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Risk assessment of nutrients: There must be a threshold for their effects

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ABSTRACT

Nutrients serve physiological functions in a dose-dependent manner and that needs to be recognized in risk assessment. An example of the consequences of not properly considering this can be seen in a recent assessment by the European Food Safety Authority (EFSA). EFSA concluded in 2022 that the intake of added and free sugars should be "as low as possible in the context of a nutritionally adequate diet". That conclusion of EFSA is based on the effects on two surrogate endpoints for an adverse effect found in randomized controlled trials with high sugars intake levels: fasting glucose and fasting triglycerides. The lowest intake levels in these trials were around 10 energy% and at this intake level there were no adverse effects on the two outcomes. This indicates that the adverse effects of sugars have an observable threshold value for these two endpoints. The most appropriate interpretation from the vast amount of data is that currently no definitive conclusion can be drawn on the tolerable upper intake level for dietary sugars. Therefore, EFSA's own guidance would lead to the conclusion that the available data do not allow the setting of an upper limit for added sugars and hence, that more robust data are required to identify the threshold value for intake of sugars.

1. Introduction

The European Food Safety Authority (EFSA) engages in identifying safe levels of intake for chemicals in foods, resulting in Health-Based Guidance Values (HBGVs) such as Acceptable Daily Intakes (ADIs, for intentionally present compounds such as additives and pesticides) and Tolerable Daily Intakes (TDIs, for unintentionally present compounds such as contaminants). For nutrients (vitamins, minerals, trace elements and macronutrients) the counterpart terminology is Tolerable Upper Intake Level (UL). Whereas the toxicological risk assessment principles are similar, nutrients may require special consideration given their roles in human physiology and this is recognized in EFSA's guidance (EFSA NDA Panel, 2021).

HBGVs such as UL are intended to represent the maximum level of the total chronic daily intake of a nutrient judged to be unlikely to pose a risk of adverse effects to humans. EFSA and its predecessor the Scientific Committee on Food has established many ULs (EFSA Scientific Committee, 2006). This process of establishing ULs is an ongoing activity and to that purpose EFSA recently published an updated draft guidance for establishing and applying tolerable upper intake levels for vitamins and essential minerals (EFSA NDA Panel, 2022a).

Recent updates of ULs by EFSA are for example those for beta-carotene (EFSA Panel on Food Additives and Nutrient Sources added to Food, 2012) glutamate (EFSA Panel on Food Additives and Nutrient Sources added to Food, 2017), and sugars (EFSA NDA Panel, 2022b). Establishment of an UL implies that hazard identification and characterization have been performed and played a key role in the process. The

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Abbreviations

ADIs	Acceptable daily intakes
AIC	Akaike information criterion
BMDL	Lower confidence limit of the Benchmark dose
E%	Energy%
EFSA	European Food Safety Authority
HBGVs	Health-based guidance values
NOAEL	No observed adverse effect level
RCT	Randomized controlled trials
SSB	Sugar sweetened beverages
TDIs	Tolerable daily intakes
UL	Tolerable upper intake level

hazard identification and characterization aim to describe the intrinsic properties (toxicity) of a chemical and to estimate how much of the chemical is necessary to produce an adverse response in humans (viz to identify a safe level of intake, at and below which no adverse effect is anticipated).

For the establishment of an ADI or TDI for non-nutritive food compounds, available toxicity data are analysed to obtain a so-called point of departure, which can be a no observed adverse effect level (NOAEL), or a lower confidence limit of a benchmark dose (BMDL) that induces a specified level of effect above background level, e.g. 10% (BMDL10). By using uncertainty factors, such as the default factors of 10 for inter- and intraspecies differences, the point of departure can serve as a starting point to establish an ADI or TDI value (Dybing et al., 2002). Food additives are an example of food-borne chemicals for which this classical risk assessment procedure can be applied. However, it is recognized that this approach cannot be applied directly to nutrients as they may exhibit a U- or inverted U-shaped dose-response curve so that there is a risk for adverse effects arising from low exposure, due to deficiency as well as from high exposure due to toxicity. To make a distinction with the conventional ADI and TDI where acceptable or 'tolerable' is meant to imply a level of intake at and below which there is no probability of harm, for nutrients the term UL is used (Dybing et al., 2002). An UL does not have a pre-determined safety factor (e.g., 100-fold) included in the value and a safety threshold is preferably based on human data, taking account of both the positive and negative effects on health as a consequence of high and low intake, and including a critical analysis of the ingredient mechanism(s) of action, role within the body, and means of metabolism and elimination (Roberts et al., 2018).

