary surveys included in the Comprehensive Database is shown on the EFSA website[4], including the number of subjects and days available for each age group. If new food consumption surveys become available during the assessment, the most recent survey for a given country and age group will be used.

The linking between the foods consumed and the food composition database for free sugars (section 6.1.2) will be done through the FoodEx2 (EFSA, 2015b) system.

6.2.2. Free sugars intake calculation

The intake of free sugars will be calculated at the individual level by multiplying the average daily consumption for each food or food group with the corresponding concentration of free sugars, summing up the respective intakes throughout the diet. In line with the Guidance of EFSA for the Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment (EFSA, 2011a), chronic free sugars intake calculations will be performed only for subjects with at least two reporting days. In this context, chronic free sugars intake refers to the arithmetic mean of all reporting days available for the same subject. The intake will be modelled using the SAS software (SAS Enterprise Guide 5.1, 2013). The mean as well as the 5th, 50^{t}h and 95th percentiles of intake will be derived for each survey and age group (and sex group, if appropriate), respectively.

Different intake scenarios could be considered in the intake calculation process, especially if more than one value for free sugars is assigned to one or more FoodEx2 codes in the food composition database.

To evaluate the accuracy of the results obtained, these will be compared with published intake values for free sugars from the same survey dataset and age group, whenever available. These data will be retrieved through a questionnaire to the National Competent Authorities of European countries (section 8.1).

7. Method to answer sub-question 3

In order to address the digestion, absorption and metabolism of different types of free sugars from different food matrices in humans, background information will be gathered by the WG experts and EFSA staff through a narrative review. Recent textbooks, authoritative reviews and research papers retrieved through searches in bibliographic databases, and selected on the basis of their relevance, will be used as sources of information.

8. Methods to answer sub-question 4

Two different methods will be used to answer sub-question 4 on the relationship between the intake of free sugars from all dietary sources and micronutrient status:

1) A questionnaire to national representatives of European countries;
2) An extensive literature search of the available evidence.

8.1. Questionnaire

A questionnaire (**Appendix C**) will be sent to the National Competent Authorities of European countries thought the EFSA's Focal points and Food Consumption Data networks, which comprise members from all 28 EU Member States, Iceland and Norway, as well as observers from Switzerland and EU candidate countries. The aim of the questionnaire is to identify:

a) National food composition data which has become available after 2012, with a focus on total sugars (section 6.1.1).
b) National food composition data on added/free sugars if available, together with the methods used to estimate added/free sugars in foods (section 6.1.2).

[4] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

c) The micronutrients of public health concern (i.e. for which intakes below the reference values have been identified in one or more age groups) at national level, used to set national dietary recommendations and FBDGs.

d) Data available at national or regional level (e.g. from national or regional food consumption surveys) on:

- Intake of total/added/free sugars;
- Biochemical markers of micronutrient status and/or micronutrient density of the diet in relation to the consumption of total/added/free sugars.

8.2. Extensive literature search

An extensive literature search of the available evidence will be undertaken to investigate the relationship between the intake of free sugars, whether total or from one or more dietary sources (in amount per day, in amount per kg/bw/day, or as % of total energy intake), and micronutrient intake, micronutrient density of the diet, biochemical markers of micronutrient status and/or signs/symptoms of micronutrient deficiency. Embase, PubMed and Scopus databases will be searched with no time limits. The methodology used in the systematic literary review conducted by Rennie and Livingston (2007) on the associations between dietary added sugar intake and micronutrient intake will be taken as starting point (e.g. objectives, inclusion criteria). The micronutrient inclusion criteria will be refined taking into account the replies received by the National Competent Authorities of European countries (section 8.1), and the literature search strategy will adapted to include free sugars, biochemical markers of micronutrient status and signs/symptoms of micronutrient deficiency.

8.3. Synthesis of the evidence

Since it is not possible to anticipate the type and amount of data that could be gathered through the extensive literature search and/or the questionnaire sent to the National Competent Authorities of European countries to answer sub-question 4, appropriate methodologies for evidence synthesis will be defined at a later stage.

9. Methods to answer sub-questions 5 and 6

Sub-questions 5 and 6 will be answered by performing systematic reviews and, possibly, dose-response meta-analyses if the available data allow doing so.

9.1. Review questions and eligibility criteria for study selection

The selection of human studies relevant to sub-questions 5 and 6 will be performed using the eligibility criteria described in Tables 3 and 4.

For sub-question 5, the minimum study duration for the inclusion of intervention studies has been selected by considering the time generally required for the stabilisation of the surrogate endpoints assessed (by target, Table 1) following a nutritional intervention. The minimum study duration for the inclusion of observational studies for sub-question 5, and for the inclusion of intervention and observational studies for sub-question 6, is based on the minimum time estimated to be needed for the disease to develop in individuals free of the disease at baseline (expert judgement).

Regarding the study location, no limits are applied. It is acknowledged, however, that the background diet may affect the relationship between the intake of free sugars and the disease/surrogate endpoints being addressed, and that major differences in the background diet may limit the extrapolation of the results obtained outside Europe to the European population. This aspect will be considered when synthesising the evidence (section 9.6).

490 **Table 3:** Eligibility criteria for human studies to address sub-question 5

Sub-question 5: What is the relationship between the intake of free sugars from all dietary sources and chronic metabolic diseases (disease and/or surrogate endpoints) in the target population?		
INTERVENTION STUDIES		
Study design	In	Randomised controlled trials Non-randomised, comparative studies of interventions [(a)]
	Out	Single-arm intervention studies with no control group
Study duration	In	Depending on the surrogate endpoints addressed, as follows (see Table 1): Adipose tissue ≥ 6 weeks Glucose homeostasis ≥ 1 week Cardiovascular system ≥ 4 weeks Liver function ≥ 2 weeks
	Out	Studies of shorter duration
Study location	In	Any location
Population	In	Adults (≥ 18 years) and children (4 months to < 18 years) from the general population, including overweight or obese subjects, subjects at risk of disease (e.g. with impaired glucose tolerance, impaired fasting glucose, NAFLD), and subjects with one or more features of the metabolic syndrome which are not on pharmacological treatment during the intervention
	Out	Studies targeting individuals with a disease (except for obesity), either untreated or under pharmacological/surgical treatment for the disease, or individuals on a therapeutic diet, including weight-loss diets Studies in individuals under physical training programs (e.g. athletes, military)
Intervention	In	Intervention: - a quantitative change in the intake of free sugars, whether total or from one or more dietary sources (in amount per day, in amount per kg/bw/day, or as % of total energy intake) - a change in the intake of one or more dietary sources of free sugars which allows quantification of free sugars intake from those sources - free sugars provided in addition to the usual diet or in replacement of other macronutrients; a restriction in the intake of free sugars (whether total or from one or more dietary sources) Method to assess the intake of free sugars: - Controlled feeding (food provided) - 24-h urinary excretion of fructose and sucrose - Food records - Diet recalls - FFQs
	Out	Intervention: - changes in free sugars intake in the context of energy-restricted diets - studies not providing sufficient information to allow quantitative estimates of free sugars intake, whether total or from one or more dietary sources (e.g. studies reporting only on the frequency of consumption of one or more dietary sources of free sugars) Method to assess intake of free sugars: - Any other method
Control	In	Differs from the intervention on the amount of free sugars only, so that any effect can be attributed to the type/amount of free sugars consumed
	Out	Differs from the intervention regarding characteristics other than the amount of free sugars which could affect the endpoints
Endpoints of interest	In	Endpoints and methods of measurement by target: *Adipose tissue* - Measured body weight, BMI, waist circumference, sagittal diameter - Body composition: body fat, lean body mass measured by neutron activation analysis (NAA), imaging techniques (DXA, MRI, CT), hydrostatic weighing, or air displacement plethysmography. - VAT assessed by imaging techniques (CT, MRI) - Ectopic fat deposition in muscle assessed by muscle biopsies or Magnetic Resonance Spectroscopy

		Glucose homeostasis - Dynamic indices of insulin sensitivity and/or beta-cell function calculated from measures of plasma glucose, serum insulin and C-peptide (when available) during clamp tests (hyperinsulinaemic-euglycaemic, hyperglycaemic), frequently sampled intravenous glucose tolerance tests (FSIGT), standard oral glucose tolerance test (OGTT), the continuous infusion of glucose with model assessment (CIGMA), or insulin suppression tests - Static indices of insulin sensitivity and/or beta-cell function calculated from fasting plasma glucose and fasting serum insulin (e.g. HOMA, QUICKI) - Indices of blood glucose control (HbA1c, fructosamine) *Cardiovascular system* - SBP and DBP (point or 24-h BP) - Blood lipids (total-c, LDL-c, HDL-c, VLDL-c, fasting TG, apoB100, apoA1, and ratios thereof) *Liver function* - Liver fat accumulation measured by CT, MRI, MRS, or liver biopsies - NAFLD/NASH activity scores as defined by the authors
	Out	- Self-reported body weight, BMI, waist circumference, sagittal diameter - Body composition assessed by BIA or skinfold thickness - Studies not including at least one of the endpoints listed above
Language	In	Full-text document in English
	Out	Articles with the full text in another language
Publication year	In	Up to March 2018
Publication type	In	Primary research studies (i.e. studies generating new data) reported in full-text articles Primary research studies reported in letters to editors if the information provided is sufficient to allow a scientific evaluation of the results Systematic reviews and meta-analyses[(b)]
	Out	Narrative reviews, expert opinions, editorials and letters to editors not reporting on primary data Meetings' abstracts and posters Conference proceedings PhD theses Grey literature
OBSERVATIONAL STUDIES		
Study design	In	Prospective, longitudinal, observational (prospective cohort and nested case-control) studies
	Out	Retrospective case-control studies Cross-sectional studies Ecological studies Case studies/case series
Study duration	In	≥ 1 year follow-up
	Out	< 1 year follow-up
Study location	In	Any location
Population	In	Adults (≥ 18 years) and children (4 months to < 18 years) from the general population Individuals at risk of disease (e.g. with impaired glucose tolerance, impaired fasting glucose, the metabolic syndrome, overweight, NAFLD) Studies in which prevalent cases of the disease endpoint of interest at baseline were excluded for data analysis
	Out	Studies targeting individuals with a disease (except for obesity), either untreated or under dietary or pharmacological/surgical treatment for the disease Studies in which prevalent cases of the disease outcome of interest at baseline were not excluded for data analysis
Exposure	In	- Studies providing quantitative estimates of free sugars intake, whether total or from one or more dietary sources (in amount per day, in amount per kg/bw/day, or as % of total energy intake)

