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Sweeteners: majority of studies confirm no adverse health effects – however, the study situation is insufficient

BfR Opinion No 004/2023 of 7 February 2023 (assessment status 23 September 2019)

The German Federal Institute for Risk Assessment (BfR) has assessed whether the increased use of sweeteners poses a health risk to the population. For this purpose, the institute evaluated data on the five most commonly used non-nutritive sweeteners – sucralose, acesulfame K, saccharin, aspartame and cyclamate.

Studies on the influence of these substances on body weight show that their intake instead of sugar, as part of a weight-loss programme with a sub-caloric diet and behavioural intervention measures, can lead to or support weight loss. However, the available data do not allow a statement as to whether the intake of non-nutritive sweeteners or the consumption of diet drinks has an effect on body weight if no accompanying weight-loss programme is followed.

From the BfR's point of view, and based on the evaluation of the available studies, no clear statement can be made as to whether the consumption of beverages containing sweeteners increases the risk of certain neurodegenerative diseases or influences the gut flora to a clinically significant extent. In the majority of studies, no negative metabolic effect of the non-nutritive sweeteners under consideration (on blood glucose, insulin secretion or insulin sensitivity) was observed.
Also, according to the current state of knowledge, it is not clear whether risk groups such as children, pregnant women or people with certain pre-existing conditions or diseases would be affected to a higher degree by any potential negative effects of sweeteners.

The BfR is of the opinion that the current data situation on the health effects of non-nutritive sweeteners is not sufficient to carry out a conclusive health risk assessment. The available epidemiological studies only consider the exposure to non-nutritive sweeteners from diet drinks. However, the actual exposure could be much higher as individual non-nutritive sweeteners as well as combinations of different non-nutritive sweeteners are also used in processed foods and cosmetics (e.g. toothpastes). Since studies to date have primarily focused on single individual non-nutritive sweeteners, there is also a need for research on the health effects of combinations of non-nutritive sweeteners.

In addition, there are some special features for individual sweeteners that have to be taken into account in the health assessment. For example, current data indicate that heating of sucralose may lead to the formation of potentially harmful and partly carcinogenic compounds. The BfR recommends to give special consideration to this aspect in the re-evaluation of sucralose as a food additive.

BfR risk profile: [Health risk assessment regarding sweeteners] (Opinion No 004/2023)					
A Affected groups	General population				
B Probability of a health impairment through regular intake of non-nutritive sweeteners	Practically impossible	**Unlikely**	Possible	Probable	Certain
C Severity of the health impairment through regular intake of non-nutritive sweeteners	**A conclusive assessment of possible health risks cannot be made based on the data currently available.**				
D Validity of available data	High: the most important data are available and free of contradictions		Moderate: some important data are missing or contradictory		**Low: numerous important data are missing or contradictory**
E Controllability by the consumer	Control not required	Controllable through precautionary measures	**Controllable through avoidance**	Not controllable	

Fields highlighted in dark blue indicate the properties of the risks assessed in this Opinion
(further information on this can be found in the text of the BfR Opinion No 004/2023 of 7 February 2023).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. It is not intended to be used to compare risks. The risk profile should only be read in conjunction with the corresponding Opinion.

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BfR)

1 Subject of the assessment

As part of the 'National Reduction and Innovation Strategy for Sugar, Fats and Salt in Finished Foods' (NRI), sugar in processed foods and beverages is in part being replaced by sweeteners. Increased sweetener use is also expected to lead to an increased intake of sweeteners in the population.

In recent years, scientific studies and systematic reviews have been published that indicate that the intake of sweeteners might have a negative effect on human metabolism. In addition, it has been discussed whether replacing sugar with calorie-free sweeteners in foods could actually benefit weight reduction.

For example, the Deutsches Ärzteblatt[1] (a German Medical Journal) discussed results from international scientific publications with regard to the question of whether possible health risks might result from the use of non-nutritive sweeteners, e.g. regarding the development of obesity and type 2 diabetes mellitus (T2DM) as well as strokes or dementia. In addition, the Ärzteblatt outlined the hypothesis according to which a possible change in the composition of the gut microbiota caused by the use of non-nutritive sweeteners could play a role in the manifestation of undesirable metabolic effects.

Against this background, the BfR has assessed in terms of health,

[1] https://www.aerzteblatt.de/pdf.asp?id=203793;
https://www.aerzteblatt.de/nachrichten/74300/Framingham-Studie-sieht-Suessstoff-als-Schlaganfall-und-Demenzrisiko;
https://www.aerzteblatt.de/blog/100174/Wie-gesund-oder-gefaehrlich-sind-kuenstliche-Suessstoffe;
https://www.aerzteblatt.de/nachrichten/66605/Kuenstliche-Suessstoffe-in-der-Schwangerschaft-machen-Kinder-dicker

I. whether and how an (increased and possibly combined) use of sweeteners might affect the risk of obesity and metabolic diseases;

II. whether there are certain sensitive groups in the population that should avoid or limit the intake of sweeteners.

2 Results

The BfR assessment of possible health effects of sweeteners focuses on those sweeteners (non-nutritive sweeteners) that do not belong to the sugar-like sugar substitutes (polyols). As far as it was evident from the human studies evaluated which substances were used in detail, the focus of the assessment was on the five synthetic non-nutritive sweeteners sucralose, aspartame, saccharin, cyclamate and acesulfame K. It should be noted that in the majority of the human studies the considered intake of sweeteners occurred via beverages.

Overall, the evaluated data is heterogeneous and also very limited for some of the population groups considered (e.g., children and pregnant women) and certain endpoints. This results in a need for further research. In particular, well-controlled intervention studies or experimental studies investigating possible health effects of non-nutritive sweeteners are necessary to derive sound conclusions on possible (long-term) effects of non-nutritive sweeteners, e.g., on taste preferences, eating behaviour, energy intake and metabolic parameters for different population groups.

I. Health assessment by the BfR as to whether and how an (increased and possibly combinatorial) use of sweeteners could affect the risk of obesity and metabolic diseases

Influence of sweeteners or the substitution of sugar by sweeteners on body weight

- **Adults**

Randomised controlled intervention studies: In adults, the substitution of sugar with non-nutritive sweeteners or of sugar-sweetened beverages with diet drinks[2] primarily has led to or supported weight loss in intervention studies when it was carried out as part of a weight-loss programme with a sub-caloric diet and was combined with behavioural intervention measures (counselling).
Prospective observational studies: In adults, a positive effect on weight development in terms of weight reduction was not shown by the consumption of non-nutritive sweeteners or diet drinks. In several cohort studies, an association between the intake of non-nutritive sweeteners or diet drinks and an increased gain in weight and/or waist circumference was observed. Due to the heterogeneity of the studies and the, in some cases, missing adjustment for baseline body mass index (BMI) or for energy intake, it is not possible to assess whether the intake of non-nutritive sweeteners promotes weight gain in the long-term. Determining a causal relationship based solely on observational studies is difficult due to possible confounding factors and biases. A possible reverse causality regarding the consumption of sweeteners in connection with overweight may also be considered. On the one hand, it seems plausible that people suffering from diabetes mellitus use sweeteners more often. On the other hand, there are indications that people with an increased risk of developing obesity use non-nutritive sweeteners to reduce health risks.

[2] The term “diet drink” is not legally defined. In this Opinion, it is used synonymously with the term “light” or “sugar-free” or “low calorie” beverage and refers to non-alcoholic soft drinks in which the sugar content is completely or partially replaced by sweeteners.

- **Children and adolescents**

Randomised controlled intervention studies: In children, randomised controlled intervention studies mostly showed that substituting sugar with non-nutritive sweeteners in beverages or in diet drinks (artificially sweetened beverages) was associated with weight loss, especially when conducted as part of a weight-loss programme.

Prospective observational studies: In children and adolescents, the consumption of sweeteners via beverages was not associated with an increase in body weight in the majority of the prospective observational studies evaluated. About a quarter of the identified cohort studies showed an association between the intake of artificially sweetened beverages and an increase in body weight in children aged 7 and older as well as in adolescents. The remaining studies did not observe an effect, or non-nutritive sweetener consumption was associated with weight loss in these age groups. In younger children aged 2-6 years, the studies did not show any weight-promoting effect of artificially sweetened beverages.

Overall, the current data situation is heterogeneous. The results of the intervention and observational studies indicate that the consumption of artificially sweetened beverages does not increase the risk of weight gain or increased body fat percentage above physiological levels in children and adolescents.

Metabolic effects of non-nutritive sweeteners on glucose and insulin metabolism

- **Adults**

Intervention Studies: In the majority of intervention studies that investigated a possible influence of individual non-nutritive sweeteners or combinations of non-nutritive sweeteners on glucose and insulin metabolism, no negative influence on the analysed parameters (e.g., blood glucose, insulin secretion, insulin sensitivity) was observed. Most intervention studies conducted with sucralose also showed no negative changes in those parameters of glucose metabolism that were tested after single or repeated administration. By contrast, few studies with sucralose indicated a possible decrease in insulin sensitivity. Given the heterogeneous study results for sucralose, the relevance of these findings cannot be conclusively assessed.

Prospective observational studies on the association between sweetener consumption (via diet drinks) and diabetes incidence showed contradictory results. Six large cohort studies of good quality found no association between the consumption of diet drinks and the incidence of T2DM, while a positive association was observed in individual, smaller cohort studies. It should be noted that a different adjustment for possible confounding variables such as BMI in the analysis of data from individual studies is a factor that could have contributed to differences between the study results.

- **Children and adolescents**

The data situation on the possible influence of non-nutritive sweeteners on metabolic factors in children and adolescents is limited. In two ***intervention studies***, however, no influence of sweeteners (aspartame or diet drinks) on metabolic risk factors (abdominal circumference, high blood pressure, blood glucose and insulin concentration, blood lipid levels) was observed.

Impact of sweetener consumption on the risk of stroke or dementia

- Five ***observational studies*** were identified that investigated whether there might be a possible association between the consumption of sweetener containing beverages (artificially sweetened beverages, diet drinks or low-calorie sodas) and the risk of stroke or dementia. Based on these studies, no conclusive statement can be made regarding an association between the consumption of sweeteners via beverages and the endpoints 'stroke' or 'dementia' in humans.

Influence of sweeteners on the gut microbiome

- Based on the current (limited) data situation, no conclusions can be drawn as to whether the intake of sweeteners has a clinically relevant effect on the gut microbiome in humans or model animals.

II. Sensitive groups in the population that should avoid or limit the intake of sweeteners

After reviewing the currently available data situation regarding the question whether there are certain sensitive groups in the population that should avoid or limit the intake of sweeteners, the BfR comes to the following conclusions:

- An assessment of the possible influence of sweeteners on early childhood development or on the health of children and adolescents is hampered by the limited data available.

  The current, limited data situation (based on aspartame) from studies investigating the impact of non-nutritive sweeteners on children's behaviour and cognitive performance does not indicate a negative impact of aspartame on the behaviour or cognitive performance of children.

  Regarding the possible effects of exposure to non-nutritive sweeteners in early life on taste preferences (taste imprinting) in early childhood and later life as well as on dietary patterns in children, open questions remain and further research is required.

- Possible short and long-term effects of the consumption of sweetener-containing beverages during pregnancy, both for the pregnant woman herself and on the development of the child, can presently not be assessed, due to the limited study situation and the inconsistent results of the existing studies.

- Long-term, well-controlled intervention studies investigating possible health effects of non-nutritive sweeteners are needed to derive sound conclusions on any possible effects of non-nutritive sweeteners on taste preferences, appetite, eating behaviour, energy intake, and metabolic parameters for different groups of the population.

- Current data on the estimation of the intake of non-nutritive sweeteners in Germany were not available to the BfR at the time this Opinion was prepared (last literature search conducted in August 2019). Based on the assumption that liquid consumption would be covered almost exclusively by the consumption of diet drinks that would be sweetened with the current maximum permissible concentration of acesulfame K or cyclamate, according to an initial rough estimate by the BfR, there is a theoretical possibility that the ADI (acceptable daily intake) for acesulfame K and cyclamate might be

exhausted or exceeded by the consumption of diet drinks, especially for toddlers and primary school children with a body weight below the median (P50) (worst case estimation). The ADI indicates the amount of a substance that can be consumed orally on a daily basis over a lifetime without any recognisable health risk. For a realistic estimation of the intake of non-nutritive sweeteners, the consumption of non-nutritive sweeteners should be determined as part of the collection of the current national data on food consumption and combined with the actual amounts of the non-nutritive sweeteners used.

- It should also be noted that a non-nutritive sweetener as an individual substance has so far been considered without concern to health as long as the respective ADI, which was derived in the context of a single substance assessment, is not exceeded. Often, however, combinations of non-nutritive sweeteners are used in products, or different foods with different non-nutritive sweeteners may be consumed throughout the day. In this context, it should be noted that there are no studies in which the health effects of non-nutritive sweetener combinations have been systematically investigated in comparison to individual substances.
  In this respect, any possible expanded future use of combinations of sweeteners as part of a sugar reduction strategy should be viewed critically. The BfR recommends closing these gaps in knowledge beforehand. In addition, efforts should be made to reduce added sugar in foods without increasing the use of individual or combinations of different sweeteners.

- Finally, there are special features for individual non-nutritive sweeteners that have to be taken into account in the health assessment. For example, current data indicate that when sucralose is heated, especially in combination with other foods, potentially harmful and partly carcinogenic compounds may be formed. The BfR therefore suggests that the findings on the possible formation of chlorinated compounds in industrially produced foods (e.g., baked goods) or through the use of sucralose by consumers in cooking and baking be brought to the attention of the EU Commission so that this aspect can be given special consideration in the re-evaluation of this sweetener as a food additive.