It is necessary to understand the toxic properties of a chemical to ensure that it can be used safely. As such, in toxicological risk assessment a distinction is made between those compounds considered to have no threshold for their effect and those that are considered to have a threshold for their effect, since the risk assessment approach for these two categories of risk differs. The classic example of chemicals considered to have no threshold are genotoxic carcinogens; for these, a NOAEL cannot be identified, and no ADI/TDI can be established. This implies that the exposure to these compounds, when their presence in food is unavoidable, must be minimized leading to strict controls determined by the levels of concern, i.e., those associated with a Margin of Exposure (point of departure such as BMDL10 divided by a conservative estimate for human exposure) of at least 10,000. Chemicals with almost all other effects, including non-genotoxic carcinogens, are considered to have a threshold for their effect and are managed by establishment of an ADI or TDI, with a conventional uncertainty factor of 100, or in the case of nutrients, an UL.

Since the extensive opinion on an UL for sugars (EFSA NDA Panel, 2022b) has significant implications for recommendations on a healthy diet and more generally for the risk assessment of (macro)nutrients, this paper will focus on the principles applied by EFSA in that opinion in the light of setting a safe level of intake for nutrients.

2. Major conclusions

The opinion of EFSA of 2022 concluded that there are insufficient data to set an UL for (added/free) sugars intake (EFSA NDA Panel, 2022b). Despite this conclusion, EFSA advises that, based on the available body of evidence and related uncertainties, the intake of added and free sugars should be "as low as possible in the context of a nutritionally adequate diet". According to EFSA, a level of intake of sugars at which the risk of dental caries/chronic metabolic diseases is not increased could not be identified over the range of observed intakes, and thus, an UL or a safe level of intake could not be set. "Over the range of observed intakes" is an important qualification, since EFSA concluded that at levels of added/free sugars intake below 10 E% in the randomized controlled trials (RCTs), the uncertainty is high regarding the *shape and direction* of the relationships. So, EFSA was unable to reach conclusions with any certainty on the direction (positive or inverse) of the relationship, if any, below a sugar intake of 10 E%. "As low as possible" is a conclusion that includes these uncertain intake levels (due to lack of data). However, there is more than one biologically plausible relationship possible for the dose-response below the range of experimental data.

For EFSA, dental caries, fasting glucose and fasting triglycerides contribute to the evidence for the conclusions. In the following sections the weight of evidence for these effects is discussed in some more detail.

2.1. Dental caries

EFSA NDA Panel (2022b): "The relationship between the intake of dietary sugars and the development of dental caries in humans is well established. EFSA observed positive linear dose-response relationships between the intake of total sugars and risk of dental caries in permanent dentition and between the intake of sucrose and risk of dental caries in primary dentition in individual prospective cohorts across a wide range of total sugars and sucrose intakes. Dose-response relationships could not be explored across the body of evidence owing to the high heterogeneity of the exposures and endpoints assessed. Therefore, the available data do not allow conclusions on the shape of the relationship between the intake of dietary sugars and risk of dental caries for any age group, or to identify a level of sugars intake at which the risk of dental caries is not increased." So, the uncertainty about the relation between the intake of sugars and dental caries is high hampering a conclusion on this endpoint. There is also no evidence for the absence of a threshold, and this uncertainty makes the conclusion "as low as possible" invalid.