		- Studies providing sufficient information to allow quantitative estimates of free sugars intake, whether total or from one or more dietary sources Eating conditions: *ad libitum* Method to assess intake of free sugars: - 24-h urinary excretion of fructose and sucrose - Food records - Diet recalls - FFQs
	Out	- Studies not providing sufficient information to allow quantitative estimates of free sugars intake, whether total or from one or more dietary sources (e.g. studies reporting only on the frequency of consumption of one or more dietary sources of free sugars) Eating conditions: under dietary controlled conditions prior to the dietary intake assessment Method to assess intake of free sugars: - Any other method
Endpoints of interest	In	Endpoints and methods of measurement by target: *Adipose tissue* - Body weight, BMI, waist circumference measured by anthropometry - Body fat, lean body mass measured by neutron activation analysis (NAA), imaging techniques (DXA, MRI, CT), hydrostatic weighing, air displacement plethysmography, BIA or skinfold thickness. - Incidence of overweight/obesity as defined by the authors *Glucose homeostasis* - Static indices of insulin sensitivity and beta-cell function calculated from fasting plasma glucose and fasting serum insulin (e.g. HOMA, QUICKI) - Blood glucose control (HbA1c, fructosamine) - Incidence of type 2 diabetes as defined by the authors - Incidence of impaired glucose tolerance or impaired fasting glucose as defined by the authors *Cardiovascular system* - SBP and DBP (point or 24-h BP) - Incidence of hypertension as defined by the authors - Blood lipid profile (total-c, LDL-c, HDL-c, VLDL-c, fasting TG, apoB100, apoA1, and ratios thereof) - Incidence of dyslipidaemia as defined by the authors - Incidence of stroke [haemorrhagic (intracerebral, subarachnoid) and/or ischaemic; fatal and/or non-fatal] - Incidence of coronary heart disease (fatal and/or non-fatal) - Incidence of myocardial infarction (fatal and/or non-fatal) - Incidence of congestive heart failure - Incidence of cardiac death - Incidence of fatal and/or non-fatal cardiovascular events (composite outcome) - Other endpoints of fatal and/or non-fatal cardiovascular events as defined by the authors *Liver function* - Liver fat accumulation measured by CT, MRI, MRS, or liver biopsies - Incidence of NAFLD or NASH as defined by the authors - Incidence of non-alcoholic liver fibrosis/cirrhosis/liver failure as defined by the authors
	Out	Self-reported body weight, BMI, waist circumference Overall mortality Studies not including at least one of the endpoints listed above
Language	In	Full-text document in English
	Out	Articles with the full text in another language
Publication year	In	Up to March 2018
Publication type	In	Primary research studies (i.e. studies generating new data) reported in full-text articles Primary research studies reported in letters to editors if the information provided is sufficient to allow a scientific evaluation of the results Systematic reviews and meta-analyses[(b)]

	Out	Narrative reviews, expert opinions, editorials and letters to editors not reporting on primary data Meetings' abstracts and posters Conference proceedings PhD theses Grey literature

(a): Prospective studies that compare the effects of two or more interventions which did not use randomization to allocate individuals or clusters to the comparison groups

(b): Systematic reviews, including meta-analyses, on this topic that will be identified during the process of literature screening will be collected for the purpose of reviewing the reference list but will not be considered to contribute to the final number of studies considered eligible unless they also contain original data.

Table 4: Eligibility criteria for human studies to address sub-question 6

Sub-question 6: What is the relationship between the intake of free sugars from all dietary sources and dental caries in the target population?		
INTERVENTION STUDIES		
Study design	In	Randomised controlled trials Non-randomised, comparative studies of interventions[(a)]
	Out	Single-arm intervention studies with no control group
Study duration	In	Studies lasting at least one year for primary dentition and at least 18 months for permanent dentition
	Out	Studies lasting < 1 year for primary dentition and < 18 months for permanent dentition
Study location	In	Any location
Population	In	Adults (≥ 18 years) and children (from birth to < 18 years) from the general population
	Out	Studies exclusively or mainly conducted in individuals with a disease, either untreated or under dietary or pharmacological/surgical treatment for the disease
Intervention	In	Intervention: - a quantitative change in the intake of free sugars, whether total or from one or more dietary sources (in amount per day, in amount per kg/bw/day, or as % of total energy intake) - a change in the intake of one or more dietary sources of free sugars which allows quantification of free sugars intake from those sources Method to assess intake of free sugars: - Controlled feeding (food provided) - 24-h urinary excretion of fructose and sucrose - Food records - Diet recalls - FFQs
	Out	Studies not providing sufficient information to allow quantitative estimates of free sugars intake, whether total or from one or more dietary sources (e.g. studies reporting only on the frequency of consumption of one or more dietary sources of free sugars) Method to assess intake of free sugars: - Any other method
Control (for intervention studies)	In	Differs from the intervention on the amount of free sugars only, so that any effect can be attributed to the type/amount of free sugars consumed
	Out	Differs from the intervention regarding characteristics other than the amount of free sugars which could affect the endpoints (e.g. dental hygiene, fluoridation)
Outcome of interest	In	Indices of dental caries measured by a trained observer
	Out	Dental caries self-reported or reported by parents Surrogate endpoints (e.g. amount of dental plaque; plaque pH)
Language	In	Full-text document in English

	Out	Articles with the full text in another language
Publication year	In	Up to March 2018
Publication type	In	Primary research studies (i.e. studies generating new data) reported in full-text articles Systematic reviews and meta-analyses[(a)]
	Out	Narrative reviews Expert opinions, editorials and letters to the editors Meetings' abstracts and posters Conference proceedings PhD theses Grey literature
OBSERVATIONAL STUDIES		
Study design	In	Prospective, longitudinal, observational (prospective cohort and nested case-control) studies
	Out	Cross-sectional studies Retrospective case-control studies Ecological studies Case studies/case series
Study duration	In	Studies lasting at least one year for primary dentition and at least 18 months for permanent dentition
	Out	Studies lasting < 1 year for primary dentition and < 18 months for permanent dentition
Study location	In	Any
Population	In	Individuals recruited from the general healthy population
	Out	Studies exclusively or mainly conducted in individuals with a disease, either untreated or under dietary or pharmacological/surgical treatment for the disease
Exposure	In	- Studies providing quantitative estimates of free sugars intake, whether total or from one or more dietary sources (in amount per day, in amount per kg/bw/day, or as % of total energy intake) - Studies providing sufficient information to allow quantitative estimates of free sugars intake, whether total or from one or more dietary sources Eating conditions: *ad libitum* Method to assess intake of free sugars: - 24-h urinary excretion of fructose and sucrose - Food records - Diet recalls - FFQs
	Out	- Studies not providing sufficient information to allow quantitative estimates of free sugars intake, whether total or from one or more dietary sources (e.g. studies reporting only on the frequency of consumption of one or more dietary sources of free sugars) Eating conditions: under dietary controlled conditions prior to the dietary intake assessment Method to assess intake of free sugars: - Any other method
Outcome of interest	In	Indices of dental caries measured by a trained observer
	Out	Dental caries self-reported or reported by parents Surrogate endpoints (e.g. amount of dental plaque; plaque pH)
Language	In	Full-text document in English
	Out	Articles with the full text in another language
Publication year	In	Up to March 2018
Publication type	In	Primary research studies (i.e. studies generating new data) reported in full-text articles Systematic reviews and meta-analyses[(b)]

	Out	Narrative reviews Expert opinions, editorials and letters to the editors Meetings' abstracts and posters Conference proceedings PhD theses Grey literature

(a): Prospective studies that compare the effects of two or more interventions which did not use randomization to allocate individuals or clusters to the comparison groups

(b): Systematic reviews, including meta-analyses, on this topic that will be identified during the process of literature screening will be collected for the purpose of reviewing the reference list but will not be considered to contribute to the final number of studies considered eligible unless they also contain original data.

9.2. Literature searches for studies meeting the eligibility criteria

For sub-questions 5 and 6, an extensive literature search will be performed in bibliographic databases. Sources of grey literature and databases of thesis/dissertations will not be searched.

The bibliographic databases listed in Table 5 will be searched in order to identify relevant studies for sub-questions 5 and 6.

Table 5: Bibliographic databases to be searched for relevant studies

Database	Platform	Types of studies
Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	Intervention studies
Cochrane Library. Cochrane Database of Systematic Reviews (CDSR)	Wiley	Systematic reviews
Cochrane Library. Database of Abstracts of Reviews of Effects	Wiley	Systematic reviews
Embase	Elsevier	Systematic reviews, intervention studies, observational studies
PubMed	NLM	Systematic reviews, intervention studies, observational studies
Scopus	Elsevier	Systematic reviews, intervention studies, observational studies

For sub-question 5, literature searches will be performed by type of endpoint. Previous systematic reviews with similar review questions, similar or broader inclusion criteria and appropriate search strategies were identified during the scoping searches (**see Appendix B**). Therefore, date limits will be applied to the searches for sub-question 5 (by endpoint) and sub-question 6 using these systematic reviews as starting point whenever possible. Studies published before these dates will be retrieved by hand-searching the reference lists of the systematic reviews (**Appendix B**) and from existing reports by other authorities/bodies (**Appendix A**). No retrospective date limits will be applied for endpoints for which no existing systematic review can be taken as starting point.

Table 6: Date limits applied to the searches and systematic reviews used as sources of relevant studies

Sub-question	Endpoints	Date limit	Systematic review
5	Adipose tissue	Intervention and observational studies: December 2011	Te Morenga et al., 2013
5	Blood pressure	Interventions: August 2013	Te Morenga et al., 2014
		Observational studies: no date limit	
5	Blood lipids	Interventions: August 2013	Te Morenga et al., 2014

		Observational studies: no date limit	
5	All other endpoints	Intervention and observational studies: no retrospective date limit	
6	Dental caries	Intervention and observational studies: November 2011	Moynihan and Kelly, 2014

Date limits might be changed should new systematic reviews on the topic be identified which are considered to adequately cover the relevant literature. Existing systematic reviews (Appendix B) with narrower inclusion criteria regarding either the exposure (e.g. limited to sugar-sweetened beverages) or the study duration (e.g. SACN, 2015; Sonestedt et al., 2012) will be hand searched.