3 Rationale

3.1 Background

According to Annex I of Regulation (EC) No 1333/2008 on food additives, in which the functional classes of food additives are defined, substances used to impart a sweet taste to foods or in table-top sweeteners are grouped in the functional class of sweeteners. The additives authorised as sweeteners are listed in Appendix II of Regulation (EC) No 1333/2008. The conditions for the use of sweeteners and the maximum permitted amounts in foods are also regulated in the EU by Regulation (EC) No 1333/2008.

Annex II (Community list of food additives approved for use in foods and conditions of use) of Regulation (EC) No 1333/2008 lists the additives authorised in the EU under the functional class of ‘sweeteners’. A distinction is commonly made between sugar-like sugar substitutes (polyols) and non-nutritive sweeteners. The polyols (E 420, E 421, E 953, E 964, E 965, E 966, E 967, E 968) are also included in additive group IV in Annex II of Regulation (EC) No 1333/2008.

In the following, non-nutritive sweeteners are understood as substances of different chemical structure which combine a high sweetening power with a negligible or almost negligible calorie content.

For the use of sugar substitutes in terms of the polyols as food additives, expert panels of the European Food Safety Authority (EFSA) – and formerly the Scientific Committee on Food (SCF) – have so far issued no health concerns, and no numerical ADI values have been derived (BfR, 2014). However, excessive consumption of polyols can lead to diarrhoea (Bauditz et al., 2008; SCF, 1984).

For non-nutritive sweeteners, ADI values have been derived during the health risk assessment as part of the authorisation procedure for additives, which are usually based on the results of animal experiments. According to the ADI concept, the approved non-nutritive sweeteners are considered safe according to international standards, provided that the ADI values for the individual substances, also in the context of the long-term overall consumption of various foods, are not exceeded (BfR, 2014).

EFSA is currently re-evaluating additives that were approved in the EU before 2009. In this context, sweeteners are also being re-evaluated[3]. In preparation for this, a protocol was developed in 2019 in which the methods for assessing the toxicity of sweeteners were defined. According to the draft of the protocol published on 5 July 2019, information from available human studies (intervention and observational studies) should be considered in addition to animal studies on toxicology. With regard to the evaluation of the human studies, it is also planned to consider, among other things, the possible influence of sweeteners on the incidence of obesity and T2DM as well as on the nervous system and the microbiome[4], provided that relevant information is available.

The dietary intake of non-nutritive sweeteners was investigated in a representative study in Germany (n= 2,291 persons, 24h dietary recall) in the period from 1988 to 1989. More than a third (35.9 %) of respondents reported consuming non-nutritive sweeteners. According to this, 24.5 % of children up to the age of 5 (n = 118), 20.8 % of 6- to 13-year-olds (n = 159) and 31.4 % of 14- to 17-year-olds (n = 121) consumed foods containing non-nutritive sweeteners. The main sources of intake were table-top sweeteners (about two-thirds) and soft drinks (about a quarter) (Bar and Biermann, 1992). Current, representative data on consumption of non-nutritive sweeteners in Germany were not available to the BfR at the time the present Opinion was elaborated.

The study by Bar and Biermann (1992) makes it clear that soft drinks can be a relevant source of non-nutritive sweetener intake in Germany. In 2017, every German consumed an average of 115.8 litres of soft drinks, of which 15.1 litres were diet drinks[5], and 32.2 litres were fruit juices or fruit nectars[6]. In recent years, so-called light variants have accounted for around a quarter of global soft drink sales (Borges et al., 2017).

Internationally, the non-nutritive sweeteners saccharin, aspartame, sucralose and acesulfame K are also referred to as high-intensity sweeteners; their use on the global market is increasing disproportionately. The relative share of high-intensity sweeteners in the global

[3] https://www.efsa.europa.eu/en/topics/topic/sweeteners.
The re-evaluation of aspartame (E 951) by EFSA was already completed in 2013 (https://www.efsa.europa.eu/it/efsajournal/pub/3496).

[4] https://www.efsa.europa.eu/sites/default/files/consultation/consultation/190705-d.pdf

[5] Lemonades, cola, cola mixed drinks, cola light and cola mixed drinks light, lemonades (light), spritzers/water plus fruit drinks, flavoured water, diet soft drinks, energy drinks, fizzy drinks, soft drinks, coffee and tea drinks containing fruit juice, fruit juice drinks

[6] Wirtschaftsvereinigung Alkoholfreie Getränke e.V. (soft drinks based on data from the Federal Statistical Office), Source: https://www.wafg.de/fileadmin/dokumente/pro-kopf-verbrauch.pdf; retrieved on 15/07/2019

sweeteners market increased from 6.8 % to 9.6 % over the past 30 years (1990-2011), while the share of polyols remained the same (0.5 %)[7,8].

In the period between 2015 and 2018, 989 foods and 1,055 beverages with the addition of non-nutritive sweeteners were launched in Germany (Mintel database GNPD, 2019[9]). Sucralose was added most frequently to foods (26 %), followed by acesulfame K (24 %), saccharin (16 %), aspartame (12 %) and cyclamate (11 %). With almost 90 %, these five non-nutritive sweeteners make up the majority of all non-nutritive sweeteners used in foods newly introduced to the German market during the period under review.

In the context of the 'National Reduction and Innovation Strategy for Sugar, Fats and Salt in processed Foods', an increase in the use of sweeteners is expected, which may be associated with an increase in the previously usual consumption amounts. In addition, it must be taken into account that many products contain a combination of various non-nutritive sweeteners, e.g., to minimise an undesired aftertaste emanating from individual non-nutritive sweeteners or to make use of the synergistic effect of different non-nutritive sweeteners in terms of sweetening power. For example, the mixture of 5 mg saccharin plus 50 mg cyclamate corresponds to the sweetening power of 125 mg cyclamate or 12.5 mg saccharin (Roth and Lück, 2012).

The present Opinion evaluates the scientific data situation on possible effects of sweeteners on body weight and on metabolic risk factors in humans (beyond the assessments carried out in the context of previous approval procedures for individual sweeteners). Thereby, the BfR focuses only on non-nutritive sweeteners in order to be able to assess the statements made in the reports in the Deutsches Ärzteblatt[1], which refer solely to the potential health effects of non-nutritive sweeteners.
Many of the human studies evaluated by the BfR do not indicate which non-nutritive sweeteners were used in detail. Insofar as it was clear from the human studies evaluated which non-nutritive sweeteners were used, the BfR Opinion focuses on the five synthetic non-nutritive sweeteners sucralose, aspartame, saccharin, cyclamate and acesulfame K. These account for the largest share of global non-nutritive sweetener sales.

3.2 Assessment as to whether and how an increased and possibly combinatorial use of sweeteners might affect the risk of obesity and metabolic diseases

To answer this question, the BfR investigated whether the consumption of non-nutritive sweeteners has an effect on the development of obesity and the associated secondary diseases (in particular T2DM and risk factors of the metabolic syndrome).

With regard to the studies discussed in the Deutsches Ärzteblatt in recent years, it was also investigated whether the use of non-nutritive sweeteners could have an effect on the risk of stroke or dementia.

Finally, a possible influence of non-nutritive sweeteners on the human gut microbiome was considered. Due to the very limited data situation in humans, animal studies were also included in the assessment.

For all points, both the available human intervention studies and observational studies, which were available as individual studies and in the form of reviews, were evaluated.

[7] https://www.thuenen.de/media/publikationen/landbauforschung-sonderhefte/lbf_sh360.pdf; retrieved on 15/07/2019

[8] https://www.bundestag.de/resource/blob/405996/c86a53d6e682837b7becb9cb80692275/wd-5-218-14pdf-data.pdf; retrieved on 15/07/2019

[9] Mintel database GNPD (Global New Products Database) is a database covering products that have been newly launched to the market: https://www.mintel.com/de/produkte/gnpd/

3.2.1 Influence of sweeteners or the substitution of sugar with sweeteners on the body weight of adults

3.2.1.1 Intervention studies

On behalf of the World Health Organization (WHO), Toews et al. (2019) published a comprehensive review to derive recommendations on the intake of non-nutritive sweeteners by children and adults. Toews et al. systematically searched for and evaluated all studies that had been published in the scientific databases *Medline*, *Medline in Process*, *Medline Daily Update*, *Embase* and in the *Cochrane Central Register of Controlled Trials* on various health-related effects of non-nutritive sweeteners, including on body weight and BMI, up to May 2017. The duration of the intervention had to be at least seven days. The review contains a meta-analysis that included five randomised controlled intervention studies on the effect of non-nutritive sweeteners on the regulation of body weight and BMI.

The result of the meta-analysis by Toews et al. (2019) showed no significant difference in body weight change between adults who received non-sugar sweeteners[10] compared to those who received sugar or another placebo (mean difference -1.29 kg, 95 % CI: -2.80 to 0.21; five studies, n = 229, very low evidence). With the exception of one study (steviol glycoside vs. cellulose, each as a capsule (Maki et al., 2008)), all studies used caloric substances (mostly sucrose) as a comparator (Kuzma et al., 2015; Maersk et al., 2012b; Raben et al., 2002; Reid et al., 2014). The effect of non-nutritive sweeteners on BMI in adults was analysed based on two studies (Raben et al., 2002; Reid et al., 2007). Both studies used sucrose as a comparative substance. The BMI was 0.6 units lower in those who consumed non-nutritive sweeteners (95 % CI: -1.19 to -0.01; n = 174, low evidence) (Toews et al., 2019).

Overall, the meta-analysis by Toews et al. (2019) showed no relevant difference in terms of body weight reduction in predominantly overweight or obese participants who consumed non-nutritive sweeteners compared to sucrose; however, a slight decrease in BMI was observed.

In addition to the intervention studies considered in the review by Toews et al. (2019), the BfR identified eight further publications on seven intervention studies whose results are included in the current assessment (Fantino et al., 2018; Madjd et al., 2018; Blackburn et al., 1997; Kanders et al., 1988; Tate et al., 2012; Peters et al., 2014; Peters et al., 2016; Sorensen et al., 2014).

Three of the intervention studies used caloric substances as a comparator (Blackburn et al., 1997; Sorensen et al., 2014; Tate et al., 2012). The overweight or obese participants achieved greater weight loss and were better able to maintain their reduced body weight (Blackburn et al., 1997) or reduced their body weight and body fat percentage in comparison to a group that consumed sucrose (Sorensen et al., 2014).

Six of the intervention studies compared the consumption of non-nutritive sweeteners or diet drinks with the consumption of water or other non-caloric drinks (Fantino et al., 2018; Madjd et al., 2018; Peters et al., 2016; Peters et al ., 2014; Tate et al., 2012). The results from these studies are inconsistent. For example, in a crossover study with 166 healthy, non-obese adults who had rarely consumed non-nutritive sweeteners prior to the study, Fantino et al. (2018) examined the effects of short-term consumption (over two days at two different time points or continuously over five weeks) of a non-nutritive sweetener-containing beverage compared to water with meals. No differences were observed between the intake of water

[10] includes both artificial and natural non-caloric sweeteners (not sugar alcohols/polyols)

and the beverage sweetened with a non-nutritive sweetener blend in terms of food choices, appetite, BMI or total energy intake. By contrast, a longer-term intervention by Madjd et al. (2018) showed that replacing diet drinks with water after the main meal resulted in additional weight loss (-1.7±2.8 kg for water vs. -0.1±2.7 kg for diet drinks) within the follow-up period of 12 months; the BMI was also significantly lower (-0.7±1 vs. -0.05±1.1 kg/m^2). The study included 71 healthy, overweight or obese participants; a six-month weight loss intervention was followed by a 12-month weight stabilisation follow-up programme (Madjd et al., 2018).

In contrast, two other studies reported that the consumption of artificially sweetened beverages was beneficial over water for weight loss and resulted in both greater weight loss during the intervention (Tate et al., 2012) and less weight gain during the follow-up (Peters et al., 2016; Peters et al., 2014).

Finally, in the study by Kanders et al. (1988), the control group was instructed to avoid the consumption of non-nutritive sweeteners, while the intervention group consumed beverages and foods sweetened with aspartame – with a dose increase over the study period (278 mg – 311 mg – 383 mg). The overweight and obese subjects who participated in a 12-week weight-loss programme received an isocaloric diet. All subjects reduced their body weight. In women, aspartame consumption was associated with greater weight loss; in men, however, there was no difference in weight loss between the intervention and control groups.

In most of the intervention studies additionally identified by the BfR, the intervention took place as part of a weight-loss programme (Blackburn et al., 1997; Kanders et al., 1988; Madjd et al., 2018; Peters et al., 2016; Peters et al., 2014; Tate et al., 2012). In two studies in which the consumption of non-nutritive sweetener-containing beverages or diet drinks was compared with caloric comparators (e.g., sucrose) and also combined with behavioural measures as part of weight-loss programmes, the substitution of sugar-sweetened drinks with non-nutritive sweetener-sweetened or diet drinks supported body weight loss and reduced the re-gain of body weight in the overweight participants during follow-up (Blackburn et al., 1997; Tate et al., 2012).

In summary, most of the identified intervention studies involved overweight and obese participants and the interventions with non-nutritive sweeteners or with diet drinks were carried out as part of a weight-loss programme in combination with a hypocaloric diet (Blackburn et al., 1997; Kanders et al., 1988; Madjd et al., 2018; Peters et al., 2016; Peters et al., 2014; Tate et al., 2012), where a reduction in body weight was observed. Thus, compared to caloric substances – in two studies compared to water (Tate et al., 2012; Peters et al., 2014) – the intake of non-nutritive sweeteners or diet drinks increased the effect of weight-loss programmes.

The studies indicate that the use of non-nutritive sweeteners in weight-loss programmes in adults may support weight loss. However, the studies do not allow a statement on whether the use of non-nutritive sweeteners instead of sugar could lead to a reduction in calorie intake and thus weight loss under real life circumstances, i.e. under less controlled conditions.