2.2. Fasting glucose

Based on the meta-regression analysis, conducted by EFSA, of the relationship between the intake of added and free sugars (between-arm difference range 8–28 E%) and fasting glucose concentrations across the body of evidence from RCTs, EFSA identified a positive and linear dose-response. EFSA NDA Panel (2022b): "The dose-response meta-regression analysis conducted by EFSA showed that an increase of at least 11E% from sugar is needed to predict a positive effect on fasting glucose. Any further increase of 10E% from sugar leads to an increase of 4 mg/dL in fasting glucose (linear dose-response)." Between-arm differences in sugars intake (E%) and risk of bias only accounted for 25.6% of the variability across studies, thus leaving most of the heterogeneity unexplained. In this context, EFSA considers that this analysis can be used to conclude on the direction of the linear dose-response relationship, but not to make a quantitative prediction of the effect of added or free sugars on fasting glucose levels.

2.3. Fasting triglycerides

EFSA NDA Panel (2022b): "A meta-regressive dose-response relationship across the BoE from RCTs was identified between the intake of added and free sugars (between-arm difference range 6–30 E%) and fasting triglycerides. The relationship was positive and linear, with no evidence for non-linearity. Most of the heterogeneity in the data set could not be explained. In this context, EFSA considers that no quantitative prediction of the effect of added (or free) sugars on fasting triglycerides can be made based on this model." Based on a systematic review of the literature, EFSA concluded that prospective cohort studies do not support a positive relationship between the intake of dietary sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases or pregnancy-related endpoints assessed (EFSA, 2022b). So, in the range of a normal intake of sugars, no adverse effects are observed according to EFSA, indicating a threshold.

EFSA could not estimate a quantitative prediction of the effect of added (or free) sugars on health outcomes. However, this is not evidence that there is no threshold. EFSA deviates from its own guidance that indicates that in such a case more data are needed to fill the gaps in knowledge, but instead concludes that the intake of added and free sugars should be "as low as possible in a nutritionally adequate diet".

The reasoning behind the advice by EFSA of "as low as possible" is based on two unsubstantiated conclusions, namely 1] there is no threshold for adverse effects, and 2] the existence of a linear dose-response relationship across the full range of intakes.

3. Threshold for health effects as the basis for toxicological risk assessment

Quantitative risk assessment for the establishment of a safe level for human exposure requires knowledge of the dose-response relationship including doses that produce no observable adverse effects. It is not possible to determine the threshold in a dose-response curve from empirical observations, due to the limited power of the models used. Hence, hazard characterization involves not only statistical considerations but also some understanding of the underlying biology and that means whether to expect a threshold. For macronutrients, like sugars, it is complex to distinguish an adaptive response versus an adverse response (Dybing et al., 2002). For sugars, the available evidence as well as biological knowledge indicates that a threshold exists at and below which sugars do not cause harm to the human body due to the existence of homeostatic mechanisms, viz. any potential adverse effects of sugars act through a threshold mechanism. In the RCTs used by EFSA, no data are available in the low-intake range (sugars intake below 10 E%), i.e., a value that corresponds to the mean intake level of added sugars among most European population groups (Löwik, 2021).

4. Dose-response

Dose-response analyses were conducted by EFSA when, according to EFSA, data allowed for this. This was possible for the association, based on RCTs, between intake of added and free sugars (E%) and fasting glucose and fasting triglycerides. As such, in the lower intake range, no adverse effects were observed for fasting glucose (see Fig. 1) or for fasting triglycerides (see Fig. 2). It is noted that in Figs. 1 and 2 the y-axis = 0 is in the lower part of the figure but not at the bottom of the figure, viz the y-axis is hit at ca 10 E%. Moreover, hardly any datapoints (one for fasting glucose and two for fasting triglycerides) were available in the lowest intake range (between-arm difference in sugars intake below 10 E%). Hence, there is no evidence to conclude that there is no observable threshold. In addition, the actual intake of sugars is even higher since the sugars from the background diet were not taken into consideration. Therefore, without sufficient data on the intake of sugars below 10 E%, the value of this threshold is likely to be an underestimate.