The search terms that will be used for the exposure and the various endpoints of interest are depicted in Appendix D. The specific search strategies for each database will be developed at a later stage. The performance of the search strings will be tested against the reference lists of the systematic reviews shown in Appendix B.

The output from the searched databases, including all indexed fields per hit (e.g. title, authors, abstract), will be exported into separate Endnote® files, allowing a count of the individual hits per database. All the studies included in the above-mentioned systematic reviews will be added to specific Endnote® libraries. Files will then be combined and duplicate records will be removed.

The files obtained will be transferred into DistillerSR® Web-Based Systematic Review Software (Evidence Partners, Ottawa, Canada) for the selection procedure (see section 9.3).

9.3. Study selection process

The whole selection process will be performed with DistillerSR®. Studies to be included in the review will be selected using a two-step selection procedure:

1) **Screening of title and abstract** to identify potentially relevant studies that will be included for full-text screening, applying the selection criteria described in section 9.1. If the information contained in the title or abstract is not relevant to the research objectives, the article will not be selected for full-text assessment. During the screening process, studies will be categorised into two groups corresponding to the two sub-questions that are the objectives of this systematic review.

   This step will be conducted by WG experts and/or EFSA staff, in duplicate. If there are doubts or divergences which cannot be resolved between the two reviewers, the full article will be screened. If the title and/or abstract make clear that the target disease or surrogate endpoints were not the subject of the investigation, but the words 'adverse effects' or 'side effects' were mentioned (irrespective of whether there were effects or not), the paper will be included to check if these effects had any relation to the target disease or surrogate endpoints. In case of doubt, the article will be included in full-text screening.

2) **Screening of full text** to assess if the article is relevant to the risk assessment.

   This step will be conducted by WG experts and/or EFSA staff, in duplicate, for the references retrieved. Possible divergences will be discussed by the whole WG on sugars, in case these would highlight the need for amendments to the inclusion/exclusion criteria. The content of the full text will be checked against the inclusion and exclusion criteria established in the protocol.

Possible divergences or doubt for inclusion of domain-specific articles will be discussed together with the relevant expert from the WG, also in case these would highlight the need for amendments to the inclusion/exclusion criteria.

Articles reporting solely on digestion, absorption or metabolism (i.e. without reporting on the target disease or surrogate endpoints), or reporting only on endpoints other than those listed in Table 1, will not be included in this research sub-questions but will be flagged for sub-questions 3 and 7, where appropriate.

Screeners will be trained using written documentation on study eligibility. Eligibility criteria will be pilot tested on a subset of records, and refined if prone to misinterpretation. The results of the different phases of the study selection process will be reported in a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009).

9.4. Data extraction from included studies

Data will be extracted from the studies using pre-defined forms that comprise data on the characteristics of the studies (e.g. study design), their key-elements (e.g. population, intervention/exposure, comparator, outcomes/endpoints, setting and duration), results, aspects related to the internal validity of the studies (e.g. confounders, randomisation), and funding source.

The data will be extracted in the original units of measurement, which will be subsequently harmonised to allow data analysis. The authors will be contacted to retrieve additional data if needed.

Clear instructions for extracting data will be developed. The data extraction forms will be created in DistillerSR® (Evidence Partners, Ottawa, Canada) and pilot tested on a subset of studies. The piloting will also be used to identify sources of contextual (i.e. related to the key elements of the studies) heterogeneity. The forms and instructions will be refined if needed.

Data will be extracted from each individual study by one EFSA staff or one WG expert. In the piloting phase, extracted data will be validated by another EFSA staff or WG expert, in order to identify sources of possible errors. The data extraction will be then conducted by one EFSA staff/WG expert. Data quality checks will be performed for each study (section 9.6).

If a full-text document reports on more than one study, the individual studies will be identified at this step to allow for data extraction at individual study level.

In the case of missing or ambiguous data, a decision will be taken by the WG on whether to include or exclude the study.

9.5. Appraisal of the internal validity of the included studies

The internal validity or risk of bias (RoB) of each individual study included in the assessment will be appraised using a customised version of the OHAT/NTP RoB tool, which is suitable for both intervention and observational studies.[5] This tool was developed based on guidance from the Agency for Healthcare Research and Quality (Viswanathan et al., 2012, 2013), the Cochrane risk-of-bias tool for non-randomised studies of interventions (Sterne et al., 2014), the Cochrane Handbook (Higgins and Green, 2011), CLARITY Group at McMaster University (2013), and other sources. The OHAT/NTP RoB tool was developed to provide a parallel approach to the evaluation of the RoB in the context of hazard identification for human risk assessment of chemicals, and to facilitate consideration of risk of bias across evidence streams (i.e. human, animal and mechanistic studies) with common terms and categories for risk of bias rating. For this assessment, the use of the tool will be limited to the aspects relevant to intervention and prospective observational studies in humans.

For each study, the appraisal will be done at outcome level, because for the same study the design and conduct may affect the RoB differently depending on the endpoints measured. Each study will be appraised by two mutually independent experts from the WG ('the reviewers'). Possible discrepancies will be discussed by the whole WG. If upon further discussion the WG cannot reach an agreement on a RoB rating for a particular domain, the more conservative judgment (the highest risk of bias) will be selected.

The OHAT/NTP RoB tool outlines 10 risk of bias questions, grouped in 6 bias domains (selection, confounding, performance, attrition/exclusion, detection, and selective reporting) - plus 'other sources of bias' -, which help identify the practices that may introduce bias (Table 7). Each RoB question addresses aspects relevant to specific study designs, i.e. 8 questions apply to intervention studies and 7 questions apply to prospective observational (cohort and nested case–control) studies (Table 7). Reviewers are required to answer RoB questions by applying a 4-level rating scale (Figure 1).

[5] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

612 The RoB questions and rating instructions provided in the tool will be tailored to the specific sub-
613 questions illustrated in this protocol.

614 **Table 7:** Extracted from OHAT/NTP RoB tool (source: OHAT Handbook - January 9, 2015)[6]

Bias Domains and Questions	Controlled intervention*	Observational
Selection Bias		
1. Was administered dose or exposure level adequately randomized?	X	
2. Was allocation to study groups adequately concealed?	X	
3. Did selection of study participants result in appropriate comparison groups?		X
Confounding Bias		
4. Did the study design or analysis account for important confounding and modifying variables?		X
Performance Bias		
5. Were the research personnel and human subjects blinded to the study group during the study?	X	
Attrition/Exclusion Bias		
6. Were outcome data complete without attrition or exclusion from analysis?	X	X
Detection Bias		
7. Can we be confident in the exposure characterization?	X	X
8. Can we be confident in the outcome assessment?	X	X
Selective Reporting Bias		
9. Were all measured endpoints reported?	X	X
Other Sources of Bias		
10. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	X	X

615 *Includes studies in humans with a controlled exposure including randomized controlled trials and non-randomized intervention
616 studies
617

++	**Definitely Low** risk of bias	There is direct evidence of low risk-of-bias practices (May include specific examples of relevant low risk-of-bias practices)
+	**Probably Low** risk of bias	There is indirect evidence of low risk-of bias practices OR it is deemed that deviations of low risk-of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias.
-/NR	**Probably High** risk of bias	There is indirect evidence of high risk-of-bias practices OR there is insufficient information (e.g. not reported or "NR") provided about relevant risk-of bias practices
--	**Definitely High** risk of bias	There is direct evidence of high risk-of-bias practices (May include specific examples of relevant high risk-of-bias practices)

618

619 **Figure 1:** Answer format for the RoB questions (source: OHAT/NTP RoB tool)[7]

620 The OHAT/NTP RoB tool encourages judging the direction of bias, when possible. Empirical evidence
621 about the direction of bias is discussed for each of the RoB questions. If there is no clear rationale for

[6] https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf
[7] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

judging the likely direction of bias, reviewers are invited to simply outline the evidence and not to attempt a guess. This approach will be followed.

Once customised, the tool will be created in the review management software DistillerSR® to allow web-based appraisal of the studies.

Specific elements identified *a priori* and that will be considered in the assessment of confounding and biases related to the exposure and outcome characterisation are discussed below.

9.5.1. Consideration of potential confounders

Confounding occurs when the relationship between the exposure and disease is to some extent attributable to the effect of another risk factor, i.e. the confounder. There are several requirements for a factor to actually act as a confounder, as described by McNamee (2003) and illustrated below. The factor must:

- be a cause of the disease, or a surrogate measure of the cause, in unexposed people; factors satisfying this condition are called 'risk factors'; and
- be correlated, positively or negatively, with exposure in the study populations. If the study population is classified into exposed and unexposed groups, this means that the factor has a different distribution (prevalence) in the two groups; and
- not be an intermediate step in the causal pathway between the exposure and the disease.

Based on recent publications, the Panel identified *a priori* an indicative list of potential factors that could confound the relationship between the intake of free sugars and surrogate endpoints for adipose tissue, glucose homeostasis, cardiovascular system, and liver function, and the relationship between the intake of free sugars and incidence of overweight/obesity, T2DM, cardiovascular disease-related endpoints, and liver disease-related endpoints: age, sex, race/ethnicity, education (or education of the parents for studies in children), smoking habits, physical activity, daily energy intake, alcohol consumption (Figure 2).