Overall, the results of the randomised controlled intervention studies show that the substitution of sugar with non-nutritive sweeteners or the substitution of sugar-sweetened beverages with diet drinks in adults led to or could support weight loss, especially when it was carried out as part of a weight-loss programme with a sub-caloric diet and combined with behavioural intervention measures (counselling).

3.2.1.2 Prospective observational studies

Whether the consumption of non-nutritive sweeteners *per se* might influence the development of overweight or obesity in adults was addressed in several prospective cohort studies.

Ten publications were identified that investigated an association between the consumption of non-nutritive sweeteners or diet drinks and a risk of overweight/obesity. Most of the identified publications reported results from US cohorts (Colditz et al., 1990; Schulze et al., 2004; Fowler et al., 2008; Nettleton et al., 2009; Mozaffarian et al., 2011; Duffey et al., 2012; Fowler et al., 2015; Chia et al., 2016). One cohort was from the United Kingdom (Parker et al., 1997) and another one from Denmark (Hinkle et al., 2019b).

In the cohort studies, consumption of foods containing non-nutritive sweeteners was not associated with a decrease in body weight. A positive association was observed in six studies (Colditz et al., 1990; Chia et al., 2016; Fowler et al., 2008; Nettleton et al., 2009; Duffey et al., 2012; Fowler et al., 2015) between intake of non-nutritive sweeteners or diet drinks and increased gain in weight and/or waist circumference scores. However, three of these studies (Chia et al., 2016; Fowler et al., 2008; Nettleton et al., 2009) did not adjust for baseline BMI. It should be noted, however, that in all studies the baseline BMI and/or waist circumference were significantly higher in non-nutritive sweetener users than in non-users. In this context, the question of a possible so-called reverse causality arises. This is because there are indications from studies that people who are overweight, have T2DM or are on a weight-loss diet are more likely to consume non-nutritive sweeteners (Grech et al., 2018; Mozaffarian et al., 2011).

With regard to a possible connection between the consumption of non-nutritive sweeteners and obesity, the results of the cohort studies appear to show that the use of non-nutritive sweeteners as an alternative to sugar had no positive effect on weight development in the sense of weight loss. However, due to the heterogeneity of the studies and the partly missing adjustment for baseline BMI or calorie intake, it cannot be estimated whether the intake of non-nutritive sweeteners promotes weight gain in the long term.

3.2.1.3 Reviews, scoping reviews and systematic reviews

A total of nine reviews were identified (Toews et al., 2019; Ruanpeng et al., 2017; Santos et al., 2018; Rogers et al., 2016; Lohner et al., 2017; Olivier et al., 2015; Azad et al., 2017; Mosdol et al., 2018; Miller and Perez, 2014) that were published between 2014 and 2019, of which six were systematic reviews with meta-analyses (Toews, 2019; Ruanpeng et al., 2017; Santos et al., 2018; Rogers et al., 2016; Azad et al., 2017; Miller and Perez, 2014) that addressed effects of non-nutritive sweetener consumption on body weight and/or metabolic parameters in humans. Most of the reviews evaluated both intervention and cohort studies. The results of the systematic reviews, in which quality assessment was performed using the Cochrane risk-of-bias tool and/or the Newcastle-Ottawa scale, are presented below.

In two meta-analyses, the authors concluded that no weight loss was achieved through the consumption of non-nutritive sweeteners (Santos et al., 2018; Toews et al., 2019); while based on two other meta-analyses, it was deduced that the use of non-nutritive sweeteners in children and adults resulted in a slight reduction in body weight and energy intake (Miller and Perez, 2014; Rogers et al., 2016).

The analysis by Santos et al. (2018), on the other hand, demonstrated neither benefits nor risks of aspartame consumption in relation to body weight and energy intake and in relation to metabolic parameters (glucose and insulin concentrations). Large differences in study design (e.g., different intervention times: 1 day to 2 years), small numbers of participants and the high degree of heterogeneity between the studies (normal weight, but also diabetic or obese study participants) were mentioned as limiting factors.

Azad et al. (2017) included seven randomised controlled trials and 30 cohort studies to assess the association between non-nutritive sweetener consumption and BMI. The analysis of the intervention studies found no effect of non-nutritive sweeteners on BMI, obesity incidence and other cardiometabolic endpoints. In contrast, the meta-analysis of the observational studies showed a slight increase in BMI and hypertension and an increase in the incidence of metabolic syndrome and T2DM.

Ruanpeng et al. (2017) analysed 11 observational studies and conducted a meta-analysis of data from two cohort studies and one cross-sectional study, which showed a positive association between the consumption of artificially sweetened beverages and the risk of overweight and obesity (pooled risk ratio (RR): 1.59; 95 % CI: 1.22-2.08). Consumption of sugar-sweetened beverages also increased the risk of overweight and obesity by 18 % (pooled RR of 11 studies: 1.18; 95 % CI: 1.10-1.27).

The results of the systematic reviews indicate that the regular consumption of non-nutritive sweeteners in cohort studies tended to be associated with an increase in body weight and an increase in BMI. The analyses of the randomised, controlled intervention studies, on the other hand, showed either a reducing or no effect of the consumption of non-nutritive sweeteners on body weight.

3.2.2 Influence of non-nutritive sweetener consumption on the development of body weight in children and adolescents

3.2.1.1 Intervention studies in children and adolescents

To date[11], only six publications on randomised, controlled studies that investigated non-nutritive sweetener consumption in children in relation to body weight development have been identified (de Ruyter et al., 2012b; Katan et al., 2016 (secondary analysis of de Ruyter 2012b); Ebbeling et al., 2012; Taljaard et al., 2013; Williams et al., 2007; Frey, 1976). Almost all identified studies used artificially sweetened beverages as exposure measure; in the study by Frey (1976), beverages and solid foods to which defined amounts of aspartame had been added as compared to sucrose were used as an intervention.
The follow-up time of the studies ranged from 12 weeks to 18 months. A total of three high-quality publications were identified (de Ruyter et al., 2012b; Frey, 1976; Katan et al., 2016), two of which (de Ruyter et al., 2012b and Katan et al., 2016) are based on the *Double-blind Randomized INtervention study in Kids* (DRINK) (de Ruyter et al., 2012a).

The results of the long-term intervention as part of the DRINK study show that substituting sugar with non-nutritive sweeteners (combination of sucralose with acesulfame K) in beverages resulted in 1 kg less weight gain than in the control group in normal-weight children aged 4 to 11 years over a period of 18 months; in addition, the proportion of body fat and skinfold thickness decreased significantly (de Ruyter et al., 2012b). Furthermore, Katan et al. (2016) evaluated these data in a secondary analysis and observed that BMI values decreased steadily over the course of the study in children with higher baseline BMI, who were unknowingly switched to sugar-free drinks (containing sucralose and acesulfame K). Children with a higher baseline BMI z-score reduced their body weight gain by 1.53 kg; children in the lower z-score BMI group, on the other hand, by 0.62 kg (Katan et al., 2016).

Frey (1976) studied body weight, serum and urine parameters in children, adolescents and young adults aged 2 to 21 years after a 13-week intervention with aspartame added to beverages and solid foods. Products sweetened with sucrose served as controls. The administration of aspartame was dosed according to age. No change in body weight was observed across all age groups after study completion. There were also no differences between the aspartame and the control group with regard to the other parameters examined. Adverse health effects of the aspartame intervention were not reported (Frey, 1976).

Two of the intervention studies mentioned above were conducted on overweight or obese adolescents:
In the study by Ebbeling et al. (2012), the intervention group had reduced their body weight more than the control group after one year as part of a 12-month multifactorial intervention (biweekly delivery of non-caloric drinks (water and artificially sweetened beverages) as well

[11] This refers to the time of elaboration of the present Opinion in 2019.

as behavioural intervention). After a further year of follow-up without intervention, the weight difference – in relation to the previously achieved weight reduction – was only marginal (Ebbeling et al., 2012). Due to the multifactorial design (consumption of water and/or artificially sweetened beverages) and the lack of information on the type and amount of non-nutritive sweeteners consumed, the validity of the study with regard to the effect of non-nutritive sweetener consumption and its generalisability is limited.
Williams et al. (2007) reported that in female adolescents who underwent a weight-loss programme with calorie restriction to 1,500 kcal per day over a 12-week period, both diets (consumption of sugar-sweetened beverages vs. non-nutritive sweetener-containing beverages) were equally effective in reducing body weight and BMI of the subjects.

Another study by Taljaard et al. (2013) showed methodological weaknesses (no measurement of physical activity, risk factor malnutrition, intervention plan not followed) and is therefore associated with a high risk of bias. Furthermore, other primary outcomes (effects of micronutrient supplementation on cognitive function and growth) were investigated. More than one in ten children examined in this study were malnourished and one in four children suffered from iron deficiency. As an intervention, participants (South African school children) were given either sugar-sweetened beverages or beverages sweetened with sucralose, which were either fortified with micronutrients or not, over a period of nine months. Relevant target figures were BMI z-score and weight-for-age z-score. Children who consumed non-nutritive sweetener-containing beverages (with or without added micronutrients) showed a higher increase in weight-for-age z-score compared to children who consumed sugar-sweetened beverages (+0.07 SD units; 95 % CI: 0.002-0.14). No difference could be established in relation to the BMI z-score. Due to the poor external validity (among other things, health problems of the test group), the validity of this study is very limited.

Some other experimental studies in children and adolescents were designed as short-term studies (interventions on only one day) (Anderson et al., 1989; Bellissimo et al., 2007; Birch et al., 1989). These were therefore not included in the current assessment.

In summary, the intervention studies conducted with children and adolescents show that a targeted and controlled replacement of sugary drinks with non-nutritive sweetener-containing drinks could reduce body weight gain in normal-weight children. Also in overweight or obese adolescents, a greater reduction in body weight was observed as part of a weight-loss programme (combined with behavioural intervention measures) when sugar in beverages was substituted with non-nutritive sweeteners. As the results of some intervention studies in obese adults have already suggested, overweight/obese adolescents could therefore possibly also benefit from a substitution as part of a secondary prevention measure for weight reduction. The generalisability of the results is limited, however, since ‘real-life’ conditions can only be simulated to a limited extent in intervention studies. In addition, the sometimes short duration of the studies, the lack of information on the type and dose of the non-nutritive sweeteners, the calorie restriction and the high drop-out rates limit the significance of the studies.

3.2.2.2 Observational studies in children and adolescents

A total of 15 observational studies – 12 cohort studies (Laverty et al., 2015; Zheng et al., 2015; Berkey et al., 2004; Blum et al., 2005; Johnson et al., 2007; Davis et al., 2018; Macintyre et al., 2018; Striegel-Moore et al., 2006; Ludwig et al., 2001; Kral et al., 2008; Newby et al., 2004; Vanselow et al., 2009) and three cross-sectional studies (Katzmarzyk et al., 2016; Forshee and Storey, 2003; O´Connor et al., 2006) – that examined associations between sweetener intake and body weight in children and adolescents – were identified. All of the observational studies discussed here looked at beverages sweetened with sweeteners or artificially sweetened beverages in comparison to mostly sugar-sweetened beverages. The observation periods ranged from six months to ten years, with study groups ranging from 100 to more than 13,000 participants.

The 12 cohort studies show heterogeneous results: In four of these studies (Laverty et al., 2015; Blum et al., 2005; Davis et al., 2018; Berkey et al., 2004 (in boys only)), non-nutritive sweetener consumption was associated with weight gain; in six studies there was no association (Johnson et al., 2007; Macintyre et al., 2018; Striegel-Moore et al., 2006; Kral et al., 2008; Newby et al., 2004; Vanselow et al., 2009). By contrast, two of the observational studies documented a reduction in body weight as well as body fat percentage after substituting sugary drinks with non-nutritive sweetener-containing drinks or water (Ludwig et al., 2001; Zheng et al., 2015).

Looking at the different age groups of children, it can be seen that in children aged 2 to 6 years, after adjustment for various confounders, no association was observed between the consumption of non-nutritive sweetener-containing beverages and body weight parameters (Johnson et al., 2007; Kral et al al., 2008; Macintyre et al., 2018; Newby et al., 2004). In older children (7 years and older) and adolescents, however, the results are heterogeneous: While three studies observed a positive association in children (Blum et al., 2005; Laverty et al., 2015) or obese adolescents (Davis et al., 2018), two other studies demonstrated a negative association between diet drinks and weight development (Zheng et al., 2015) and an increase in the consumption of non-nutritive sweetener-containing beverages was negatively associated with the incidence of obesity (Ludwig et al., 2001). Furthermore, in two studies in girls aged 9-10 years (Striegel-Moore et al., 2006) and in adolescents (Vanselow et al., 2009), no association between non-nutritive sweeteners or artificially sweetened beverages and body weight was observed. By contrast, in another study with children aged 9-14 years, a positive correlation (weight gain) was observed in boys, but not in girls (Berkey et al., 2004).

The three cross-sectional studies also show inconsistent results:
Using data from 1,572 children, aged 2-5 years, taken from the *National Health and Nutrition Examination Survey*, O'Connor et al. (2006) did not find any association between the type of beverage consumption – including artificially sweetened beverages and sugar-sweetened beverages – and BMI. Katzmarzyk et al. (2016), on the other hand, showed a positive association between the consumption of artificially sweetened beverages and BMI z-score only in girls aged 9-11 years. However, no adjustment was made for numerous potential confounders (Katzmarzyk et al., 2016). Also in the study by Forshee and Storey (2003), the BMI was weakly positively associated with the consumption of non-nutritive sweetener-containing carbonated beverages in children aged 6-19 years.