Figs. 1 and 2 clearly illustrate the existence of observable thresholds for the health effects. The two conducted meta-regressive dose-response linear models (fasting glucose and fasting triglycerides) show that the lowest intake levels, around and below 10 E% do not induce any change in fasting glucose or fasting triglycerides and hence there is no adverse effect. This can be seen by drawing a horizontal line through the origin (zero, zero) of the graphs. The estimated intercepts of the dose-response curves have a negative value which confirms the (common sense) visual observation of a threshold.

According to EFSA, it is not possible to establish a threshold, but this appears to be based purely on statistics. This is not the same as a scientific argument that there is no threshold. In fact, there is evidence for a threshold in the published literature. For instance, Khan et al. (2019a) found a threshold at 13 E% for added sugars in relation to cardiovascular mortality. Also, the dietary guidelines 2020–2025 for Americans recommend limiting calories from added sugars to no more than 10E% each day (US Department of Agriculture and US Department of Health and Human Services, 2020).

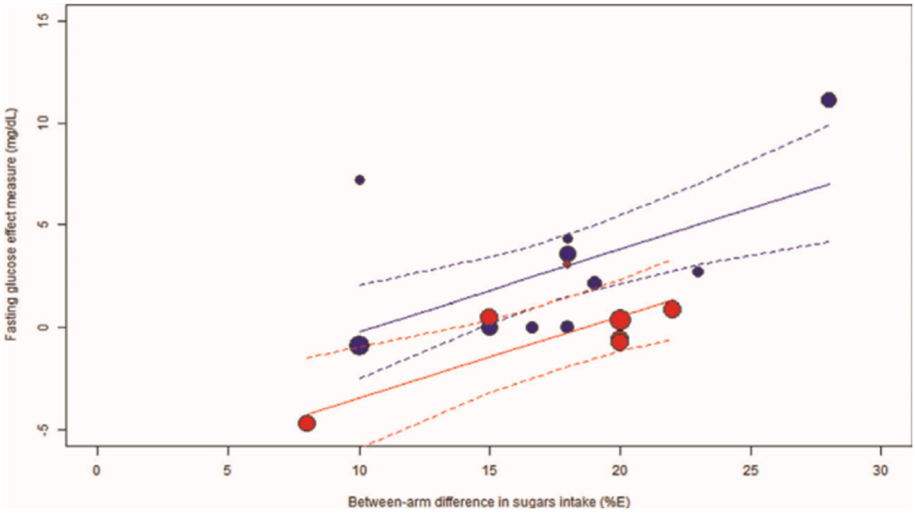

Fig. 1. Meta-regressive dose-response linear model between the intake of added and free sugars (E%) and fasting glucose.
Source: EFSA NDA Panel, 2022b (original, without changes, from the opinion of EFSA; license Creative Commons Attribution are in force: https://creativecommons.org/licenses/by-nd/4.0/)

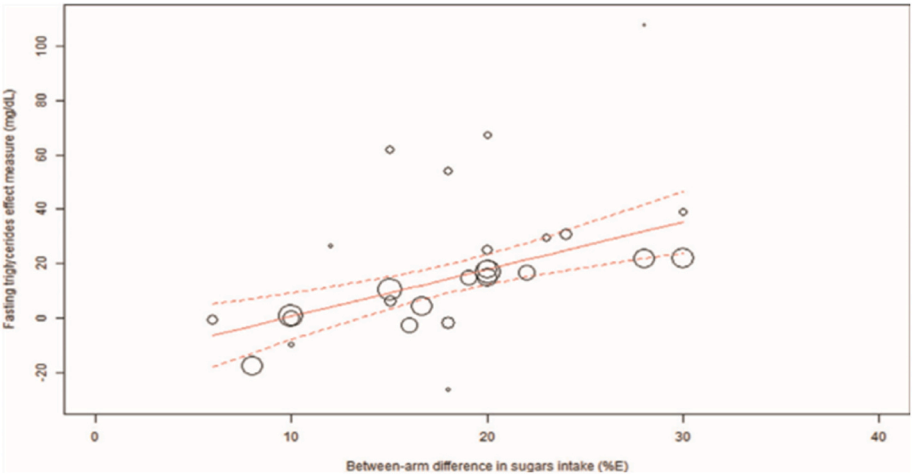

Fig. 2. Meta-regressive dose-response linear model between the intake of added and free sugars (E%) and fasting triglycerides.
Source: EFSA NDA Panel, 2022b (original, without changes, from the opinion of EFSA; license Creative Commons Attribution are in force: https://creativecommons.org/licenses/by-nd/4.0/)