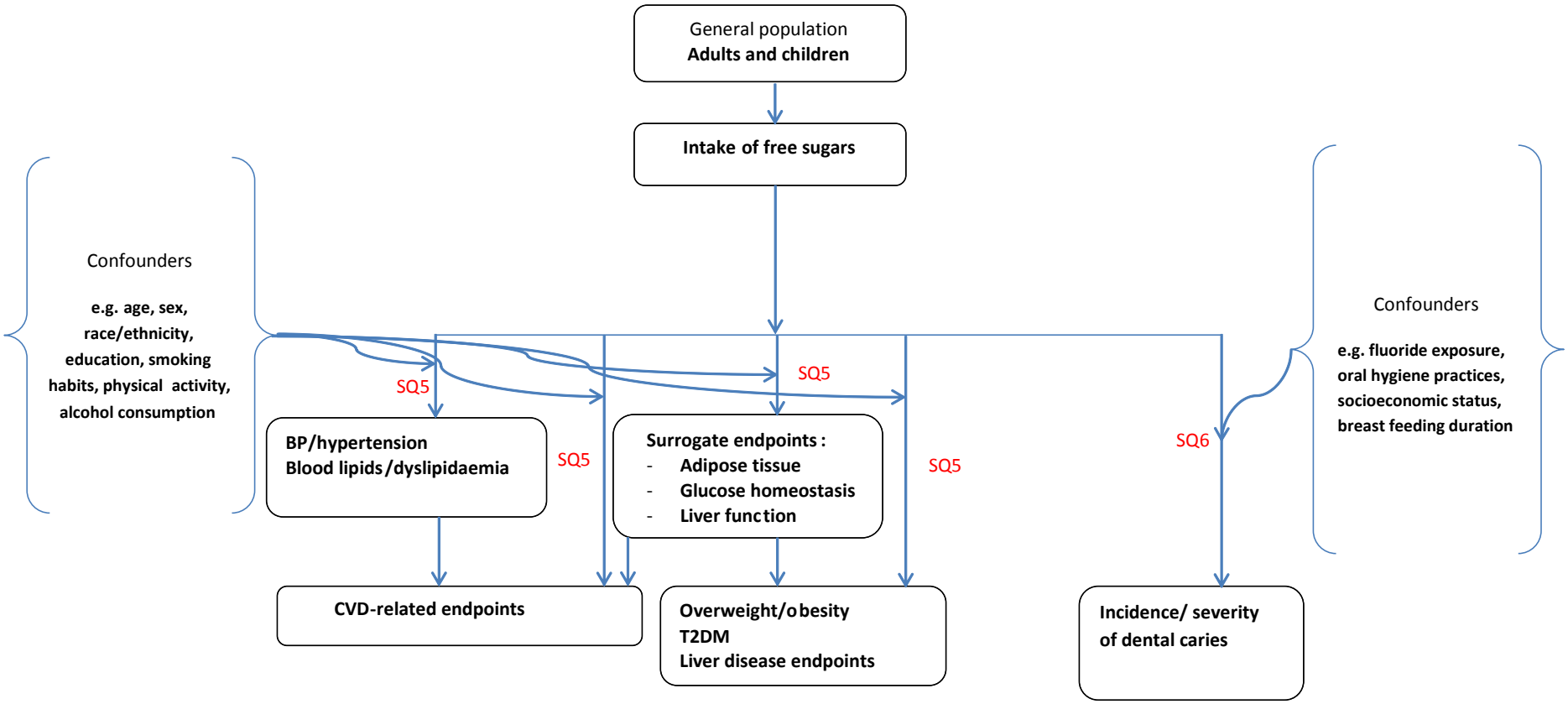
The Panel also identified *a priori* an indicative list of potential factors that could confound the relationship between the intake of free sugars and dental caries: fluoride exposure (e.g. water fluoride, use of fluoride toothpaste, supplements), oral hygiene practices, socioeconomic status, and breast feeding duration for studies on young children.

When assessing RoB in observational studies, the reviewers will consider, for each study, whether these factors can confound the association on a case-by-case basis. Additional confounders may be identified by the reviewers. The reviewers will consider whether the confounding variables were measured reliably and consistently within each study and whether the design and/or the data analysis adequately accounted for potential confounding (e.g. multivariable analysis, stratification).

Blood pressure, blood lipids and adipose tissue-related surrogate endpoints could be considered mediators in the causal pathway between the intake of free sugars and cardiovascular disease-related endpoints. In this context, adjustment for blood pressure, blood lipids or body weight/BMI could be considered a potential source of over-adjustment bias. The same applies to body weight/BMI and daily energy intake in relation to the incidence of overweight/obesity, T2DM, and liver disease-related endpoints.

The OHAT/NTP RoB tool does not include a separate question for confounding in human intervention studies because randomisation and allocation concealment should adequately address the issue of confounding. It recognizes, however, that in some cases appropriate procedures for randomisation and allocation concealment may fail in accounting for confounding. For example, in the context of this assessment, confounding could be a concern if there are important differences among study groups in baseline characteristics. In accordance with the OHAT/NTP guidance, for intervention studies where confounding is strongly suspected despite the fact that randomisation and allocation concealment are rated at "probably low" or "definitely low risk of bias", confounding will be addressed under "other potential threats to internal validity" (OHAT/NTP, 2015).

Figure 2: Conceptual framework for the systematic reviews on the intake of free sugars and surrogate/disease endpoints



9.5.2. Confidence in the exposure characterisation

The exposure of interest for the assessment is the daily intake of free sugars from all dietary sources. It is acknowledged however, that few (if any) of the available individual studies investigating the health effects of dietary sugars may have used the definition of free sugars as described in this protocol to characterise the intervention/exposure. In this context, the confidence in the exposure characterisation that will be assessed in relation to the RoB of individual studies refers to the confidence on the methods used to characterise the exposure to free sugars or any component of this as defined by the authors, and not the extent to which the exposure investigated on each study reflects the intake of free sugars from all dietary sources as defined in this protocol. The latter aspect will be discussed when integrating and weighing the evidence in light of the identified uncertainties to derive a daily intake of free sugars from all dietary sources which is not associated with adverse health effects (see section 12).

In assessing risk of bias, reviewers will consider the risk of errors in the estimate of sugar intake for individuals, and related risks of misclassification of individuals according to their exposure. The accuracy of sugar intake estimates may be affected by i) the method used to assess sugar intake (e.g. 24-h urinary excretion of fructose and sucrose vs dietary records vs diet recalls vs FFQs; specificity of FFQs for the exposure of interest; validation; number of days recorded); ii) the accuracy of 24-h urine collections and the accuracy of reporting dietary intakes (e.g. self vs dietitian assisted compilation of FFQs); iii) systematic changes in habitual diet prior to the intake assessment. The reviewers will consider the resulting misclassification in appraising the studies.

9.5.3. Confidence in the outcome assessment

Confidence in the outcome requires valid, reliable, and sensitive methods to assess the outcome applied consistently across groups (OHAT/NTP, 2015). Outcome misclassification or measurement error may be unrelated to the exposure (non-differential) or related to the exposure (differential).

Factors that will be considered by the reviewers while assessing bias in relation to the outcome assessment include: 1) the objectivity of the outcome assessment, 2) the consistency in measurement of endpoints, and 3) the blinding of the outcome assessors (for knowledge of the exposure) (OHAT/NTP, 2015).

9.5.4. Summarising the internal validity of each individual study

Each study will be reported using a tabular summary form which will include the key elements of the study and a summary of the results of the critical appraisal.

When all the studies have been summarised in this way, the WG will consider whether and how to combine the scores from the RoB questions at the level of individual studies. The WG may consider using an algorithm to combine the questions in a weighted or unweighted manner: if so, the rationale for the chosen algorithm will be documented. Alternatively, the RoB scores may be kept separate for each RoB question and taken into account in the synthesis of evidence. The results of the RoB assessment will be taken into account in the weight of evidence assessment and uncertainty analysis; sections 11 and 12).

9.6. Synthesis of the evidence

Data from included individual studies will be considered separately for each type of study design and for each disease and surrogate endpoint to derive single lines of evidence.

Information on inclusion criteria, RoB assessment and endpoints as extracted from the individual studies will be summarised in evidence tables. Data quality checks will be performed for each study. For each variable, the proportion of missing observations will be assessed; range checks will be carried out for all included variables to ensure that all values are reasonable; categorical variables will be tabulated, and key variables will be cross-tabulated to check for internal consistency. For intervention studies, results from intention-to-treat analyses will be preferred over per-protocol analyses if both are reported. In the case of missing data, flexible and transparent strategies will be pursued, such as requesting missing data from the authors, re-doing the analysis or placing the original results in adequate context according to the feasibility and adequacy of these approaches on

a per-study basis. Effect estimates such as relative risks and odds ratios for dichotomous variables for disease endpoints, and differences in means for continuous variables for surrogate endpoints along with measures of their statistical precision (usually 95% confidence intervals) will be extracted from the studies and reported in the assessment.

Statistical heterogeneity across study-specific findings will be taken into account in the statistical model and evaluated by visual inspection of forest plots and the I^2 statistic (Higgins and Thompson, 2002; Higgins et al., 2003), and an attempt will be made to identify its sources.

Whenever data allow for a meaningful quantitative synthesis of the evidence, effect estimates from intervention and observational studies will be pooled separately and assessed through meta-analysis and dose-response meta-analysis, using most recent biostatistical methods (Orsini et al. 2012; Discacciati et al. 2015; Crippa & Orsini, 2016). Dose-response meta-analysis is a statistical technique that aims to characterise the smooth and gradual change in non-linear responses along the range of a quantitative exposure using aggregated data from several studies. Dose-response meta-analyses of the relation between free sugars intake and human health will be performed separately on intervention and observational studies and on specific dichotomous (disease) endpoints or continuous surrogate endpoints, using fixed- and random-effects models as appropriate.

Meta-analyses will also be carried out in selected study subgroups, using both unadjusted and adjusted models. For intervention studies, an effort will be made to assess the dose-response relations between free sugars intake and the various endpoints. Expected major sources of heterogeneity or effect modification will be taken into consideration when assessing the association between free sugar intake and disease/surrogate endpoints. In addition to the meta-analyses stratified by study design (intervention versus observational studies), subgroup/stratified analyses will be performed according to age, gender, type of dentition (for dental caries), type of sugar/food source, country or continent, and other factors suspected or known to modify the association between free sugars intake and the endpoints assessed. Subgroup and sensitivity analyses will also be performed according to the risk of bias of the included studies, the degree of control for confounding, the methodology and quality of the exposure assessment, duration of follow-up for both the intervention and the observational studies, and possibly by the source of study funding. If needed, sensitivity analyses will be performed to evaluate the robustness of the findings and the possible influence of different biases on the summary pooled effect estimates (Arah, Cibah and Greenland 2008; Rothman et al, 2012; Corbin et al, 2017). Influence analysis will be carried out by examining whether removal of single studies influences the results of the meta-analyses, and the reasons underlying such an influence on the effect estimates, if any (Rothman et al, 2012).