Limiting factors of the observational studies are primarily the non-recording of the consumption of foods sweetened with non-nutritive sweeteners (usually only drinks were recorded), the lack of possibility to investigate isolated effects of individual sweeteners, the lack of information on the type and dose or the lack of quantifiability of the non-nutritive sweeteners due to the given study design, the possible bias due to self-reporting in questionnaires on food consumption (FFQs, food frequency questionnaires), the mostly missing collection of biomarkers, the distortion of the results due to residual and unrecorded confounding factors as well as the possibility of so-called reverse causality (e.g., due to a higher consumption of non-nutritive sweeteners in people who are overweight). Cross-sectional studies in particular are susceptible to this form of bias, in which cause and effect cannot be distinguished (Pereira, 2013). As an important limitation, it must also be noted that non-nutritive sweetener-containing drinks were often tested against sugar-sweetened drinks and not against water, or in some cases also against several different beverages, such as milk or fruit juice. Furthermore, it cannot be ruled out that growth processes play a role within the time window in which the children were observed, which can influence the measurements of body weight and BMI, since the increase in height and weight is subject to large individual fluctuations. In addition, significant life phase transitions, e.g., the transition from preschool or kindergarten to primary school, can have an impact on the mental health of the child. Studies also show

that especially overweight people and people who want to lose weight, as well as female adolescents and people with a higher socio-economic status consume non-nutritive sweeteners more frequently (Mozaffarian et al., 2011; Vanselow et al., 2009).

Overall, it can be stated that the results of the observational studies on possible associations between non-nutritive sweetener consumption via beverages and weight development in children and adolescents are heterogeneous. About a quarter of the identified cohort studies showed an association between the intake of diet drinks (artificially sweetened beverages) and body weight gain, but only in children aged 7 and older as well as adolescents, while the remaining studies in these age groups did not observe an effect or non-nutritive sweetener consumption was associated with weight loss. In younger children aged 2 to 6 years, the identified studies showed no association between artificially sweetened beverages and body weight.

In the studies, the consumption of non-nutritive sweeteners via beverages was usually not evaluated as a primary variable, but as a comparative variable to sugar consumption. The type and dose of non-nutritive sweeteners in beverages were not specified in any of the studies; mostly only the general terms ‘artificially sweetened beverages’ or also ‘diet drinks’, ‘diet fruit drinks’ were used to describe the drinks.

The associations shown in observational studies are influenced by a variety of factors. For the assessment of a possible attributable risk[12] of non-nutritive sweeteners in observational studies, individual living and environmental conditions have to be considered as a multi-layered network of relationships. Future study planning of observational studies with children and adolescents should especially take into account the type and dose of non-nutritive sweeteners, the total energy intake, the use of a validated dietary protocol, the family background, possible growth processes as well as critical transitions of life phases (kindergarten, school).

3.2.2.3 Systematic reviews, meta-analyses and reviews

A total of 12 reviews were identified (Young et al., 2019; Toews et al., 2019; Karalexi et al., 2018; Duran Aguero et al., 2018; Archibald et al., 2018; Magnuson et al., 2017; Reid et al., 2016; Rogers et al., 2016; Bellisle, 2015; Fernstrom, 2015; Freswick, 2014; Brown et al., 2010), which investigated whether non-nutritive sweetener intake affects body weight regulation and metabolic health in children and adolescents. Six of the reviews were systematic reviews (Young et al., 2019; Toews et al., 2019; Karalexi et al., 2018; Reid et al., 2016; Rogers et al., 2016; Brown et al., 2010); three of these included a meta-analysis (Toews et al., 2019; Karalexi et al., 2018; Rogers et al., 2016). The results of the latter three systematic reviews, which were quality assessed using the Cochrane risk-of-bias tool and/or the Newcastle-Ottawa scale, are presented below:
Rogers et al. (2016) analysed data from 81 relevant human studies (adults, children) and 90 animal studies which involved consumption of low energy sweeteners (LES, i.e. products predominantly sweetened with non-nutritive sweeteners)[13] with *ad libitum* access to food energy. It was investigated whether exposure to non-nutritive sweeteners (versus sugar or unsweetened alternatives) had effects on energy intake or body weight:
In 62 of 90 animal studies, exposure to non-nutritive sweeteners had no effect on body weight. The results of twelve prospective cohort studies showed inconsistent associations

[12] The attributable risk indicates the percentage by which the incidence of disease in a population is reduced when a risk factor is eliminated.

[13] LES were defined by Rogers et al. (2016) as: „…*sweeteners and sweetener systems that contribute negligible energy to the product (i.e., typically <15 % of the ‘standard’ or control caloric sweetener system, in most cases sucrose)*.” In particular, products were considered whose sweetness mainly came from: “… *intense and non-caloric sweeteners (e.g., saccharin, aspartame, cyclamate, sucralose, acesulfame-K, stevia, erythritol)“.*

between non-nutritive sweetener consumption and BMI (−0.002 per year, 95% CI: -0.009 to -0.005).

The meta-analysis of the short-term randomised controlled human trials showed reduced total energy intake for LES versus consumption of sugar-sweetened foods or beverages before an *ad libitum* meal (-94 kcal, 95 % CI: -122 to -66), with no difference from water (-2 kcal, 95 % CI: -30 to 26). The meta-analysis of the long-term randomised controlled trials (4 weeks to 40 months) showed that the consumption of non-nutritive sweeteners compared to sugar led to a relatively reduced body weight (9 studies; -1.35 kg, 95 % CI: -2.28 to -0.42) and a similar relative reduction in body weight compared to water (three studies; -1.24 kg, 95 % CI: -2.22 to -0.26). The evidence from randomised controlled intervention studies showed that non-nutritive sweeteners neither increased energy intake nor body weight compared to either a caloric (sugar) or a non-caloric (water) control. It was concluded that using non-nutritive sweeteners instead of sugar could lead to a reduction in energy intake and contribute to a decrease in body weight in children and adults (Rogers et al., 2016).

In a more recent review by Toews et al. (2019), 56 human studies with adults and children, 35 of which were observational studies, were evaluated on behalf of the WHO. Based on the results of this analysis, the WHO plans to derive a general recommendation for the intake of non-nutritive sweeteners in children and adults. The influence of no or a low intake of non-sugar sweeteners – excluding sugar alcohols/polyols – on possible parameters such as body weight, BMI and dietary behaviour was compared with a higher intake. Eight of the included studies investigated the consumption of artificial sweeteners and their effects on children's health. The results show that there was a smaller increase in BMI (z-score) in children associated with the use of non-nutritive sweeteners compared to sugar (-0.15, n = 528), but no significant change in body weight (-0.60 kg, n = 467). On this basis, Toews et al. (2019) concluded that the use of non-nutritive sweeteners is not associated with health benefits for consumers, but that on the contrary, possible adverse health effects from the consumption of non-nutritive sweeteners could not be ruled out.

Karalexi et al. (2018) investigated the association between the consumption of non-nutritive sweeteners and adverse metabolic effects explicitly in childhood and systematically summarised the results of 13 observational studies: While a small increase in BMI (OR 1.15; 95 % CI: 1.06-1.25) was associated with non-nutritive sweetener consumption compared to non-consumption, there was no association with other parameters such as hip circumference and body fat percentage.

In summary, the heterogeneous study data currently available indicate that the consumption of non-nutritive sweetener-containing beverages in children and adolescents is not associated with an increased risk of weight gain beyond physiological levels or an increase in body fat percentage.

3.2.3 Metabolic effects of non-nutritive sweeteners on glucose and insulin metabolism in adults

3.2.3.1 Intervention studies: influence of non-nutritive sweeteners on blood glucose levels, glucose metabolism and appetite-regulating hormones in adults

With respect to the possible influence of non-nutritive sweeteners on blood glucose levels, glucose metabolism and appetite-regulating hormones, 19 studies with aspartame (Shigeta et al., 1985; Nehrling et al., 1985; Okuno et al., 1986; Colagiuri et al., 1989; Rodin, 1990; Melanson et al., 1999; Hall et al., 2003; Siegler et al., 2012; Higgins et al., 2018; Anton et al., 2010; Maersk et al., 2012a; Tey et al., 2017a and b; Horwitz et al., 1988; Higgins and Mattes, 2019; Härtel et al., 1993; Steinert et al., 2011; Bryant et al., 2014; Temizkan et al., 2015), six

studies with saccharin (Cooper et al., 1988; Horwitz et al., 1988; Suez et al., 2014; Higgins and Mattes, 2019; Härtel et al., 1993; Bryant et al., 2014), 16 studies with sucralose (Mezitis et al., 1996; Baird et al., 2000; Ma et al., 2009; Ma et al., 2010; Ford et al., 2011; Brown et al., 2011; Wu et al., 2012; Pepino et al., 2013; Grotz et al., 2003; Grotz et al., 2017; Lertrit et al., 2018; Romo-Romo et al., 2018; Gomez-Arauz et al., 2019; Steinert et al., 2011; Temizkan et al., 2015; Higgins and Mattes, 2019) and four studies with combinations of non-nutritive sweeteners (Brown et al., 2012; Olalde-Mendoza and Moreno-Gonzalez, 2013; Sylvetsky et al., 2016; Bonnet et al., 2018) were identified.

Overall, in the majority of the intervention studies, no negative influence of non-nutritive sweeteners on glucose metabolism was observed. None of the intervention studies with aspartame indicated any adverse effects on plasma glucose and plasma insulin levels or insulin sensitivity. The same applies to the non-nutritive sweetener saccharin: In five out of the six studies relevant to the research question, no influence of saccharin intake on insulin secretion and blood glucose was observed (Bryant et al., 2014; Cooper et al., 1988; Härtel et al., 1993; Higgins and Mattes, 2019; Horwitz et al., 1988). Only Suez et al. (2014) reported higher blood glucose levels in four out of seven participants after saccharin ingestion.

Also in the intervention studies with acesulfame K, no effects of non-nutritive sweetener intake on blood glucose, insulin or appetite-regulating intestinal hormones (GLP-1, PYY) were observed (Bryant et al., 2014; Härtel et al., 1993; Steinert et al., 2011; Sylvetsky et al., 2016). Even after administration of acesulfame K in combination with aspartame (as a single administration or for over 12 weeks), no elevating effect on blood glucose or change in insulin levels or insulin sensitivity could be detected (Bonnet et al., 2018; Olalde-Mendoza and Moreno-Gonzalez, 2013).

By contrast, there are partly contradictory results for the non-nutritive sweetener sucralose: On the one hand, no negative changes in the tested glucose metabolism parameters (blood values for glucose, insulin, C-peptide; insulin response in a glucose tolerance test) and with regard to appetite-regulating intestinal hormones (GLP-1, GIP) were detected in nine intervention studies after a single dose of sucralose (Brown et al., 2011; Ford et al., 2011; Grotz et al., 2003; Ma et al., 2009; Ma et al., 2010; Mezitis et al., 1996; Steinert et al., 2011; Sylvetsky et al., 2016; Temizkan et al., 2015) and in four intervention studies after repeated sucralose intake over a period of up to 13 weeks (Baird et al., 2000; Grotz et al., 2003; Grotz et al., 2017; Higgins and Mattes, 2019). On the other hand, three intervention studies reported reduced insulin sensitivity (compared to water control), as deduced from oral glucose tolerance tests (OGTT) after both a single (Pepino et al., 2013) and repeated (14 days or 4 weeks) (Lertrit et al., 2018; Romo-Romo et al., 2018) intake of sucralose. Furthermore, Gomez-Arauz et al. (2019) reported a significantly higher increase in insulin levels in the OGTT after a single intake of sucralose. In view of the heterogeneous study results, the (patho-)physiological significance of the above-mentioned results cannot be conclusively assessed. Further investigations are necessary to clarify possible effects of sucralose on glucose tolerance or insulin blood levels.

3.2.3.2 Prospective cohort studies in adults on the possible association between the consumption of non-nutritive sweeteners and the risk of type 2 diabetes mellitus

Regarding the question of whether there might be a possible association between the consumption of non-nutritive sweeteners via artificially sweetened beverages and the risk of T2DM, 12 relevant publications on prospective cohort studies were identified (Schulze et al., 2004; Palmer et al., 2008; Lutsey et al., 2008; Nettleton et al., 2009; de Koning et al., 2011; Duffey et al., 2012; Romaguera et al., 2013; Bhupathiraju et al., 2013; Fagherazzi et al., 2013; Fagherazzi et al., 2017; Sakurai et al., 2014; O'Connor et al., 2015).
Seven of these studies are based on data from US cohorts (Bhupathiraju et al., 2013; de

Koning et al., 2011; Duffey et al., 2012; Lutsey et al., 2008; Nettleton et al., 2009; Palmer et al ., 2008; Schulze et al., 2004). Two studies rely on data from the prospective French cohort study 'E3N-EPIC' (Fagherazzi et al., 2017; Fagherazzi et al., 2013). One study analysed data from the UK-EPIC (European Prospective Investigation into Cancer and Nutrition) cohort (O'Connor et al., 2015). Another study analysed data from the entire European EPIC cohort study (Romaguera et al., 2013), and a relatively small cohort study is based on data from Japanese factory workers (Sakurai et al., 2014).

In all 12 studies, exposure to non-nutritive sweeteners was recorded as the consumption of diet drinks. The beverage consumption of the study participants was determined and compared with the new cases of diabetes during the study period.

The results of the studies were inconsistent:
In the majority of the studies, high consumption of non-nutritive sweetener-containing beverages was associated with an increased incidence of T2DM under certain evaluation conditions (often without adjustment for BMI). However, in most of these studies, there were already more overweight participants in the group consuming diet drinks than in the control group. Overweight/obesity is considered an important confounding factor for T2DM risk. Accordingly, after adjustment for baseline BMI, six cohort studies with large numbers of participants (Bhupathiraju et al., 2013; de Koning et al., 2011; O'Connor et al., 2015; Palmer et al., 2008; Romaguera et al ., 2013; Schulze et al., 2004) found no statistically significant association between the consumption of non-nutritive sweetener-containing beverages and an incidence of T2DM.