5. Linearity

According to EFSA, whenever dose-response relationships could be established between the exposure to sugars and an endpoint of interest, these were positive and linear. The linearity of the dose response relationship was a central argument for EFSA to conclude that even a minimal amount of sugars is associated with (adverse) health effects. According to EFSA NDA Panel (2022b) the increase in risk is proportional to the increase in intake, and all intake levels of sugars corresponds to a different risk. As shown by Figs. 1 and 2 the estimated line does not go through the origin (zero/zero).

However, the statistics applied (estimate of a p-for-trend in a linear regression) deliver no proof for the conclusion for the absence of a threshold. A p-for-trend evaluates the existence of the *direction* of a trend over the entire intake range and does not evaluate the *shape* of the curve. High intake levels function as a lever and 'force' beneficial, absent, or small effects of low intakes to adjust to the line estimated over the entire intake range.

In its Scientific Opinion, EFSA did not assume a single non-linear association between the intake of total, added and free sugars, fructose, and the consumption of sugar sweetened beverages (SSB) and fruit juice with any of the endpoints. All were (assumed to be) linear, whereas there are papers in the literature that clearly show non-linear associations. Indeed, EFSA concluded for fasting glucose that "(suggesting) … a non-linear fit to the dose-response relationship might be justified. However due to the better fit of the linear model (Akaike information criterion (AIC) is 74.87 versus 77.47; In statistics, AIC is used to compare different models and determine which one has the best fit with the data), the latter was retained for drawing conclusions." But it should be noted that two models are indistinguishable if the difference of their AICs is less than 2. Here it is only 2.6. For fasting insulin, EFSA concluded that "(indicating) … a non-linear shape of dose-response relationship might be justified", albeit there was appreciable uncertainty in the shape of the curve. For fasting triglycerides, the AIC for EFSA's linear model was 228.38, and for the non-linear model it was 222. Note that a lower AIC indicates a better fit to the data.

Khan et al. (2019a) showed that the relationship between the intake of sugars and cardiovascular mortality is non-linear. In another paper by Khan et al. (2019b) a non-linear dose-response relationship between 100% fruit-juice and cardiovascular disease incidence was observed. Liu et al. (2019) found non-linear dose-response curves between the consumption of fruit drinks, 100% fruit juice, yoghurt, and sweet-snacks with hypertension. In a meta-analysis, Zhang et al. (2021) found a non-linear association between the consumption of SSB and the risk of metabolic syndrome. None of these papers are in the references of the opinion and thus they were not used by EFSA in its consideration of the evidence for the existence of non-linear relationships It is somewhat surprising that there is no significant discussion in the EFSA-opinion of the consequences of the uncertainty in the nature of the dose-response relationship at low levels of intake on the conclusions reached.

EFSA has more than ample examples where there is a dose-effect relationship for adverse effects for dietary ingredients above a threshold: this threshold has been defined by EFSA as the no-observed adverse effect level (NOAEL) or the lower confidence limit of the benchmark response resulting in 10% effect above background level (BMDL10). Whether the dose response curve above this threshold is linear or not does not affect the mere existence of a threshold. An example for a linear dose response curve with a threshold would be genotoxicity caused by oxidative stress which is generally accepted to be thresholded. A general example would be effects caused by compounds that are also formed endogenously either by the body itself or by its intestinal microbiome.