The possibility of publication bias will be investigated using one or more of the following approaches: a) visual inspection of funnel plots to investigate the association between study size and effect size (Light and Pillemer, 1984); b) Egger's regression test (Egger et al., 1997; Sterne and Egger, 2005); and c) trim-and-fill analysis (Duval and Tweedie, 2000; Rothstein et al., 2005) following the approach of Peters et al. (2007).

If there are studies that are relevant but cannot be included in meta-analyses (e.g. due to differences in study design), their contribution to the assessment will be integrated with the results of the meta-analysis by a weight of evidence approach (section 11). If none of the relevant studies for an effect are suitable for meta-analysis, evidence synthesis for that effect will be performed by a weight of evidence approach (section 11).

9.7. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed as detailed above (section 9.2) will be repeated approximately three months before the planned date of endorsement of the draft opinion by the Panel. Databases and keywords will be those of the original searches. Date limits will be defined based on the cut-off date of the preceding searches. The papers retrieved by these additional searches will be screened for relevance applying the same criteria.

Relevant studies will be reviewed by the Working Group experts and their contribution to the assessment will be integrated (with the results of a meta-analysis or otherwise) by a weight of evidence approach (section 11), but will not be considered for inclusion in any meta-analysis.

10. Methods to answer sub-question 7

In order to address the mode(s) of action for possible adverse health effects of free sugars identified in sub-question 5, background information will be gathered by the WG experts and EFSA staff through a narrative review. Recent textbooks, authoritative reviews and research papers retrieved through searches in bibliographic databases, and selected on the basis of their relevance, will be used as sources of information. The mode of action by which sugars can contribute to the development of dental caries (sub-question 6) is considered to be well known.

11. Methods for integrating and weighing the evidence to set a level of intake for free sugars

Integration of evidence will be performed at a number of levels and by different methods, according to what is appropriate given the available evidence. For sub-questions 5 and 6, the following integration steps may be needed:

- Where appropriate, different studies for the same endpoint will be combined by meta-analysis.
- Results from meta-analysis will be integrated with evidence from other relevant studies on the same endpoint (if there are any that could not be included in the meta-analysis) by a weight of evidence approach.
- For effects where meta-analysis is not feasible, relevant studies will be integrated by a weight of evidence approach.
- Where appropriate, results for different endpoints of the same type (e.g. disease and surrogate endpoints relating to the same chronic disease) may be integrated by a weight of evidence approach.

The outcome of sub-questions 5 and 6 will be integrated with the outcomes of sub-questions 3, 4 and 7 by a weight of evidence approach. The results of this will form the Panel's conclusions on the levels of intake for free sugars: this may result in more than one level of intake, depending on whether there is material variation between effects and/or population groups.

The results of sub-question 1 (levels of free sugars in foods and beverages) will be integrated by calculation with food consumption data to address sub-question 2, resulting in intake assessments for the European population.

Risk characterisation will be performed by comparing results of the intake assessment (from sub-questions 1 and 2) with the levels of intake for free sugars from all dietary sources which are not associated with adverse health effects (from sub-questions 3, 4, 5, 6 and 7).

In several of the steps described above, integration will be performed by a weight of evidence approach using expert judgement. The methods will vary, depending on the evidence to be integrated and the specific considerations involved. In each case, the principles of EFSA's guidance on weight of evidence will be applied (EFSA, 2017). Evidence will be organised into lines of evidence, where helpful. Relevance, reliability (including the risk of bias evaluations described in earlier sections) and consistency will be taken into account when weighing the evidence. Formal (EFSA, 2014) or semi-formal (EFSA, 2018) methods for expert knowledge elicitation (EKE) will be used where appropriate. Detailed protocols will be established for each stage of the weight of evidence process before it is performed. Each stage of the process will be documented, including the reasons for any deviations from the protocol.

12. Evaluating the uncertainty in the body of evidence

Uncertainties in the estimates of free sugar intake in European countries may arise from inaccuracies in mapping food consumption data according to the FoodEx2 classification, from analytical errors or from errors in estimating the levels of total sugars in the national food composition tables, from errors in attributing levels of free sugars to foods from their content of total sugars, and from replacing missing values by values of similar food groups in the free sugars intake estimation process. These uncertainties may, in principle, result in both too high and too low estimates of free sugars intake.

For disease and surrogate endpoints, once the individual studies are appraised for internal validity and after synthesising the evidence for each endpoint, line of evidence (i.e. intervention studies separately from observational studies) and sub-question, the uncertainties in the body of evidence will be identified, including factors such as the consistency of results, the precision of effect/association estimates and/or dose–response models, the internal and external validity (directness, generalisability, applicability) of the included studies, and gaps in knowledge.

Uncertainty analysis will be performed following approaches recommended by EFSA (2018) for case-specific assessments. Uncertainty affecting each sub-question will be identified, and taken into account when evaluating the overall uncertainty for the main outcomes of the assessment: levels of intake of free sugars not associated with adverse health effects and risk characterisation. The overall uncertainty will be evaluated by expert judgement using either formal or semi-formal EKE methods (EFSA 2014, EFSA 2018). For the levels of intake of free sugars not associated with adverse health effects, the weight of evidence (section 11) and uncertainty analysis may be addressed together in a single EKE procedure. Detailed protocols cannot be specified in advance, but will be established for each stage of the uncertainty analysis before it is performed. Each stage of the process will be documented, including the reasons for any deviations from the protocol.

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Abbreviations

AI	Adequate intake
AUSNUT	Australian food and nutrient database
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BP	Blood pressure
CIGMA	Continuous infusion of glucose with model assessment
CT	Computed tomography
CVD	Cardiovascular disease
DRV	Dietary reference value
DBP	Diastolic blood pressure
DXA	Dual-energy X-ray absorptiometry
FBDG	Food-based dietary guidelines
FFQ	Food frequency questionnaire
FoodEx2	Standardised food classification and description system developed by EFSA
FSANZ	Food Standards Australia New Zealand
FSIGT	Frequently sampled intravenous glucose tolerance tests
HDL-c	High-density lipoprotein cholesterol
HFCS	High-fructose corn syrups
HOMA	Homeostasis model assessment
LDL-c	Low-density lipoprotein cholesterol
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver diseases
NAA	Neutron activation analysis
NASH	Non-alcoholic steato-hepatitis
NME	Non-milk extrinsic
NTP	National toxicology program
OGTT	Oral glucose tolerance test
OHAT	Office of health assessment and translation
PAL	Physical activity level
PC	Prospective cohort studies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUICKI	Quantitative insulin sensitivity check index
RI	Reference Intake range
RoB	Risk of bias
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TG	Triglycerides

1045	ToR	Terms of reference
1046	Total-c	Total cholesterol
1047	UL	Tolerable upper level of intake
1048	VAT	Visceral adipose tissue
1049	VLDL-c	Very low-density lipoprotein cholesterol

Appendix A – Overview of dietary reference values and recommendations

In 2010, in the context of setting dietary reference values for carbohydrates and dietary fibre, the European Food safety Authority (EFSA, 2010) concluded that the available data **did not allow the setting of a UL for total or added sugars**, neither an Adequate Intake (AI) nor a Reference Intake range (RI). However evidence on the relationship between patterns of consumption of sugar-containing foods and **dental caries**, **weight gain** and **micronutrient intake** should be considered when establishing nutrient goals for populations and recommendations for individuals and when developing food-based dietary guidelines (FBDG).

The evidence-based Guideline of the German Nutrition Society (GNS) on carbohydrate intake and prevention of nutrition-related diseases (GNS, 2012) recommended reducing the consumption of SSBs, but did **not provide a quantitative limit for sugar intake** or any components of this. The basis for this recommendation was probable evidence that high consumption of SSBs increases the risk of obesity and type 2 diabetes in adults, and the high consumption of SSBs particularly among adolescents and young adults in Germany.

The Nordic Nutrition Recommendations (NNR, 2012) limited the intake of **added sugars** (sucrose, fructose, and starch hydrolysates) to **< 10% of the total energy intake** for the general population to ensure adequate intakes of micronutrients and dietary fibre (**micronutrient density of the diet**), which was found particularly important for children and persons with a low energy intake. It was also recommended to limit the consumption of SSBs because associated with an increased **risk of type-2 diabetes** and **excess weight-gain**, and to avoid frequent consumption of sugar-containing foods to reduce the **risk of dental caries**.

The UK Scientific Advisory Committee on Nutrition (SACN, 2015) recommended that the average population intake of **free sugars** (all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and unsweetened fruit juices) should not exceed **5% of total energy intake** for age groups from 2 years upwards. Evidence from intervention studies showing that increasing sugars intake **increases energy intake** in individuals consuming an *ad libitum* diet and that SSBs beverages are linked to **weight gain** in children and adolescents, and evidence from prospective cohort studies showing that the consumption of sugars is associated with increased **risk of dental caries** and intake of SSBs are associated with an **increased risk of type 2 diabetes** mellitus were at the basis of this recommendation.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) issued an opinion on the establishment of recommendations on sugar intake (ANSES, 2016). The opinion focused on the metabolic effects of sugars in food, whether naturally present or added, and their involvement in the development of chronic diseases (metabolic diseases, cancer and cardiovascular diseases). ANSES set an upper intake limit for **total sugars** of **100 g/day** for the adult healthy population, which excludes lactose and galactose naturally present in milk and dairy products. The upper intake limit was calculated from the minimum daily consumption of fructose (50 g) for which a significant increase in **blood concentrations of triglycerides** was observed in intervention studies, and considering that an intake of 50 g of fructose corresponds to an intake of 100 g of sucrose.

The Institute of Medicine of the US National Academy of Sciences (IOM, 2002) concluded that there was **insufficient evidence to set a UL for added sugars** (sugars and syrups that are added to foods during processing or preparation). However, a maximal intake level of **≤ 25 % of total energy intake** was suggested to prevent the displacement of foods that are major sources of essential micronutrients (**micronutrient density of the diet**).