Another five cohort analyses reported a statistically significant association between the consumption of diet drinks and the incidence of T2DM, which remained significant even after adjustment for BMI. These include two publications by Fagherazzi and colleagues, which are two analyses of the same cohort (Fagherazzi et al., 2017; Fagherazzi et al., 2013), two relatively small US cohort studies (Duffey et al., 2012; Nettleton et al., 2009) and a small Japanese study (Sakurai et al., 2014).

In the cohort study by Lutsey et al. (2008) consumption of diet drinks was associated with a significantly increased risk of developing metabolic syndrome; however, this study did not adjust for BMI.

Overall, six large cohort studies of good quality (including four from the US and two from Europe) showed no association between the consumption of diet drinks and the incidence of T2DM, while a positive association was seen in smaller cohort studies. The question arises whether the observed association between the consumption of diet drinks and an increased risk of diabetes is rather due to the concomitant circumstance that overweight people resort to diet drinks more often (e.g., to prevent further weight gain). Since obesity is an important risk factor for T2DM, this can influence and distort the results (i.e. 'reverse causality'). Another limitation of the existing epidemiological studies is the fact that the assumed exposure to non-nutritive sweeteners was based exclusively on the consumption of diet drinks. As many other products such as toothpaste, mouthwash, chewing gum or ready-made meals also contain non-nutritive sweeteners, the actual exposure to the non-nutritive sweeteners can differ substantially.

3.2.3.3 Systematic reviews and meta-analyses in adults

Nicole et al. (2018) conducted a meta-analysis of randomised controlled trials investigating the impact of non-nutritive sweeteners such as aspartame, saccharin, steviosides or sucralose on blood glucose levels. Based on these data, it was concluded that the consumption of non-nutritive sweeteners was not associated with a subsequent increase in blood glucose levels or an increase in glucose concentration over time.

In a meta-analysis, Imamura et al. (2016) analysed data from 17 prospective cohort studies to investigate a possible association between the consumption of certain beverages (sugar-sweetened beverages, artificially sweetened beverages or fruit juices) and the occurrence of T2DM. The analysis revealed that habitual consumption of sugar-sweetened beverages was associated with a higher incidence of T2DM (18 % increase per serving/day, 95 % CI 9-28 %; 13 % increase after adjusting for overweight). The consumption of artificially sweetened beverages or fruit juices also showed a positive association with the incidence of T2DM (for artificially sweetened beverages: 25 % increase per serving/day, 95% CI 18-33 %; 8 % increase after adjustment for overweight). According to the authors, however, the significance of the analysis for artificially sweetened beverages and fruit juices was limited due to the heterogeneity of the studies considered, bias and the influence of possible confounding variables (residual confounding).

In another meta-analysis of prospective cohort studies with adults, Kim and Je (2016) reported a positive association between the intake of sugar-sweetened beverages or artificially sweetened beverages and the risk of hypertension. The dose-dependent analysis showed that the additional intake of one serving/day of sugar-sweetened beverages was associated with an 8 % increased risk of hypertension (analysis of six studies). The additional consumption of one serving of an artificially sweetened beverage per day resulted in a 9 % increase in the risk of hypertension, taking into account four studies. Although adjustment was made for confounders (BMI), the possibility that other confounding factors might have influenced the results for the artificially sweetened beverages was discussed. It could not be ruled out that people who had risk factors for developing hypertension consumed more diet drinks (Kim and Je, 2016).

3.2.4 Metabolic effects of non-nutritive sweeteners on glucose and insulin metabolism in children and adolescents

As part of two experimental studies (Knopp et al., 1976; Williams et al., 2007), the effect of non-nutritive sweeteners on metabolic risk factors was investigated in children and adolescents over a period of three months.
Knopp et al. (1976) were unable to demonstrate any significant differences with regard to the parameters blood pressure, blood glucose concentration or lipid profile in the context of an intervention with high-dose aspartame (2.7 g/day vs. placebo). Williams et al. (2007) also did not observe significant differences in blood pressure, blood glucose concentration, lipid profile (TG, cholesterol, LDLC, HDLC) or abdominal circumference in obese female adolescents who consumed either sugar-sweetened beverages or diet soda.

In a study with adolescents and young adults aged 12 to 25 years, no changes in serum glucose and insulin concentration time courses (expressed as area under the curve, AUC) was observed by glucose tolerance test when participants consumed diet soda sweetened with acesulfame K and sucralose compared to carbonated water ten minutes prior to glucose intake for the glucose tolerance test. However, after consumption of the diet soda, there was an increased AUC for the incretin glucagon-like peptide 1 (GLP-1) during the glucose tolerance test. It was concluded that the intake of the non-nutritive sweetener enhanced the glucose-dependent secretion of GLP-1, but that the non-nutritive sweeteners alone (without glucose) had no effect on GLP-1 secretion (Brown et al., 2009).

Another intervention study investigated the acute effects of non-nutritive sweeteners in healthy adolescents and participants with type 1 diabetes mellitus (T1DM) and T2DM. After consumption of diet soda sweetened with acesulfame K and sucralose or water – followed by a 75 g glucose intake ten minutes later – the time-dependent change in blood concentrations of the intestinal hormones glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY) and GLP-1 was determined up to 180 minutes after glucose ingestion (measured in plasma samples). It was shown that diet drink intake led to increased GLP-1 concentrations

(increased AUC) after glucose administration over time in participants with T1DM and in healthy subjects, but not in participants with T2DM. The secretion and plasma concentrations of GIP and PYY were not affected by ingestion of the diet drink. Furthermore, there was no detectable difference in glucose concentration between diet drink or water intake in healthy participants and participants with T1DM (Brown et al., 2012).

In summary, it can be stated that the data on the possible influence of non-nutritive sweeteners on metabolic factors in children and adolescents is limited. In two intervention studies, no influence of non-nutritive sweeteners on metabolic risk factors (abdominal circumference, hypertension, blood glucose and insulin concentrations, lipid profile) was observed. Nevertheless, there are indications that non-nutritive sweeteners could have a metabolic relevance. The release of the so-called incretins – intestinal hormones with a “catalytic” function for the insulin-producing beta cells of the pancreas and also with a central nervous satiety effect – depends on sugar molecules in the chyme, but also on a sweet signal. The entero-endocrine cells responsible for incretin release require an intracellular signal of glucose metabolism and also carry extracellular sweet receptors (as well as bitter receptors) (Dyer et al., 2005; Margolskee et al., 2007; Montmayeur and Matsunami, 2002). The pancreas also has sweet receptors (Nakagawa et al., 2009). While some incretins (GLP-1, PYY) are consistently described as metabolically beneficial and are now also used therapeutically (GLP-1 analogues), there is also evidence for an adverse effect of GIP in the mouse model, e.g., towards non-alcoholic fatty liver (Keyhani-Nejad et al., 2015). In the case that non-nutritive sweeteners would contribute to an increase in GIP concentrations or a decrease in GLP-1 or PYY concentrations, such changes could represent metabolically adverse effects.

Further (long-term) intervention studies could help to clarify still open questions, e.g., with regard to a possible influence on taste preferences, appetite and metabolic health in children and adolescents.

3.2.5 Influence of non-nutritive sweetener consumption on the risk of stroke and dementia

Since the discussion of the results from the Framingham Heart Study in the Deutsches Ärzteblatt[14] addressed a possible association between the use of non-nutritive sweeteners and a risk of stroke or dementia, the BfR also conducted a corresponding literature review on non-nutritive sweeteners in relation to the endpoints of stroke and dementia. In this context, five observational studies in adults (Bernstein et al., 2012; Gardener et al., 2012; Mossavar-Rahmani et al., 2019; Pase et al., 2017a; Pase et al., 2017b), but no intervention studies, were identified. The questions of these studies related to whether there could be a possible association between the consumption of artificially sweetened beverages, diet soft drinks or low-calorie sodas and the risk of stroke or dementia. However, it is important to note that the composition of the beverages, also with regard to individual sweeteners, was not defined.

In the cross-sectional study by Pase et al. (2017a) a significant association was observed between the consumption of diet soft drinks and impaired cognitive performance of visual and verbal memory as well as reduced brain volume, and it was concluded that these neurological criteria were preclinical markers for Alzheimer's disease. From the BfR’s point of view, however, the significance of this study is limited due to the cross-sectional design and the resulting lack of temporal correlation.

In the second study by Pase et al. (cohort study, 2017b), however, a significant association was shown between the consumption of artificially sweetened beverages and dementia diagnosed according to established clinical criteria. Here, the effect was only significant in the statistical model that adjusted for energy intake and physical activity, but not for the waist-to-hip ratio, cardiovascular risk factors, or BMI. After the model was additionally adjusted for cardiovascular risk factors and T2DM, the association between a higher intake of artificially

[14] https://www.aerzteblatt.de/nachrichten/74300/Framingham-Studie-sieht-Suessstoff-als-Schlaganfall-und-Demenzrisiko

sweetened beverages and dementia was no longer significant. As Pase et al. (2017b) themselves acknowledged, T2DM, a recognised risk factor for dementia, occurred more frequently in individuals who regularly consumed artificially sweetened beverages, so reverse causality cannot be ruled out (that people with diabetes might tend to consume more non-nutritive sweeteners with the intention of preventing a worsening of their health condition). Obesity and/or T2DM with or without insulin resistance are suspected to negatively influence cognitive decline, including memory (Uranga and Keller, 2019). Parameters that are being discussed as risk factors in the development of cognitive impairments – such as obesity, insulin resistance, diabetes or cardiovascular risk factors – would consequently have to be considered as possible confounders in the study analysis.

Four cohort studies reported on the endpoint stroke. In three studies (Bernstein et al., 2012; Mossavar-Rahmani et al., 2019; Pase et al., 2017b), the consumption of low-calorie soft drinks, diet soft drinks and artificially sweetened drinks (> 1/day to ≥ 7/day compared to no consumption) was associated with a higher risk of stroke. This effect was not observed in the study by Gardener et al. (2012), but was observed in a combined analysis of the endpoints stroke, myocardial infarction and death due to cardiovascular diseases (Gardener et al., 2012).

However, limitations must also be considered with regard to these results: Bernstein et al. (2012), for example, did not adjust for classic cardiovascular risk factors or for BMI and energy intake in relation to haemorrhagic stroke. Mossavar-Rahmani et al. (2019) did not find any significant interaction between BMI and the consumption of artificially sweetened beverages with regard to stroke when using BMI as a continuous variable. However, when results were stratified by BMI, there was an association between high consumption of these beverages and an increased risk of ischemic stroke in those who had a BMI above 30. Based on the observations, a possible non-linear relationship between BMI and risk of stroke was suspected. In the analyses by Pase et al. (2017b), adjustments were made for the confounders waist-to-hip ratio, physical activity and energy intake, but not for BMI.

In all of the aforementioned observational studies, consumption frequencies were determined using questionnaires (FFQs); a breakdown of the non-nutritive sweeteners contained in the beverages was not reported, nor was any consumption of other foods containing non-nutritive sweeteners. In addition, in some studies, beverage consumption was only recorded at the beginning of the study. A change in lifestyle and dietary behaviour over the years can therefore not be ruled out. In many cases, possible confounders were not taken into account.

Overall, it is noted that no reliable conclusion can be drawn on the basis of the studies mentioned above as to whether the consumption of non-nutritive sweeteners via beverages is causally related to the development of stroke or dementia in humans. The question of whether people with pre-existing conditions that might predispose them to a higher regular consumption of non-nutritive sweetener-containing beverages, such as people with diabetes mellitus, might have a higher sensitivity to possible adverse effects of non-nutritive sweeteners than other population groups, can also not be answered on the basis of the available study data.

3.2.6 Influence of sweeteners on the gut microbiome

3.2.6.1 Animal studies to investigate effects on the microbiome

The vast majority of studies to date investigating the possible effects of sweeteners on the gut microbiome *in vivo* have been carried out in experimental animals, in particular in rodents (rats, mice).

Rodent studies showed that administration of high doses of individual sweeteners (saccharin, cyclamate, sucralose, acesulfame K) well in excess of their respective ADIs, resulted in

weight gain or enlargement of the caecum (appendix) or an increase in the contents of the caecum (Sims and Renwick, 1983; Anderson and Kirkland, 1980; Gaunt et al., 1976; Mayer et al., 1978a and Mayer et al, 1978b); Goldsmith et al., 2000; Mann et al., 2000). Compared to rodents, the caecum in humans is only a small section of the large intestine and has hardly any fermentation properties (Nguyen et al., 2015). The significance of the caecum effects that occurred at high doses of non-nutritive sweeteners in the animal experiments is therefore unclear for humans.

Rodents administered high doses of sweeteners, repeatedly showed symptoms such as polydipsia, polyuria and diarrhoea (Anderson et al., 1988; Chowaniec and Hicks, 1979; Goldsmith, 2000; JECFA, 1990; Palmnäs et al., 2014; Schoenig et al., 1985).
Furthermore, effects on the composition of the faecal microbiome and metabolite as well as bile acid profiles (serum, faeces, caecum) could be observed after administration of individual sweeteners as commercial products in various animal models, especially in rodents (Bian et al., 2017a; Suez et al., 2014; Anderson, 1980; Palmnäs et al., 2014; Bian et al., 2017b; Bian et al., 2017c; Kille et al., 2000; Uebanso et al., 2017). However, many of these studies contain numerous methodological weaknesses. In some studies, body weight, energy or feed intake, as well as fluid intake changed after administration of individual sweeteners (Anderson and Kirkland, 1980; Palmnäs et al., 2014; Wang et al., 2018). A change in these parameters alone can influence the gut microbiome. In further studies, no information was given on the parameters mentioned above; therefore, their results on the gut microbiome must be viewed with caution.