Frequently a J- (for instance for alcohol) or U-shaped dose-response is found in cohort studies. For essential nutrients the association with health risks is U-shaped with increased risks at low intake levels because of deficiencies and at high intake levels due to toxicity (see for instance Liu et al., 2022). Furthermore, there are many results in the literature that show the absence of a significant health risk in the lower intake categories of sugars (and other dietary components) supporting the concept of a threshold for sugars. Five references are mentioned at the end of this response and one example is included in the paper. A good example is the large (340,234 subjects) European (eight countries) cohort study (with 11,684 incident Type 2 Diabetes cases) and a subcohort of 15,374 subjects. In the full adjusted multivariate model, only the highest consumption category of total soft drinks and of sugar sweetened soft drinks (>1 glass/day) has a significant elevated risk for Type 2 Diabetes (InterAct consortium, 2013).

6. Should sugars be considered the same as non-threshold chemicals, such as genotoxic carcinogens for the purpose of risk assessment?

Traditionally the view has been that, based on the underlying mechanism and biology, non-cancer and non-genotoxic cancer endpoints can be assumed to exhibit thresholds in their dose response relationships (Dybing et al., 2002). Hence, even without identification of a threshold in the experimental (including observational) data, the risk assessment for these chemicals is conducted on this basis, for example by

extrapolating from a lowest observable adverse effect level (Dybing et al., 2002). A linear dose-response relationship without a threshold for the intake of sugars and adverse health outcomes, as assumed by EFSA, even in the presence of similar evidence for an alternative interpretation, is not in line with knowledge of non-genotoxic effects. The conclusion that exposure should be 'as low as possible' implies that EFSA frames sugars similar to a genotoxic carcinogen, where exposure to minuscule amounts could be harmful. However, no (toxicological) evidence is presented or published in the literature that sugars exhibit such an action. 'As low as possible' in risk management of chemicals is only applicable to genotoxic carcinogens, i.e., chemicals for which there is no threshold for (adverse) effects. It is based on analogy with ionization radiation, where one "hit" to a critical gene in a single cell may increase the risk of developing cancer. Sugars are, however, not 'foreign' compounds but normal constituents of the diet and body and play an essential physiological role, e.g., the monosaccharide glucose is a major fuel and a building block for homomers for storage and of a large variety of heterooligomeric body constituents. Moreover, the body produces up to 200 g per day of glucose via gluconeogenesis in the absence of dietary carbohydrate intake. There are numerous homeostatic and biochemical interrelationships involving endogenous sugars, critical to the functioning of the cell and the organism.

7. Mode of action

Although much is known about the metabolic and physiologic effects of sugars, and some of this is presented in the Scientific Opinion of EFSA, this knowledge is not integrated in the hazard characterization of the risk assessment. Effects of sugars on health are the result of multifaceted biological interactions with biochemical, cellular, and molecular processes. For hazard characterization purposes, an understanding of the mode of action is needed for an appropriate interpretation and extrapolation of the results.

The absence of a threshold for an endogenously produced substance, like glucose and fructose, without considering the endogenous levels is not scientifically plausible. For an endogenous substance as low as possible (or ALARA – as low as reasonably achievable) is even the wrong concept.

The existing physiologic and metabolic pathways, which are also described by EFSA NDA Panel (2022b), indicate that the human body can manage, by typical biological phenomena such as homeostasis and repair, a certain amount of sugars without negative effects. Physiological responses are well regulated by homeostatic mechanisms to maintain cellular equilibrium and normal function. At low levels of exposure there is sufficient plasticity in the various cellular systems (Dybing et al., 2002).

8. Healthy diet

'As low as possible' may introduce unintended consequences by introducing other and unpredicted dietary risks if consumers do not understand what is meant when reference is made to added free sugars. It could well result in a reduction in consumption of fruits for example with effects on intake of essential nutrients.

Any advice should be within the boundaries of the guidelines of a healthy diet (Roberts et al., 2018) as EFSA NDA Panel (2022b) concluded with " … in the context of a nutritionally adequate diet". This implies that as low as possible is not in line with this context since nobody has or should aim for an intake of zero sugars. No guidance however is provided as to how the advice on sugars should be interpreted with respect to nutritional adequacy. Moreover, glucose is endogenously produced and, in most circumstances, the predominant energy source for the brain.