The 2015–2020 Dietary Guidelines for Americans (HHS & USDA, 2015) recommended that individuals aged 2 years and older should derive **< 10 % of total energy intake** from **added sugars** in order to achieve healthy eating patterns within calorie limits (**micronutrient density of the diet**). This recommendation was based on food pattern modelling and national data on intakes of calories from added sugars.

The World Health Organisation (WHO) appraised the evidence available on the effects of **free sugars** on the risk of non-communicable diseases in adults and children, with a particular focus on **weight gain** and **dental caries** (WHO, 2015). The WHO recommended reducing the intake of free sugars to

< 10% of total energy intake in both adults and children, with a **conditional** recommendation to reduce it further to **< 5% of total energy intake**.

Finally, two professional associations have issued recommendations on sugar intake for children only (up to 18 years of age).

The American Heart Association (AHA) reviewed the scientific evidence on the cardiovascular health effects of **added sugars** in **children** (AHA, 2016). Strong evidence was found to support an association between the intake of added sugars and **increased cardiovascular disease risk** in children through **increased energy intake**, **increased adiposity**, and **dyslipidemia**. AHA provided recommendations that **added sugars** (all sugars used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table) should be consumed up to a **maximum amount** of **25 g per day** by **children > 2 years** of age, and **avoided** by **children <2 years** of age.

In 2017, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition (2017), reviewed the scientific evidence on the relationship between sugars intake and: a) the development of sweet taste or flavour preference, and b) health outcomes. The Committee concluded that a preference for sweet taste is driven by an interplay of many factors and that the association between high consumption of SSBs in early and late childhood could not be demonstrated to be causal. Building on the conclusions reached by WHO (2015), SACN (2015) and the AHA (2016) regarding the effect of sugars intake and different health outcomes in paediatric populations, the Committee recommended that intakes of **free sugars** should be reduced and minimised with a desirable **upper limit of <5% energy intake in children and adolescents** aged 2–18 years. This represents 15 to 28 g of free sugars for girls and 16 to 37 g for boys. Intakes should be **even lower in infants and toddlers <2 years**.

A tabulated overview of these recommendations is given in Table A1.

Table A1. Summary of existing recommendations on sugar intake

Guideline	Target population	Sugar fraction	Recommendation	Basis (endpoint)	Other endpoints assessed	Review method
EFSA, 2010	General population	Added sugars	Consider when setting FBDGs	Dental caries Body weight Micronutrient density	Glucose homeostasis, risk of T2DM, blood lipids, blood pressure, CVD risk	Narrative
GNS, 2012	General population	SSBs	Limit consumption	Obesity Risk of T2DM	BP/hypertension, metabolic syndrome, CHD risk, cancer	Systematic
NNR, 2012	General population	Added sugars	<10E%	Micronutrient density	Dental caries (frequency of intake), weight gain and risk of T2DM (SSBs), glucose homeostasis, blood lipids, blood pressure, CVD risk, uric acid	Systematic
SACN, 2015	General population (>2 years)	Free sugars	≤ 5E%	Energy intake	Dental caries (frequency of intake), weight gain and risk of T2DM (SSBs), blood lipids, blood pressure, CHD, glucose homeostasis	Systematic
ANSES, 2016	Adults	Total sugars	100 g/day	Fasting triglycerides	Weight gain, glucose homeostasis, blood lipids, intrahepatic lipids and risk of NAFLD, uric acid, blood pressure	Systematic
IoM, 2002	General population	Added sugars	<25E%	Micronutrient density	CHD risk, energy intake, body weight, blood lipids, cancer	Narrative
DGA, 2015	General population	Added sugars	<10E%	Micronutrient density	-	Food pattern modelling and national data on added sugars intake
WHO, 2015	General population	Free sugars	<10E% <5E% conditional	Body weight Dental caries	-	Systematic
AHA, 2016	Children	Added sugars	25 g/day ≥ 2 years Avoided < 2 years	Energy intake Adiposity Dyslipidaemia CVD risk	Micronutrient density, blood pressure, risk of NAFLD, glucose homeostasis, risk of T2DM	Narrative
ESPGHAN, 2017	Children	Free sugars	≤ 5E% ≥ 2 years (lower for < 2 years)	Dental caries Weight gain (SSBs) CVD and T2DM (fructose)	Preference for sweet taste	Narrative/systematic

Appendix B – Systematic reviews and meta-analysis on the relationship between added/free sugars and their sources and surrogate/disease endpoints

A scoping literature search was performed to identify systematic reviews and meta-analysis published in English since 2009 addressing the health effects of added sugars/non-milk extrinsic sugars/free sugars or any of its dietary sources.

The full list of references identified is reported in Table B1 together with the specific exposure and outcome(s) of interest. All reviews for which the exposure of interest was added, free or total sugars from all dietary sources are presented in Table B2. Based on the inclusion criteria identified for sub-questions 5 and 6 (see section 9.1), reviews having the same or wider inclusion criteria were used as a basis to update or build new literature searches (see section 9.2).

Table B1. Overview of systematic reviews and meta-analysis published since 2009 on the relationship between sugars and their sources and surrogate/disease endpoints

Reference	Outcome (population subgroup)	Exposure
Anderson, 2009	Caries (adults and children)	Sucrose including sucrose-based carbonated soft drinks, baked goods, sweets and table sugar, as added to other foods and drinks.
Avery, 2015	Obesity (children)	Sugar-sweetened beverages (SSBs)
Bucher della Torre, 2016	Obesity (children)	SSBs
Chung, 2014	Liver health (adults)	Fructose
Fattore, 2017	Blood lipids, blood pressure (adults)	Free sugars (fructose, sucrose, and glucose)
Gibson, 2008	Obesity (adults and children)	Sugar-sweetened soft drinks (SSD)
Gibson, 2013	Blood lipids, blood pressure, glucose metabolism (adults)	Sucrose
Greenwood, 2014	Risk of T2DM	SSD
Huang, 2014	Risk of CVD	SSBs
Imamura, 2015	Risk of T2DM	SSB, fruit juice
Jayalath, 2014	Blood pressure	Fructose-containing sugar (high-fructose corn syrup, sucrose, and fructose)
Jayalath, 2015	Blood pressure	SSBs containing free or bound fructose
Kelishadi, 2014	Blood lipids, Blood pressure, Glucose metabolism	Fructose
Keller, 2015	Blood lipids, Blood pressure, Glucose metabolism, Risk of CVD	SSBs
Kim, 2016	Blood pressure	SSBs and artificially-sweetened beverages
Ma, 2015	Obesity (adults and children)	Fructose, glucose, SSB, HFCS
Malik, 2010	Risk of T2DM	SSBs
Malik, 2013	Obesity (adults and children)	SSBs
Malik, 2014	Blood pressure	SSBs
Moynihan, 2014	Dental caries (adults and children)	Total sugars, free sugars, added sugars, sucrose, NME sugars
Pérez-Morales, 2013	Obesity (children)	SSBs
SACN, 2015	Blood lipids, blood pressure, dental caries, glucose metabolism, obesity, risk of CVD, risk of T2DM	Total carbohydrate, sugars reported as a nutrient (fructose, sucrose, lactose, glucose), table sugar and other extrinsic sugars (syrups), food format (solid vs. liquid, which includes SSBs)

Sonestedt, 2012	Blood lipids, blood pressure, glucose metabolism, risk of CVD, risk of T2DM	SSBs, sugars, sucrose and fructose
Te Morenga, 2013	Obesity (adults and children)	Free sugars
Te Morenga, 2014	Blood lipids, blood pressure	Sugar (sucrose) or free sugars
Wang, 2014	Blood lipids	Fructose
Xi, 2014	Risk of T2DM	Fruit juice
Xi, 2015	Blood pressure, risk of CVD	SSBs
Zeng, 2015	Obesity (adults and children)	SSBs

Table B2. Selected systematic reviews with research question partially or completely overlapping with the present work.

	Sub-question 5					Sub-question 6
Systematic review	**Fattore, 2017**[8]	**SACN, 2015**	**Sonestedt, 2012**	**Te Morenga, 2013**	**Te Morenga, 2014**	**Moynihan, 2014**
Endpoints	BP, blood lipids and body weight	All	Glucose metabolism, BP, blood lipids, risk of T2D, risk of CVD	Obesity	BP, blood lipids	Caries
Databases	PubMed/MEDLINE, EMBASE, Cochrane Library Hand search	Medline MEDLINE In-Process & Other Non-Indexed Citations Embase CAB Abstracts ISI Web of Science BIOSIS The Cochrane Library Hand search	PubMed SveMed+	OVID Medline, Embase PubMed, CiNAHL, Scopus, Web of Science	OVID Medline, Embase PubMed, CiNAHL, Scopus, Web of Science Grey literature Hand search	MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, LILACS, CNKI, Wanfang South African Department of Health databases
Search dates	Up to 22 October 2015	1990-December 2010	Jan 2000-Oct 2010 Update Nov 2010-Dec 2011	Up to December 2011	1960 to August 2013	1950-Nov 2011
Language limit	English	English	English or a Nordic language	English	English	No limit
Study type	Intervention studies	RCT PC	RCT PC	RCT PC	RCT	Intervention, cohort, population, or cross-sectional
Study duration	≥ 2wks	RCT > 6 wks (≥ 3 d for energy intake/satiety) PC > 3 y	RCT ≥ 4 weeks (drop out ≤ 50%) PC ≥ 4 y	RT ≥ 2 wks PC ≥ 1 y	RCT≥ 2 wks	
Population	Adults	Adults/children	Adults/children	Adults/children	Adults/children	Adults/children

[8] Not used as primary source of information as the endpoints were assessed under isocaloric conditions

Appendix C – Questionnaire to National Competent Authorities of European countries

NAME:

COUNTRY:

AFFILIATION:

E MAIL:

DATE:

- The EFSA's food composition database was compiled as a deliverable of the procurement project "Updated food composition database for nutrient intake" delivered in 2013 (Roe et al., 2013). Fourteen national food database compiler organisations participated in this data collation project, providing information from national food composition databases up to 2012. Within the EFSA's food composition database, 12 countries provided data on **total sugars**[9] covering about 1290 FoodEx2 codes. Data on **added sugars**[10] was scarce and mostly indicated their absence in certain foods. No data on **free sugars**[11] were reported.