In toxicity studies on subacute or chronic effects, the administration of various sweeteners (e.g., cyclohexylamine (cyclamate metabolite), sodium saccharin, aspartame, sucralose or acesulfame K) at high doses (>0.6 % in the diet) led to a lower body weight increase in rodents compared to the control group. This may be mainly due to a lower feed intake of the animals, with partially increased fluid intake (Gaunt et al., 1976; Goldsmith, 2000; Ishii et al., 1981; JECFA, 1990; Schoenig et al., 1985). In the identified studies on the microbiome, usually only one dose of the sweetener was compared with the control group. A dose-response relationship for changes in the microbiome after sweetener intake can therefore not be derived.

3.2.6.2 Effects on the human gut microbiome

There is ample evidence that the intestinal flora may be involved in the development of obesity and other chronic diseases (e.g., intestinal diseases) (Lynch and Pedersen, 2016). For this reason, the BfR also assessed potential effects of non-nutritive sweeteners on the human gut microbiome. The literature search identified only a small number of human studies that investigated the relationship between the intake of non-caloric sweeteners and effects on the gut microbiome (Frankenfeld et al., 2015; Suez et al., 2014; Wills et al., 2014; Wills et al., 1981; Farup et al., 2018; Young et al., 2018).
In a cross-sectional study, 31 adults were divided into groups, based on the results of a four-day dietary protocol: persons who had consumed either aspartame (5.3-112 mg/day) and/or acesulfame K (1.7-33.2 mg/day), or neither sweetener. On the day after the four-day survey period specified for the dietary protocol, participants provided a stool sample. Analysis of the faecal microbiome of those who had consumed sweeteners showed no differences in the abundance of bacterial classes and the ratio of *Bacteroidetes* to *Firmicutes*, but there were differences in microbial diversity as compared to non-consumers (Frankenfeld et al., 2015).

In an observational study, 381 non-diabetic participants were asked about their intake of non-caloric artificial sweeteners using a dietary questionnaire. A correlation between sweetener

intake and bacterial abundance was found, independent of BMI, with elevated levels of *Enterobacteriaceae*, *Deltaproteobacteria* and *Actinobacteria* in the participants' faecal samples[15] (study outlined by Suez et al., 2014; raw data not published).
Healthy adults from the study by Suez et al. (2014), who reported that they did not consume any non-caloric sweeteners, were given a high dose of saccharin (120 mg three times a day) for one week, which corresponded in total to the ADI of saccharin of 5 mg/kg body weight. Depending on the glycaemic response after a glucose tolerance test, the seven subjects were divided into so-called 'responders' (n=4) and 'non-responders' (n=3). The 'responders' had transiently increased glucose levels in the glucose tolerance test on days 5-7 of the study compared to days 1-3. Analysis of the microbiome revealed differences in composition between 'responders' and 'non-responders' both before and after one week of saccharin intake. After transplantation of the 'responder' microbiome into germ-free mice, an increased occurrence of *Bacteroides fragilis (Bacteroidales)* and *Weissella cibaria (Lactobacillales)* and a lower frequency of *Candidatus Arthromitus (Clostridiales)* were found, comparable to the human microbiota of the donors (Suez et al ., 2014).
Regarding this study, it should be noted that the composition of the gut flora seemed to change from day to day both in the group of 'responders' and in the group of 'non-responders'. Due to these fluctuations, the BfR is of the opinion that it is not possible to conclude on a causal relationship between saccharin intake and changes in the glucose tolerance test on the basis of changes in the gut flora in the subjects examined. Another weakness of this human study with seven participants is that there was no control group (without any sweetener intake). Although glucose tolerance tests can be influenced, for example, by very low carbohydrate intake during the preceding days, the study by Suez et al. (2014) provided no further details on the composition of individual diets before or during the test period. From the BfR´s point of view, the reliability of this human study involving only seven participants is limited.

In a cross-sectional study by Farup et al. (2018), faecal samples from 90 severely obese participants (BMI >40) were examined using a GA-Map™ dysbiosis test and an alternative dysbiosis index was established using another cohort with irritable bowel syndrome to characterise and distinguish between different ('good' and 'bad) forms of dysbiosis (imbalance between bacterial species). An association between the consumption of non-nutritive sweeteners (via beverages) and the occurrence of dysbiosis was found, that was deemed to represent 'bad' dysbiosis, based on the alternative dysbiosis index established by Farup et al. (Farup et al., 2018).

Wills et al. (1981) observed changes in stool consistency in men given sodium cyclamate for a period of seven months. The intake of 10 or 16 g/day of sodium cyclamate led to softer stools and an increase in diarrhoea symptoms in the volunteers, whereby these effects were reversible by reducing the dose and did not occur at a dose of 5 g/day (Wills et al., 1981). The composition of the intestinal or faecal bacterial populations was not examined in this study. The applied doses, at which the gastrointestinal effects occurred in humans after cyclamate consumption, were 20 and 30 times higher than the ADI of cyclamate (7 mg/kg bw/day), based on a body weight of 75 kg.

In a published conference abstract by Young (EASD Congress 2018), a study was presented in which the participants received 92 mg sucralose and 52 mg acesulfame K for 14 days via oral capsules. The microbiome in the faecal samples was examined using shotgun metagenomic sequencing and low levels of *Eubacterium cylindroides*, *Bifidobacterium*, *Lactobacillus* and *Bacteroides* were detected, while the number of 11 pathogenic bacterial strains increased according to the report (Young, 2018).

Overall, the identified animal and human studies indicate that the intake of certain sweeteners may contribute to a change in the gut microbiome. Since usually only one dose was

[15] https://clinicaltrials.gov/ct2/show/NCT01892956?term=NCT01892956&rank=1

tested in the animal studies on the microbiome, it was not possible to establish any dose-response relationships that might in principle support an association between sweetener intake and changes in the microbiome.

Finally, it is important to consider that various factors can change the composition of the microbiome, e.g., the type of diet or taking certain medications (Zhi et al., 2019). The temporal dynamics and the heterogeneity of the microbiome (both between different animal species and between individual humans) represent two other essential factors that make it much more difficult to compare study results both between and within a species.

The health risk assessment of sweeteners focuses on the question of whether sweeteners (depending on the dose) could have adverse health effects. In order to increase the informative value of future studies, it would be important to determine the functionality and relevance of certain changes in the microbiome with regard to possible undesirable health effects, e.g., with respect to weight gain or development of T2DM. A possible change in the microbiome under test substances could theoretically be considered as a predictive marker for an undesirable effect if it would correspond to a specific microbiome risk profile that had already been characterised with regard to an increase in the risk of certain undesirable effects.

Overall, the existing data on a postulated association between the consumption of certain sweeteners and the occurrence of relevant adverse health effects that could be mediated by a change in the gut microbiome are incomplete. In particular, the few human studies to date have numerous methodological weaknesses. Their informative value with regard to health effects in connection with the consumption of sweeteners in amounts that do not exceed the respective ADI is considered to be low. From the BfR's point of view, their relevance for the risk assessment of sweeteners, individually or in combination, cannot be conclusively assessed at present.

3.3 Are there certain sensitive groups in the population that should avoid or limit the intake of sweeteners?

The question arises whether children might show a special sensitivity to adverse effects of non-nutritive sweeteners during (early childhood) development. In the following, studies conducted with subpopulations (children, pregnant or breastfeeding women) were assessed, in which the influence of non-nutritive sweeteners on eating behaviour, general behaviour and cognitive performance as well as on other adverse effects and diseases had been investigated.

3.3.1 Assessment in relation to eating behaviour (satiety, sweet taste) in children and adolescents

3.3.1.1 Feeling of satiety

In a study by de Ruyter et al. (2013), the consumption of sugar-sweetened or non-nutritive sweetener-containing beverages in children (in addition to a snack during the morning school break) produced a comparable feeling of satiety. The parameter 'satiety' of the respective drink was recorded using a 5-point scale questionnaire – one minute before, one minute after and 15 minutes after consumption of the snack and the drink; the parameter 'wanting' one minute before and the parameter 'liking' one minute after consumption of the snack.
The increase in the feeling of fullness (by one point according to subjective assessment) was assessed using an adjusted odds ratio (OR) and was 0.77 (95 % CI: 0.46-1.29) one minute after intake of sugar-sweetened versus artificially sweetened beverages and 1.44 (95 % CI: 0.86-2.40) after 15 minutes. The group that consumed sugary drinks liked the sugar-sweetened drink more (adjusted OR 1.63; 95 % CI 1.05-2.54) and had a slightly stronger craving

for it than those children who received the artificially sweetened drink (adjusted OR 1.65; 95 % CI 1.07-2.55) (de Ruyter et al., 2013).

3.3.1.2 Sweet taste

The preference for sweet taste is most pronounced in infants. They are born with a preference for sweet taste. From an evolutionary perspective, infants and young children are therefore particularly receptive to sweet, energy-rich foods (such as breast milk). The sensation of sweet taste also exerts an analgesic effect - mediated via endogenous opioids and non-opioid components such as dopamine (Pepino and Mennella, 2005). A study with newborns showed that both a sugar solution and an aspartame solution (with the same sweetening power) compared to water or polycose (polysaccharide made up of glucose units) were able to calm crying babies (Barr et al., 1999), suggesting that the infants could not distinguish between sucrose and aspartame, but reacted solely to the sweet taste of these two solutions. It was also shown that children liked higher concentrations of sucrose and aspartame compared to adults. Regardless of age, sweet preference did not differ between obese and non-obese participants (Bobowski and Mennella, 2017).

Preferences for sweet taste declines to adult levels in mid to late adolescence, which coincides with the cessation of physical growth (Mennella and Bobowski, 2015). The question arises whether children who grow up in an environment in which they are habitually exposed to sugar, sweetened and highly processed foods at a particularly early age develop a higher susceptibility to overconsumption of these products and whether this learned behaviour shapes their dietary behaviour later in life (Baker and Baker, 2015).

Sweet taste receptors are mediated through different classes of taste receptors. Taste receptor cells are secondary sensory cells that form synapses with afferent neurons of the cranial nerves. Sweet compounds are detected by T1R heterodimers (T1R2+T1R3). Compounds detected include sucrose, fructose, glucose and the artificial sweeteners saccharin, acesulfame K, aspartame, cyclamate, thaumatin, and steviol glycosides. Saccharin and acesulfame K also interact with the bitterness receptors T2R44 and T2R43 (Yarmolinsky et al., 2009). Steinert et al. (2011) showed that sweet receptors in the intestine reacted more strongly to glucose from food, weaker to fructose and to an even less extent to calorie-free non-nutritive sweeteners such as aspartame. Only glucose caused a stimulation of GLP-1 and PYY secretion and a drop in ghrelin levels, while fructose had a much smaller effect and artificial sweeteners *per se* had no effect.

Currently, there is insufficient evidence to be able to assess whether dietary intake of sweeteners could significantly influence satiety and sweet taste in terms of imprinting a sweet preference in children and adolescents.

3.3.2 Assessment in relation to behaviour and cognitive performance in children

The number of studies investigating the influence of non-nutritive sweeteners on the above parameters in children is limited. The effect of aspartame has been tested, in particular, since aspartame (α-aspartyl-l-phenylalanine-o-methyl ester) is metabolised in the body to the two amino acids aspartic acid and phenylalanine as well as methanol. In the following, the results of selected randomised controlled intervention studies on non-nutritive sweeteners that were conducted in children and adolescents with regard to the target variables behaviour and cognition (Kruesi et al., 1987; Wolraich et al., 1994; Shaywitz et al., 1994) are presented.

In Wolraich et al. (1994) a 3-week intervention with aspartame (38 mg aspartame/kg body weight per day) did not lead to changes in behaviour or cognitive performance in children who, according to their parents, were sensitive to sugar. Neither sucrose nor aspartame (38 mg/kg bw) affected the behaviour or cognitive function of preschool or school children. This

is also confirmed by the results of Shaywitz et al. (1994): In the crossover study, 15 children (11 boys and 4 girls aged 5-13 years) with attention deficit hyperactivity disorder received one tablet of aspartame (34 mg/kg body weight per day) or a placebo every morning for two weeks each. Aspartame intake did not lead to behavioural or cognitive changes (Shaywitz et al., 1994). A study by Kruesi et al. (1987) also showed that the intake of beverages sweetened with aspartame or saccharin in 30 male preschool children (2-6 years) did not influence their aggressive behaviour.

As part of its re-evaluation of aspartame, EFSA also assessed possible effects on children's behaviour and cognition and concluded that aspartame had no effects on children's behaviour and cognitive performance (EFSA, 2013).

Overall, the current human studies do not indicate a negative impact of aspartame on behaviour and cognitive performance in children.

3.3.3 Assessment in relation to other adverse effects or diseases in children and adolescents

3.3.3.1 Diseases of the internal organs (liver, kidneys)

No recent study could be identified that investigated effects of non-nutritive sweeteners on parameters of liver and kidney metabolism in children and adolescents. Two studies from the 1970s did not observe any changes in blood creatinine concentrations after intervention with aspartame in children and adolescents (Frey, 1976; Knopp et al., 1976).