9. Prospective cohorts

Epidemiological cohort studies are part of the evidence used by EFSA in their Scientific Opinion. However, these studies cannot identify an UL because the relationship is a statistical association, and such studies by their very nature cannot prove that the observed relationship is causal. Furthermore, the results of these studies are hampered by human variability, measurement error, uncontrolled confounding, selection bias and statistical imprecision (Van den Brandt et al., 2002). For instance, it is likely that the respondents underreport the intake of sugars due to socially desirable answers, recall bias and data from most cohorts are based on food frequency questionnaires with a limited number of included food items (Kroes et al., 2002). The contribution to risk assessment of specific food substances depends on the quality of the exposure information. A relation of the intake of sugars with health problems is confounded by energy intake since sugars intrinsically deliver energy. In the prospective cohorts the associations with sugars were mostly adjusted for energy, but this does not rule out the possibility of residual confounding.

10. Uncertainty means more data needed

According to EFSA NDA Panel (2022b) there is evidence for a positive and causal relationship between the intake of added and free sugars and risk of some chronic metabolic diseases. The level of certainty in the relationship is *moderate* for obesity and dyslipidaemia (>50–75% probability), *low* for Non-Alcoholic Fatty Liver Disease/Non-Alcoholic Steatohepatitis and Type 2 Diabetes Mellitus (>15–50% probability) and *very low* for hypertension (0–15% probability). And it should be noted that this applies to moderate levels of intake and not to low levels of intake. EFSA is aware that the assignment of the (un)certainty levels is subjective. This implies that only the highest certainty level (>75%) should be accepted as sufficient evidence, for an association with an effect of sugars. In statistics the acceptable uncertainty is normally below 5%. The level of certainty in the body of evidence for all the observed associations (except for sugar sweetened beverages: SSB) was considered moderate to very low. For added and free sugars not one association had a high (75–100%) certainty level. The obvious conclusion for EFSA to draw would be *insufficient evidence*, a term with which EFSA and the European Commission are very familiar in the process of scientific substantiation of health claims.

11. 'Insufficient data'

The Opinion of EFSA concludes that the available data do not allow the setting of an UL or a safe level of intake for either total, added, or free sugars. The Protocol (2018) and Opinion (2022b) of EFSA describe clearly what should be done in a case of insufficient data (see Fig. 3). All three identified steps require a quantification. This was not possible, whereby the last step must result in 'identify gaps in knowledge' because of insufficient data. For EFSA this means identification of the gaps in the body of knowledge and a request to fill these gaps with good scientific research. This research should at least address the question: 'What are the human studies that will result in the most useful and relevant data to assess any potential risk to human health from excessive intake of sugars?"

This research should at least address the question: 'What are the human studies that will result in the most useful and relevant data to assess any potential risk to human health from excessive intake of sugars?" In our opinion future studies required to better support the risk assessment of added sugars should consist of a double blind randomized clinical trial to unequivocally identify the cause and effects. In such a study, endpoints to be measured include at least fasting glucose and fasting triglycerides since EFSA found a dose-response for these endpoints with the E% of sugars. Figs. 1 and 2 suggest a threshold at about 10 E% (between arm difference; sugars from the diet were not taken into

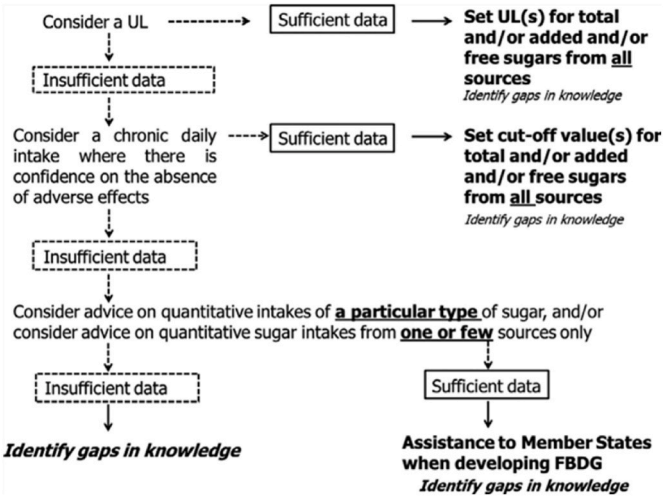

Fig. 3. Stepwise process to provide scientific advice on total/added/free sugars.
Source: EFSA NDA Panel, 2018, 2022b (original, without changes, from the opinion of EFSA; license Creative Commons Attribution are in force: https://creativecommons.org/licenses/by-nd/4.0/)