- In contrast to dietary reference values (DRVs) or recommended nutrient intakes, Food-Based Dietary Guidelines (FBDGs) are the expression of the principles of nutrition education mostly as foods. They represent the form in which advice is provided to people to assist them in selecting a diet to meet their needs for health and to cover their nutrient requirements. In setting FBDG for individual countries or regions, it is important to prioritise those nutrients consumed at levels not in accordance with DRVs and for which there is evidence of an important health relationship in that specific country or region.

In the context of setting a level of intake of free sugars from all dietary sources which is not associated with adverse health effects, EFSA would like, through this questionnaire, to gather information on the following:

a) National food composition data which has become available after 2012, with a focus on **total sugars**
b) National food composition data on **added/free sugars** if available, together with the methods used to estimate **added/free sugars** in foods
c) The micronutrients of public health concern (i.e. for which intakes below the reference values have been identified in one or more age groups) at national level, used to set national dietary recommendations and FBDGs
d) Data available at national or regional level (e.g. from national or regional food consumption surveys) on:
   - Intake of **total/added/free sugars**;
   - Biochemical markers of micronutrient status and/or micronutrient density of the diet in relation to the consumption of **total/added/free sugars**

To answer this questionnaire, please tick the relevant boxes. If you have doubts or queries in relation to the compilation of this questionnaire, please contact us at: nda@efsa.europa.eu

[9] Include all monosaccharides (glucose, fructose, galactose) and disaccharides (sucrose, lactose, maltose, trehalose), whatever the source. For packaged foods with a label, this information is mandatory in Europe.
[10] Include all sugars (mono- and disaccharides) used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table
[11] Include all monosaccharides and disaccharides added to foods by the manufacturer, cook, and consumer plus sugars naturally present in honey, syrups, and fruit juices

1. Did your country participate in the EFSA's procurement project "Updated food composition database for nutrient intake" (CFT/EFSA/DCM/2011/03)[12]?

   ☐ yes ☐ no

   If the answer is no → please go directly to question No. 3

2. Has your national food composition database been updated since 2012?

   ☐ yes ☐ no

   If the answer is yes, please provide the link to a website where the database can be downloaded from or a contact address/details of the person(s) responsible for the maintenance/update of the database

3. Does your national food composition database contain information on **added sugars** and/or **free sugars**?

   ☐ yes ☐ no

   If the answer is yes, please specify in detail the methodology that has been used to estimate the content of added sugars and/or free sugars in foods

4. Please specify the last national food consumption survey(s) carried out in your country, indicating the year (or time frame) in which the survey was conducted, the method used for data collection (food diaries, food records, 24-h dietary recalls, other), the number of days in which data was collected for each subject, and the age group(s) included in the survey. Regional food consumption surveys should only be indicated if they targeted specially infants (up to 12 months of age). Food consumption surveys using food–frequency questionnaires for data collection should not be indicated.

Name of survey	**Type of survey (National/regional)**	**Year (range)**	**Method for data collection**	**Number of days/subject**	**Age groups included**

*Add as many rows as needed

5. Please indicate whether there are publications available (in any language) on the intake of total sugars, added sugars, and/or free sugars in your country at national level (from the most recent national food consumption surveys):

Author/year	**Total sugars**	**Added sugars**	**Free sugars**
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no

*Add as many rows as needed

Please provide the full list of references

[12] Final report available at http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2013.EN-355/epdf

6. Does your country have some type of Food-Based Dietary Guidelines (FBDG)?

☐ yes ☐ no

Please specify the **national** FBDG available in your country, indicating who was involved in their development (government bodies, scientific societies, industry, on-profit organisations, other) and provide and link to the full text of the FBDGs, if available. If more than one **national** FBDG is available in your country (e.g. established by different bodies; FBDG targeting only specific age groups), use as many rows as needed.

a) FBDG's name ; Body/organisation ;

b) FBDG's name ; Body/organisation ;

c) FBDG's name ; Body/organisation ;

Please indicate where the FBDGs in your country can be found (e.g. recommendations, reports, websites…):

If possible, please attach a copy of each FBDG for your country or provide the link to a website where they can be downloaded from or a contact address. Please also provide a link to an English translation if available.

If more than one national FBDG is available in your country, please answer questions 7 to 17 for each FBDG available, clearly indicating the FBDG to which each answer refers to.

7. To which population groups are the FBDG in your country directed?
Please note that age ranges below are only indicative

☐ General population
☐ Old adults (>65 years)
☐ Adults (18-65 years)
☐ Adolescents (14-18 years)
☐ Others
☐ Infants (up to 12 mo)
☐ Young children (1-3 years)
☐ Pre-school children (3-6 Years)
☐ Schoolchildren (6-14 years)
☐ Pregnant women
☐ Lactating women

8. In which year were (the most recent) FBDG established:
9. In which year were they most recently updated?
10. Are the FBDG evaluated and/or monitored?

☐ yes ☐ no

if yes, please specify:

11. What is the origin of the FBDG used in your country?

11.1 ☐ fully translated from the CINDI dietary guide, WHO

11.2 ☐ fully translated FBDG from other country, please specify the country:

11.3 ☐ specially developed for your country

11.4. ☐ adapted for your country, please specify which FBDG were taken as basis:

If the answer is 11.1 or 11.2 → please go directly to question No. 18

12. Which dietary reference values (nutrient based recommendations, recommended daily intakes etc.) were used in assessing adequacy of the diet?

☐ Not assessed

☐ Values from own country

☐ Values from other country/authoritative body: please specify

13. Please identify the micronutrients of public health importance for the population (or specific subgroups thereof) that were consumed at levels below the dietary reference values in your country, if any:

☐ Vitamin A
☐ Thiamine (Vitamin B1)
☐ Riboflavin (Vitamin B2)
☐ Niacin (Vitamin B3)
☐ Folate (vitamin B9)
☐ Cobalamin (vitamin B12)
☐ Vitamin C
☐ Vitamin D
☐ Vitamin E
☐ Vitamin K
☐ Other vitamins:

☐ Calcium
☐ Copper
☐ Iodine
☐ Iron
☐ Magnesium
☐ Selenium
☐ Zinc
☐ Other minerals

Please specify how these inadequate intakes were identified an whether these were based on median intakes, mean intakes or otherwise:

If no micronutrient is identified → go directly to question No. 14

14. Please identify the population groups consuming levels of micronutrients below the dietary reference values in your country:

☐ General population. Micronutrients:

☐ Infants. Micronutrients:

☐ Young children. Micronutrients:

☐ Pre-school children. Micronutrients:

☐ Schoolchildren. Micronutrients:

☐ Adolescents. Micronutrients:

☐ Adults. Micronutrients:

☐ Old adults. Micronutrients:

☐ Others . Micronutrients:

15. Were dietary reference values (nutrient based recommendations, recommended daily intakes, etc.) limiting the intake of total sugars, added sugars or free sugars taken into account when developing FBDGs in your country?

☐ yes ☐ no

16. Were diet-related health problems in your country taken into account when developing FBDG in relation to the consumption of total /added/free sugars?

☐ yes ☐ no (if "no" → go directly to question No. 17)

17. Which diet-related health problems were considered to develop recommendations for limiting the intake of total /added/free sugars consumption in your country? Please tick as many as needed

☐ Cardiovascular diseases ☐ Brain function

☐ Dyslipidaemia ☐ Mental health

☐ Hypertension ☐ Dental caries

☐ Type 2 diabetes ☐ Overweight/obesity

☐ Nutrient deficiencies ☐ Cancer

☐ Others (please specify)

In the context of the most recent national (or regional if specific for infants) food consumption survey(s) conducted in your country (e.g. in the last 10 years):

18. Were biological samples collected to assess biochemical markers of micronutrient status?

☐ yes ☐ no (if "no" → go directly to question No. 21)

19. Please indicate the biomarkers of micronutrient status that were assessed:

If possible, please indicate whether these data is publically available and where it can be found (or provide the link to a website where they can be downloaded from). Please also provide a link to an English translation if available.

20. Please indicate whether there are publications available (in any language) on the relationship between the intake of total sugars, added sugars, and/or free sugars and the micronutrient density of the diet and/or biochemical markers of micronutrient status in your country at national level (from the most recent national food consumption surveys):

Author/year	Total sugars	Added sugars	Free sugars
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no

*Add as many rows as needed

Please provide the full list of references

21. Please add any general or specific comment, you might have:

We kindly ask you to send back the filled survey by e-mail to: nda@efsa.europa.eu

Thank you very much for your participation in this survey!

Appendix D – Exposure and endpoints search terms for sub-questions 5 and 6

Subject index terms, where available, will be combined with free-text terms. Free-text terms will be searched in title and abstract fields in Embase and PubMed; and in title, abstract and keyword fields in the Cochrane Library databases and Scopus.

Exposure

Free sugars		
Subject index terms[13]		**Free-text terms[14] (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, PubMed)	**Emtree (Embase)**	
"Monosaccharides"[Mesh:noexp] "Glucose"[Mesh:noexp] "Fructose"[Mesh] "Galactose"[Mesh] "Disaccharides"[Mesh:noexp] "Sucrose"[Mesh:noexp] "Lactose"[Mesh] "Trehalose"[Mesh] "Maltose"[Mesh] "Dietary Sugars"[Mesh] "Dietary Sucrose"[Mesh] "High Fructose Corn Syrup"[Mesh] "Honey"[Mesh] "Molasses"[Mesh] "Carbonated Beverages"[Mesh] "Energy Drinks"[Mesh] "Fruit and Vegetable Juices"[Mesh] "Beverages/adverse effects"[Mesh] "Candy"[Mesh] "Chocolate"[Mesh]	'sugar intake'/exp 'glucose intake'/exp 'fructose intake'/exp 'lactose intake'/exp 'sugar'/exp 'monosaccharide'/de 'glucose'/exp 'fructose'/exp 'galactose'/exp 'disaccharide'/de 'sucrose'/exp 'maltose'/exp 'lactose'/exp 'trehalose'/exp 'syrup'/exp 'honey'/exp 'molasses'/exp 'sweetened beverage'/exp 'soft drink'/exp 'energy drink'/exp 'sports drink'/exp 'fruit and vegetable juice'/exp 'carbonated beverage'/exp 'confectionary'/de	Sugar* OR Sucrose* OR Fructose* OR Galactose* OR Lactose* OR Trehalose* OR Maltose* OR Glucose* + dieta* OR diete* OR diet OR diets OR intake* OR consum* OR feed* OR food OR foods OR supplement* Disaccharide* Di saccharide* Monosaccharide* Mono saccharide* Simple carbohydrate* Refined carbohydrate* Syrup* Honey Candy Candies Sweet Sweets Sweetened Pastr* Confection* Patisserie Soft + drink* OR beverage* Softdrink* Fizzy + drink* OR beverage* Carbonated + drink* OR beverage*

[13] [Mesh] indicates that the MeSH term will be exploded, including in the search the terms below in the MesH hierarchy if available. [Mesh:noexp] indicates that the MesH term will not be exploded, the terms below in the MeSH hierarchy will not be searched. /exp indicates that the Emtree term will be exploded, including in the search terms below in the Emtree hierarchy if available. /de indicates that the Emtree term will not be exploded, the terms below in the Emtree hierarchy will not be searched.