3.3.3.2 Early menarche

Mueller et al. (2015) investigated the effect of diet drinks on the timing of menarche in a long-term study in 1,988 girls and found that the consumption of caffeinated and artificially sweetened beverages was associated with an increased risk of premature onset of menarche (artificially sweetened beverage consumption: 0 to <1 serving/d and ≥1 serving/d, RR: 1.25 and 1.66, respectively; reference: 0 servings) (Mueller et al., 2015). A limitation of this study is the lack of information as to which ingredients in the beverages or beverage categories could have caused the associations shown. It is therefore not possible to delineate which ingredients or combinations of ingredients might have been associated with the increased risk of premature menarche. In addition, the observed effect of premature menarche could also have been a consequence of weight gain, a change in dietary pattern or a desire to lose weight, resulting in an increased consumption of artificially sweetened beverages.

3.3.4 Effects of non-nutritive sweetener consumption during pregnancy and breastfeeding on offspring

In the US, the prevalence of non-nutritive sweetener consumption among pregnant women increased from 16.2 % in 1999-2004 to 24.0 % in 2007-2014, with the highest prevalence in 2005-2006 (38.4 %). This trend was mainly caused by the increase in the consumption of artificially sweetened beverages (9.9 % in 1999-2004 versus 18.3 % in 2007-2014). The prevalence of low calorie sweetener consumption was highest among non-Hispanic white pregnant women and increased with education and income. No differences in non-nutritive sweetener consumption were observed in relation to pre-pregnancy BMI or depending on the trimester of pregnancy (Sylvetsky et al., 2019).

3.3.4.1 Congenital heart defects (CHD)

In a study in Norway, Dale et al. (2019) investigated the association between the intake of sucrose-sweetened soft drinks during the first trimester of pregnancy and the risk of congenital heart defects in offspring. A total of 88,514 pregnant women participated in the study (as part of the Norwegian Mother and Child Cohort Study, MoBa). The consumption of artificially sweetened beverages by the pregnant women showed no association with the incidence of congenital heart defects in the offspring. Adjustment was made for the following covariates: year of birth, parity, maternal age at birth, education, T2DM, BMI and smoking before pregnancy (Dale et al., 2019).

3.3.4.2 Effects on the body weight of offspring

The following section presents the results of one randomised controlled trial and three cohort studies on non-nutritive sweeteners conducted in pregnant women in relation to the target variable offspring body weight and non-nutritive sweetener consumption.

Intervention Study

Renault et al. (2015) showed that the consumption of non-nutritive sweetener- and sugar-containing beverages during pregnancy could increase the risk of excessive weight gain in obese women during pregnancy, although the associations were unclear. In the three-arm intervention study, 342 women were assigned to either the control group, intervention group 1 (physical activity), or intervention group 2 (physical activity plus nutritional intervention). Intervention group 2 was instructed to both change their diet to an energy-reduced Mediterranean diet and to walk 11,000 steps a day. Compared to the control group, intervention group 2 had a lower relative risk of gaining excessive weight (RR 0.73; 95 % CI: 0.57–0.94), while there was no difference between intervention group 1 and the control group in terms of weight gain. In addition, an analysis of all participants was performed to examine associations between dietary variables and gestational weight gain during pregnancy. Consumption of foods with added sugars represented the only variable associated with excess weight gain during pregnancy. Women at 11-14 weeks' gestation who reported drinking ≥1 artificially sweetened carbonated soft drink per day at baseline showed an average 2 kg higher weight gain, although the trend for consumption of artificially sweetened soft drinks was not significant. An interesting finding of this study is the observation that pregnant women with high weight gain more often consumed non-nutritive sweetener-containing soft drinks to regulate their weight, so reverse causality cannot be ruled out (Renault et al., 2015).

Cohort studies

The Deutsches Ärzteblatt summarised the results of a cohort study from 2016 in the title as follows: "Artificial sweeteners in pregnancy make children fatter". At the same time, however, it was pointed out that this did not prove causality. The results of the prospective cohort study by Azad et al. (2016) with 3,033 mother-child pairs cited there, showed that the daily intake of artificially sweetened beverages by pregnant women was associated with an increased risk of an increase in BMI z-score (0.20; adjusted 95 % CI: 0.002-0.38) in infants. The comparison group included women who did not consume artificially sweetened beverages. In addition, the daily intake of non-nutritive sweetener-containing beverages by pregnant women was associated with an increased risk for the children to be overweight at one year of age (adjusted OR 2.19; 95 % CI: 1.23-3.88). The prevalence of non-nutritive sweetener-containing beverage consumption during pregnancy was almost 30 %, with 5 % of participants reporting daily consumption of artificially sweetened beverages. By contrast, 77 % of participants reported drinking sugar-sweetened beverages, 23 % of them daily. However, consumption of sugar-sweetened beverages was not associated with infant BMI z-score (0.07; 95 % CI: -0.06 to 0.19, daily consumption vs. non-consumption). Pregnant participants who had diabetes (pre-existing diabetes or gestational diabetes) more often consumed artificially sweetened beverages, but less frequently sugar-sweetened drinks. Consumption of both artificially and sugar-sweetened beverages was associated with maternal smoking, higher BMI,

unhealthy dietary behaviour and shorter duration of breastfeeding. Limitations of the study are the possible bias in self-reported nutrient intakes, as the food consumption questionnaire (FFQ) was not specifically validated for beverage consumption. In addition, neither the type nor the dose of non-nutritive sweeteners used in the beverages could be identified, and non-nutritive sweetener intake via solid food consumption could not be taken into account (Azad et al., 2016).

Zhu et al. (2017) showed that primary school-aged children whose mothers had gestational diabetes during pregnancy and consumed at least one artificially sweetened beverage per day had a higher risk of being overweight or obese than children whose mothers were healthy and preferred water instead of artificially sweetened beverages during pregnancy. For this purpose, 918 mother-child pairs from the Danish National Birth Cohort were included in the study. However, daily consumption of a drink sweetened with either non-nutritive sweeteners or sugar during pregnancy showed an adverse effect: at the age of 7, their children were at an equally high risk of being overweight or obese. In contrast, pregnant women who replaced sweetened beverages with water reduced their children's risk of obesity by 17 % (Zhu et al., 2017).

Another cohort study by Gillman et al. (2017), however, could not confirm these results for children of primary school age. The aim of this study was to determine the impact of the consumption of sugary and non-nutritive sweetener-containing beverages during the first and second trimester of pregnancy on possible obesity-associated secondary diseases in school children (median age: 7.7 years) in 1,078 mother-child pairs participating in the preterm cohort study within the framework of the Project Viva. Women who already had T1DM or T2DM or who had suffered from gestational diabetes in their previous pregnancy were excluded from participating in the study. In the second trimester, participants consumed an average of 0.6 ± 0.9 (range 0.0-8.3) servings of sugar-sweetened beverages (sugary soda, fruit drinks) or an average of 0.2 ± 0.5 servings of artificially sweetened beverages (diet soda) per day. Almost 60 % of the pregnant women consumed less than half a serving of sugar-sweetened beverages daily and only about 8 % of the participants drank two or more servings of it per day. The results show that a quarter of the primary school-aged children were overweight or obese. The incidence of obesity was highest among children (BMI ≥ 85th percentile) whose mothers had consumed at least two or more sugar-sweetened beverage servings per day in the second trimester of pregnancy (category ≥3 vs. 0 to <0.5 sugar-sweetened beverages/day: 45 % vs. 22 %). In contrast, consumption of artificially sweetened beverages showed no association with the incidence of obesity in children (Gillman et al., 2017).

Reviews

Two reviews were identified that examined the potential adverse effects of sugar and non-nutritive sweetener consumption during pregnancy on maternal and child health.

Araujo et al. (2014) investigated the effects of non-nutritive sweetener exposure during pregnancy on the long-term disease risk in offspring with a particular focus on metabolic diseases. They pointed out that the results of studies in mice suggested that long-term consumption of non-nutritive sweeteners, especially aspartame, may increase the risk of obesity and of developing metabolic syndrome in the course of life (Collison et al., 2012a; Collison et al., 2012b). The paper also discussed biological mechanisms in the human organism, which could underlie possible adverse metabolic effects of non-nutritive sweeteners, such as increased intestinal glucose uptake, alterations of the gut microbiome, induction of oxidative stress and dysregulation of the appetite and reward systems. Araujo et al. (2014) concluded that the consumption of non-nutritive sweeteners in pregnant and breastfeeding women should be done with particular caution and that further studies are needed.

Goran et al. (2018) also pointed out that the consumption of sugar and non-nutritive sweeteners during pregnancy could affect the long-term health of the offspring. The authors stated that there were indications that the consumption of non-nutritive sweeteners and added sugars during pregnancy may contribute to increased body weight gain and the development of pregnancy complications such as gestational diabetes and preterm birth. It was noted that further research was required in this area, as the consumption of sugar and non-nutritive sweeteners might have negative effects on pregnancy and the health of offspring (Goran et al., 2018).

Overall, some observational studies in pregnant women indicate that exposure to both sugar-sweetened beverages and beverages sweetened with non-nutritive sweeteners may have health effects on child development at one year of age and at around seven years of age (Azad et al., 2016; Zhu et al., 2017). In this context, an increased risk of weight gain beyond the physiological level and an increase in the incidence of obesity in the course of early childhood have been discussed in particular. Since, however, a causal relationship cannot be derived and the possible underlying (biological) mechanisms for the observed effects are currently not known, further research is required. Since the study situation is limited and the results are inconsistent, it cannot be conclusively assessed whether the consumption of non-nutritive sweetener-containing beverages during pregnancy has a long-term negative effect on the development of the child.

3.3.4.3 Assessment of non-nutritive sweetener consumption in relation to the risk of preterm birth in pregnancy

Possible associations between the consumption of artificially or sugar-sweetened beverages and the risk of preterm birth[16] were investigated in three observational epidemiological studies (Halldorsson et al., 2010; Englund-Ogge et al., 2012; Petherick et al., 2014) and two reviews (Goran et al., 2018; Araujo et al., 2014).

In two large prospective cohort studies from Denmark and Norway, each with around 60,000 participants, there was a statistically significant increase in the risk of preterm birth with increasing consumption of artificially sweetened drinks (carbonated and non-carbonated) compared to non-consumption during pregnancy.
In the study by Halldorsson et al. (2010), the prevalence of preterm birth was 4.62 %, with preterm birth being medically induced in one third of the cases. Pregnant women who drank four or more artificially sweetened beverage servings per day, had an adjusted OR of 1.78 (95 % CI 1.19–2.66, carbonated) or OR of 1.29 (95 % CI 1.05–1.59, non-carbonated) relative to non-consumers, with the risk being highest for medically induced preterm births (OR 1.75; 95 % CI: 1.34–2.30), but not significant for spontaneous preterm births (OR 1.20; 95% CI: 0.95–1.51). It also mattered whether the preterm birth was early (< 32 weeks gestation) or late (< 37 weeks gestation): OR 1.67 (< 32 weeks gestation) vs. 1.31 (< 37 weeks gestation). In contrast, no association was observed for the consumption of sugar-sweetened carbonated or non-carbonated drinks. Adjustments were made for factors predisposing to preterm birth: maternal age, maternal height, pre-pregnancy BMI, partnership status, parity, smoking during pregnancy, and socio-economic status. The study has the following limitations: The type and dose of non-nutritive sweeteners ingested could not be specified; furthermore, no other dietary sources of non-nutritive sweeteners (e.g., non-nutritive sweeteners added to coffee, tea or other foods) were considered for the exposure assessment. Residual confounding factors may have skewed the results.

[16] A preterm birth is defined as a birth that occurs before the 37th week of pregnancy. Data on the date and type of birth (spontaneous or medically induced) were obtained from the national birth register of the respective country.

Englund-Ogge et al. (2012) tried to reproduce the results of Halldorsson et al. (2010) and addressed the postulated association between the consumption of artificially and sugar-sweetened beverages as well as hot beverages (coffee, tea) sweetened with non-nutritive sweeteners and the risk of preterm birth as the primary outcome measure. In contrast to the results of the Danish study, they observed a much weaker association between artificially sweetened beverage consumption and preterm birth: the OR in the highest artificially sweetened beverage consumption category (>1 servings/day) vs. no consumption was 1.11 (95 % CI 1.00–1.24). In addition, the association between sugar-sweetened beverage intake of more than one serving/day and the risk of preterm birth was stronger with an adjusted OR of 1.25 (95% CI 1.08–1.45). There were no significant trends between the risk of preterm birth and increasing consumption of both artificially and sugar-sweetened beverages (Englund-Ogge et al., 2012).

EFSA assessed both studies in 2013 as part of its re-evaluation or reassessment of aspartame and came to the conclusion that the epidemiological data available up to that point did not indicate that the consumption of artificially sweetened beverages causally increases the risk of preterm birth. It was assumed that even with high exposure to artificially sweetened beverages, the risk of preterm birth was not or hardly increased and that the observed associations could be attributed to residual confounding and inconsistencies in the association patterns (EFSA, 2013).

Another study by Petherick et al. (2014), involving around 9,000 healthy pregnant women, suggested that consumption of sugar-sweetened cola drinks might increase the risk of preterm birth, but not the consumption of colas sweetened with non-nutritive sweeteners. When consuming more than four servings of sugar-sweetened beverages per day compared to non-consumption the OR was 1.81 (1.03–3.17). However, the prevalence of cola consumption among participants was low; only one in seven women reported drinking sugar-sweetened cola and only one in 20 participants consumed cola sweetened with non-nutritive sweeteners. Adjustments were made for a range of factors including BMI, height, marital status, parity, smoking, education and ethnicity, but not for energy intake.

Overall, the current study situation does not allow to conclude on a possible association between the consumption of artificially sweetened beverages and the risk of preterm birth. Based on the current state of research, the underlying reasons or mechanisms for the associations reported in cohort studies between the consumption of beverages sweetened with non-nutritive sweeteners or sugar and the risk of preterm birth are not known.