account). The amount of added sugars in the arms should be such that at least two groups are dosed below, one at and two above the apparent threshold for the effects derived from Figs. 1 and 2 while taking the amount of sugars in the diet should be into account. The data in Figs. 1 and 2, can be used for an assessment of the potential threshold. The point where the estimated linear line (or the lowest line of the confidence interval) hits the zero-horizontal exposure line can provide the basis for the threshold. The data in Figs. 1 and 2, can be used for an assessment of the potential threshold. The point where the estimated linear line (or the lowest line of the confidence interval) hits the zero-horizontal exposure line can provide the basis for the threshold. Since honey, syrups, fruit and vegetable juices are sources of free sugars the best metric to use is added sugars. To obtain small difference in the intake of sugars in the diet among the participants in the trial the participants should be instructed about the food products that can and cannot be consumed. The duration of the study should in accordance with the protocol of EFSA be at least 4 weeks for a stable level of the endpoints. A longer duration is desirable and then extra intermediate blood samples can be taken from the subjects. Non-smoking healthy men and women, with a body mass index of 20–25 kg/m2, and in a well-defined age range (for instance 21–50 years old), should be included. Based on the clinical relevance of the difference in the levels of the endpoints (for instance 10% above the normal value) between the start and end of the trial power calculations should indicate the number of subjects that have to be included in the trial. Also, whether for example this 10% change can be considered as an adverse change in these endpoints, and exceeds the general interindividual variability within the human population, may need to be better defined to enable a well-informed risk assessment.

12. General conclusion

Whereas EFSA concluded in 2022 that the intake of added and free sugars should be "as low as possible in the context of a nutritionally adequate diet", EFSA framed the risk assessment of sugars in the same way that they would for a genotoxic carcinogen, i.e., without a threshold for an adverse effect. That conclusion of EFSA is based on the effects on two surrogate endpoints for a disease: fasting glucose and fasting triglycerides in RCTs with high sugars intake levels. The lowest intake levels in these trials were around 10 E% and this intake level did not result in adverse effects. Arguably, this threshold could have been used as the basis of an UL. However, if EFSA was the view that there was an unacceptable degree of uncertainty, the only possible interpretation of the available data would be that no definitive conclusion can be drawn on an UL for dietary sugars. Therefore, the conclusion of EFSA from 2010 (EFSA Scientific Committee, 2010) on sugars would still be valid: the available data do not allow the setting of an upper limit for added sugars, an adequate intake or a reference intake range.

It is important to separate the science, i.e., the risk assessment, from policy, i.e., the need to address obesity in the population. Policy must be based on the best, most accurate science. It is difficult to see how sound policy could be developed on the basis of the EFSA Opinion that the intake of added and free sugars should be as low as possible, given the range of nutritional and other factors that would need to be considered in determining what is a nutritionally adequate diet.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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Michiel RH. Löwik: Writing – original draft, preparation, Writing – review & editing, Conceptualization. **Arne Astrup:** Writing – review & editing, commentary, review. **Alan R. Boobis:** Writing – review & editing, commentary, review. **Philip C. Calder:** Writing – review & editing, commentary, review. **Hannelore Daniel:** Writing – review & editing, commentary, review. **Ivonne MCM. Rietjens:** Writing – review & editing, commentary, review. **John L. Sievenpiper:** Writing – review & editing, commentary, review. **Hans Verhagen:** Writing – original draft, preparation, Writing – review & editing, Conceptualization.

Declaration of competing interest

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MRHL and HV are member of the Nutrition Consultants Cooperative in the Netherlands.

The respective interests identified above are not considered to constitute a conflict of interest for this paper.

Data availability

No data was used for the research described in the article.

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