[14] Asterisk symbol '*' indicates truncation. Plus sign '+' indicates the search terms will be linked with the Boolean operator AND.

	'sugar confectionary'/exp	Soda + drink* OR beverage Energy + drink* OR beverage* Sports + drink* OR beverage* SSBs OR SSDs + beverage OR drink SSB OR SSD + beverage OR drink Juice* Smoothie*

Endpoints

Adipose tissue		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Adipose Tissue"[Mesh:noexp] "Abdominal Fat"[Mesh:noexp] "Intra-Abdominal Fat"[Mesh] "Subcutaneous Fat, Abdominal"[Mesh] "Subcutaneous Fat"[Mesh] "Body Weights and Measures"[Mesh:noexp] "Body Fat Distribution"[Mesh] "Adiposity"[Mesh] "Body Mass Index"[Mesh] "Body Size"[Mesh:noexp] "Body Weight"[Mesh: noexp] "Body Weight Changes"[Mesh] "Weight Gain"[Mesh] "Weight Loss"[Mesh] Overweight[Mesh] Obesity[Mesh:noexp] "Obesity, Morbid"[Mesh] "Pediatric Obesity"[Mesh] "Obesity, Abdominal"[Mesh] "Sagittal Abdominal Diameter"[Mesh] "Waist Circumference"[Mesh] "Body Composition"[Mesh] "Body Constitution"[Mesh:noexp]	'adipose tissue'/de 'abdominal fat'/exp 'abdominal subcutaneous fat'/exp 'intraabdominal fat'/exp 'body fat'/exp 'body fat distribution'/exp 'fat pad'/exp 'weight, mass and size'/de 'body weight'/de 'lean body weight'/exp 'weight change'/exp 'weight fluctuation'/exp 'weight gain'/de 'weight reduction'/exp 'weight variation'/exp 'obesity'/exp 'body mass'/exp 'body size'/exp 'sagittal abdominal diameter'/exp 'waist circumference'/exp 'body composition'/de 'body distribution'/exp 'body constitution'/exp	Adipos* Fat pad Fat pads Body fat* Fatty tissue* Body size Abdominal fat Intra-abdominal fat Intraabdominal fat Fat distribut* Ectopic fat Waist circumference* Abdominal diameter Obese* Obesi* Obeso* Overweight* Weight + gain OR loss OR chang* OR reduc* OR maint* OR watch* OR variation OR control* OR Body OR lean Body mass Bmi Body composition* Body constitution*

Glucose homeostasis		
Subject index terms		**Free-text terms**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	**(Cochrane Library, Embase, PubMed, Scopus)**
"Diabetes Mellitus, Type 2"[Mesh] "Hyperinsulinism"[Mesh:noExp] "Insulin Resistance"[Mesh] "Metabolic Syndrome"[Mesh] "Blood Glucose"[Mesh] "Insulin/blood"[Mesh] "Hyperglycemia"[Mesh] "Glucose Intolerance"[Mesh] "Carbohydrate Metabolism"[Mesh] "Glycated Hemoglobin A"[Mesh] "Fructosamine"[Mesh] "Metabolic Diseases"[Mesh:NoExp]	'non insulin dependent diabetes mellitus'/exp 'hyperinsulinism'/exp 'hyperinsulinemia'/exp 'insulin resistance'/exp 'metabolic syndrome X'/exp 'glucose blood level'/exp 'insulin'/exp AND 'blood'/exp 'hyperglycemia'/exp 'glucose intolerance'/exp 'hemoglobin A1c'/exp 'fructosamine'/exp 'fructosamine blood level'/exp 'metabolic disorder'/de	Diabet* + type 2 OR type II OR type2 OR typeii Late OR adult* OR matur* OR slow* OR stabl* + onset + diabetes Non-insulin-depend* + diabetes Noninsulin depend* + diabetes Hyperinsulinism Hyperinsulinemia Insulin + resistan* OR sensitivity OR tolerance OR intolerance OR control OR fasting Metabolic syndrome Glucose + tolerance OR intolerance OR fasting OR blood Hyperglycemia* Glycated OR Glycosylated + Hemoglobin OR haemoglobin Hemoglobin A Haemoglobin A Hemoglobin A1c Haemoglobin A1C Hemoglobin Aic Haemoglobin AiC HbA1c HbA(1c) HbA1 HbA 1c Hb A1c Hb a 1c Fructosamine + blood OR serum OR plasma

Cardiovascular system		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Cardiovascular Diseases"[Mesh] "Stroke"[Mesh] "Hypertension"[Mesh] "Prehypertension"[Mesh] "Atherosclerosis"[Mesh] "Ischemic Attack, Transient"[Mesh] "Heart Diseases"[Mesh] "Myocardial Ischemia"[Mesh] "Angina Pectoris"[Mesh] "Acute Coronary Syndrome"[Mesh] "Myocardial Infarction"[Mesh] "Non-ST Elevated Myocardial Infarction"[Mesh] "ST Elevation Myocardial Infarction"[Mesh] "Coronary Disease"[Mesh] "Cardiovascular System"[Mesh] "Blood Pressure"[Mesh] "Cholesterol"[Mesh:noExp] "Cholesterol, HDL"[Mesh] "Cholesterol, LDL"[Mesh] "Cholesterol, VLDL"[Mesh] "Dyslipidemias"[Mesh:noExp] "Hyperlipidemias"[Mesh:noExp] "Hypercholesterolemia"[Mesh] "Hyperlipoproteinemias"[Mesh] "Lipids "[Mesh] "Triglycerides"[Mesh] "Lipoproteins"[Mesh:NoExp] "Apolipoproteins"[Mesh]	'cardiovascular disease'/exp 'coronary artery disease'/exp 'cerebrovascular accident'/exp 'atherosclerosis'/exp 'transient ischemic attack'/exp 'heart infarction'/exp 'non ST segment elevation myocardial infarction'/exp 'ST segment elevation myocardial infarction'/exp 'acute coronary syndrome'/exp 'abnormal blood pressure'/de 'hypertension'/exp 'prehypertension'/exp 'heart disease'/exp 'angina pectoris'/exp 'heart death'/exp 'congestive heart failure'/exp 'cardiovascular system'/exp 'blood pressure'/exp 'cholesterol'/de 'cholesterol ester'/exp 'high density lipoprotein cholesterol'/exp 'low density lipoprotein cholesterol'/exp 'very low density lipoprotein cholesterol'/exp 'cholesterol metabolism'/exp 'disorders of cholesterol metabolism'/exp 'dyslipidemia'/exp 'hyperlipidemia'/exp 'hypercholesterolemia'/exp 'hypertriglyceridemia'/exp 'lipid blood level'/exp 'cholesterol blood level'/exp 'triacylglycerol blood level'/exp 'triacylglycerol'/exp	CV disease* CVD CVDs CHD CHDs Cardiovascular OR coronary OR heart OR cardiac + disease* OR disorder* OR event* OR risk* OR complication* OR outcome* OR morbidit* OR mortalit* OR death* OR failure* Stroke* Cerebrovascular accident* Apoplex* Acute coronary syndrome Angina* Stenocardia Heart muscle OR cardiac muscle OR myocardial OR myocardium OR cardiac OR coronary OR heart OR transient OR cardiomyophath* + ischemi* OR ischaem* Myocardial infarct* Heart attack* STEMI NSTEMI Blood pressure Arterial pressure Diastolic Systolic Blood pressure Prehypertens* Hypertens* Atherosclero* LDL-C HDL-C Cholesterol Hypercholesterol* Hypertriglycer*

	'lipoprotein'/de 'apolipoprotein B100'/exp 'apolipoprotein A1'/exp	Dyslipidemi* Dyslipoproteinemi* Hyperlipidemia* Hyperlipemi* Lipidemi* Lipemi* Hyperlipoprotein* Lipid Lipids Lipoprotein* Triglycerid* triacylglycerol Fasting TG Apolipoprotein* ApoB100 ApoB Apo B Apo B100 ApoA1 ApoA ApoAi Apo A Apo A1 Apo Ai

Liver function		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Fatty Liver"[Mesh:noexp] "Non-alcoholic Fatty Liver Disease"[Mesh] "Liver Cirrhosis"[Mesh:NoExp] "Liver Failure"[Mesh]	'liver fat'/exp 'fatty liver'/de 'nonalcoholic fatty liver'/exp 'liver cirrhosis'/exp 'liver fibrosis'/exp 'liver failure'/exp	Fatty liver NAFLD Steatohepatiti* Steatohepatiti* NASH Steatos* Fat liver accumul* Cirrhos* OR Fibros* OR failure* OR insufficienc* + liver OR Hepatic

Dental caries		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Oral health"[Mesh] "Dental Caries"[Mesh] "Cariogenic Agents"[Mesh] "DMF Index"[Mesh] "Diet, Cariogenic"[Mesh]	'dental health'/exp 'dental caries'/exp 'cariogenic agent'/exp 'cariogenic diet'/exp 'caries assessment'/exp 'DMF index'/exp 'DMFS index'/exp 'DMFT index'/exp	Oral health Dental health Caries Carious Cariogen* Dental OR teeth OR tooth OR root + decay* OR white spot* OR cavit* DMF DMFT DMFS DFT DEFT DEFS