3.3.4.4 Gestational diabetes and cardiometabolic risk markers

In a prospective cohort study, Hinkle et al. (2019b) investigated possible associations between artificially sweetened beverage consumption in 607 women with a high-risk pregnancy (due to diagnosed gestational diabetes) from the Danish National Birth Cohort from 1996 to 2002. After a follow-up of 9-16 years, artificially sweetened beverage consumption was recorded again and cardiometabolic risk markers (HbA1c, insulin, HOMA-IR, TG, HDL, LDL, liver enzymes, BMI, liver fat percentage) were determined as part of the *Diabetes and Women's Health Study*. After adjustment for the covariates (pre-pregnancy BMI, educational level, smoking, physical activity, chronic diseases, age), no significant associations between artificially sweetened beverage consumption (during pregnancy and follow-up) and cardiometabolic risk markers were detectable (Hinkle et al., 2019b).

In a different study, Hinkle et al. (2019a) investigated associations between the consumption of sugar-sweetened beverages, artificially sweetened beverages, coffee and tea during pregnancy and the risk of developing gestational diabetes. For this purpose, 2,802 pregnant women filled out a nutrition questionnaire in each trimester. Associations between consump-

tion of the above-mentioned beverages and cardiometabolic biomarkers were also investigated in two subgroups. Gestational diabetes affected 4.3 % of the women during pregnancy. More than 70 % of the pregnant women reported that they had never consumed artificially sweetened beverages in the first trimester. Consumption of one serving of a beverage sweetened with non-nutritive sweeteners in the first trimester compared to subjects who did not consume non-nutritive sweeteners was not associated with an increased risk of gestational diabetes (RR = 0.53; 95 % CI: 0.16-1.80). Similar results were also shown in the second and third trimesters (Hinkle et al., 2019a).

In conclusion, an association between the consumption of artificially sweetened beverages during pregnancy and a risk of gestational diabetes and cardiometabolic diseases cannot be deduced on the basis of the currently available studies.

3.3.4.5 Asthma and chronic rhinitis

Maslova et al. (2013) investigated the association between the intake of artificially sweetened beverages during pregnancy in a study involving 60,466 pregnant women from the Danish National Birth Cohort, and the risk of their children in developing asthma and allergic rhinitis at 18 months of age and over a seven-year follow-up. 13 % of pregnant women in this study reported consuming beverages sweetened with artificial sweeteners. The prevalence of asthma in children was 17 % at the age of 18 months and 4 % at 7 years of age. Compared with not consuming non-carbonated artificially sweetened beverages during pregnancy, consumption of at least one non-carbonated artificially sweetened beverage serving per day was associated with an increased risk of asthma in three of the four case definitions (OR 1.23; 95 % CI: 1.13–1.33) for asthma at 18 months of age, but not for daily consumption of carbonated artificially sweetened beverages. In the analysis of the association between carbonated artificially sweetened beverages and asthma diagnosed during the first seven years of life, an OR of 1.30 (95 % CI: 1.01–1.66) was determined. However, this association was not evident with non-carbonated artificially sweetened beverage consumption. Allergic rhinitis was not significantly associated with daily artificially sweetened beverage consumption. Adjustment was made for various confounders: maternal age, smoking, parity, pre-pregnancy BMI, physical activity, breastfeeding, socio-economic status, sex of the child, asthmatic and allergic diseases of the parents, and energy intake during pregnancy (Maslova et al., 2013). In the context of the overall evaluation, the reported associations can only be acknowledged as weak indications, considering the inconsistent results regarding artificially sweetened beverages with and without carbonic acid.

A correlation between the consumption of artificially sweetened beverages during pregnancy and the diagnosis of asthma or allergic rhinitis in the offspring cannot be derived on the basis of the study situation.

3.3.5 Non-nutritive sweeteners in breast milk and amniotic fluid

3.3.5.1 Breast milk

The results of observational studies and reviews carried out in breastfeeding women on the target variables of maternal consumption of non-nutritive sweeteners and possible exposure of infants to non-nutritive sweeteners in breast milk are presented below (Tab. 1). The *Drugs and Lactation Database* (LactMed®) of the US *National Library of Medicine* (NLM) was used as data source[17]. It contains information on drugs and other chemicals to which breastfeeding mothers may be exposed, the concentrations of these substances in breast milk and infant blood, and possible adverse effects in the infant. A peer review panel validates the data, which are updated at regular intervals.

[17] https://toxnet.nlm.nih.gov

In a recent study by Rother et al. (2018) on the pharmacokinetics of sucralose and acesulfame K, 34 exclusively breastfeeding women (14 normal weight, 20 obese) consumed 355 ml of a diet coke sweetened with 68 mg sucralose and 41 mg acesulfame K before eating a standardised breakfast. (Note: ADI value according to SCF: 0–15 [sucralose] or 0–9 [acesulfame K] mg/kg bw). Habitual consumption of non-nutritive sweeteners was recorded using a dietary questionnaire. Breast milk samples were collected from the same breast prior to ingestion of the test drink and every hour over a period of six hours. Acesulfame K rapidly appeared in breast milk after consumption of the test drink, while sucralose was not detectable until two hours after ingestion, with large inter-individual variations in concentrations. The median peak concentration of sucralose in breast milk was 0.0081 mg/l; that of acesulfame K was 0.95 mg/l and thus above the perceptible concentration for sweet taste (Couper and Couper, 2018). In an earlier study, Sylvetsky et al. (2015) had already detected the sweeteners acesulfame K, sucralose and saccharin in breast milk in 12 of 20 breastfeeding subjects.

At present, it is not known whether the sweeteners aspartame, acesulfame K and sucralose, which have been detected in breast milk, could have a clinically relevant impact on infant health. Furthermore, no threshold value has yet been determined for the respective non-nutritive sweetener in breast milk, above which adverse metabolic effects could possibly occur.

Tab. 1: Non-nutritive sweeteners in breast milk; source: LactMed (https://toxnet.nlm.nih.gov).

Sweeteners	Summary
Aspartame	Aspartame is not detectable in breast milk after intestinal uptake by the mother because it is rapidly metabolised. Extremely large intakes of aspartame (≃17 cans of artificially sweetened beverages or 100 *packets* [of non-nutritive sweetener in sachets for use in coffee, tea, etc.]) may slightly increase the phenylalanine concentration in breast milk. Within 12 hours, phenylalanine levels in milk return to baseline (Stegink et al., 1979; Franz, 1986; Sylvetsky et al., 2015).
Saccharin	Twenty breastfeeding women completed a questionnaire on breastfeeding behaviour and dietary intake of non-nutritive sweeteners within the previous 24 hours and submitted breast milk samples for analysis. Non-nutritive sweetener intake was mainly from artificially sweetened beverages and sweetener *packets* (non-nutritive sweetener in sachets for use in coffee, tea, etc.). Out of 14 women who reported the intake of non-nutritive sweeteners, saccharin concentrations of 0.01–1.42 mg/l were found in breast milk of four women (note: ADI value according to SCF: 0–5 mg/kg bw) (Sylvetsky et al., 2015). Due to the low saccharin concentration in breast milk, the uptake by the infant following alimentary intake by the mother is low. In the context of an assessment, Rother et al. (2015) and Sylvetsky et al. (2015) concluded that, from their point of view, saccharin was not expected to cause adverse effects in breastfed infants.
Acesulfame K	There are no well-controlled data on the extent of transfer of acesulfame K into breast milk. Variable concentrations of acesulfame K have been detected in the breast milk of breastfeeding mothers who reported consuming non-nutritive sweetener-containing beverages and so-called sweetener *packets* in the past 24 hours. Low levels of acesulfame K were also detected in breast milk of some mothers who reported not having consumed non-nutritive sweeteners (Rother et al., 2015; Rother et al., 2018; Sylvetsky et al., 2015).
Sucralose	Sucralose was detected in the breast milk of some breastfeeding mothers who reported consumption of artificially sweetened beverages and so-called sweetener *packets* within the previous 24 hours, and of all women who had received a sucralose-sweetened soft drink (Rother et al., 2015; Rother et al., 2018; Sylvetsky et al., 2015).

Sweeteners	Summary
Cyclamate	No data available.

3.3.5.2 Non-nutritive sweeteners in amniotic fluid

A human foetus swallows a significant amount of amniotic fluid, especially during the last trimester of pregnancy. The flavours and ingredients in foods eaten by the mother can be transferred to the fetus in this way (Cooke and Fildes, 2011). A human study was identified that investigated the transfer of cyclamate into the amniotic fluid: Pitkin et al. (1970) showed that radiolabelled cyclamate administered intravenously to women in early pregnancy was detectable in foetal tissues with the highest concentrations in the liver, spleen and kidneys. The cyclamate concentration in the foetus was less than one percent of the intravenous dose received by the pregnant woman (Pitkin et al., 1970).

Pitkin et al. (1971) also detected saccharin in amniotic fluid samples from pregnant rhesus monkeys over 40 years ago. The radioactively labelled saccharin was administered intravenously and absorbed to a limited extent by the foetus via the placenta. Saccharin was detectable in all foetal tissue samples, but not in the central nervous system of the foetus. Furthermore, an animal study in primates showed that ^{14}C-labelled cyclohexylamine (a metabolite of cyclamate) was detectable in the amniotic fluid (Filer, 1974).

Zhang et al. (2011) conducted an animal study in mice and investigated whether maternal exposure to the non-nutritive sweetener acesulfame K during pregnancy or lactation affected the sweetness preference of their adult male offspring. Acesulfame K was detected in amniotic fluid four hours after oral infusion of acesulfame K and intragastric administration of acesulfame K solution (10 mg/ml, 2 ml) (Zhang et al., 2011). Maternal exposure to acesulfame K during pregnancy or lactation reduced the preference thresholds for acesulfame K and sucrose in adult mice.

3.4 Further comments on the assessment of possible health effects of non-nutritive sweeteners and outlook regarding further studies

In the context of the current health assessment performed by the BfR, primarily human studies (intervention and observational studies) were considered.

Provided that they meet the relevant quality criteria (e.g., randomisation, consideration of control group(s), sufficient number of participants, clearly specified test substance, testing of different dosages), intervention studies can be highly informative (‘gold standard’) with regard to the assessment of a possible causal relationship between exposure to certain non-nutritive sweeteners and health effects. It should be noted that intervention studies that (like many of the intervention studies considered here) are only designed for a short or medium-term period of time are only suitable to a limited extent for assessing possible long-term developments. Nevertheless, short-term intervention studies may well provide insight into acute metabolic changes and/or energy intake under the influence of non-nutritive sweeteners. It can also be a disadvantage that in intervention studies under certain predefined conditions (e.g., following a defined diet plan or behavioural interventions), aspects that could play a role in long-term health developments under real-life conditions (e.g., free choice of diet, food consumption *ad libitum*) are omitted.

In observational studies in terms of prospective cohort studies, it can be advantageous that the observation takes place against the background of real dietary conditions, often over a very long period of time (over many years) and with a large number of participants. However, although associations may be shown, it is difficult to derive a causal relationship between exposure to (certain) non-nutritive sweeteners and health effects on the basis of observational studies. Possible confounders that could influence the result, such as existing overweight or a family predisposition to metabolic syndrome, play a role. In addition, the question of a possible reverse causality often arises in the context of the observational studies considered here. It is plausible that individuals with an increased risk of developing obesity or metabolic syndrome might also tend to use non-nutritive sweeteners to mitigate these risks. Consequently, it may be difficult to disentangle direct (patho-)physiological effects of a non-nutritive sweetener from possible behavioural aspects related to the use of non-nutritive sweeteners in everyday life. A precise characterisation and consideration of behavioural and dietary patterns that might be associated with the consumption of sweeteners or diet drinks is important for the interpretation of data from observational studies and for the assessment of their informative value.

A considerable uncertainty in the assessment also results, among other things, from the fact that in many human studies dealing with possible effects of non-nutritive sweeteners, the non-nutritive sweeteners involved are not broken down or indirect parameters are used to estimate exposure (e.g., frequency of consumption of certain portions of diet drinks). This is particularly true of observational studies. In the observational studies available to date, the intake of non-nutritive sweeteners via beverages (whose composition was often not defined in detail) was typically taken as a basis and the potential intake via other foods was not taken into account.

To generally consider non-nutritive sweeteners as a whole with regard to possible health effects would make sense in particular under the assumption that the effects to be investigated are group effects that could in principle be caused by each and all of the non-nutritive sweeteners. For the assessment practice, this presupposes that the postulated effects are based on common mechanisms and that these mechanisms have been characterised in detail. However, the studies (mostly animal experiments) considered in the context of authorisation procedures show that different non-nutritive sweeteners differ in their toxicological profile.

Any special features for individual non-nutritive sweeteners must therefore be taken into account in assessment of their potential health risks. For example, from the BfR's point of view, the current data situation on sucralose indicates that heating sucralose, particularly in combination with other foods, may result in the formation of compounds that are potentially harmful to health and partially carcinogenic. The BfR therefore suggests that "*the findings on the possible formation of chlorinated compounds in industrially produced foods (e.g., baked goods) or in the course of use of sucralose by consumers in cooking and baking should be brought to the attention of the EU Commission so that this aspect can be given special consideration in the re-evaluation of this sweetener as a food additive"* (BfR, 2019).

Thus, the precise characterisation of the effects of non-nutritive sweeteners as individual substances is important in order to be able to distinguish individual effects from group effects. It should also be noted that exposure to a non-nutritive sweetener has so far been considered harmless to health as long as the respective ADI, which was derived in the context of the individual substance assessment in the course of the authorisation procedure. Often, however, combinations of non-nutritive sweeteners are used in products, or different foods with different non-nutritive sweeteners may be consumed throughout the day. In this context, the BfR points out that there is a lack of studies in which the health effects of non-nutritive sweetener combinations are systematically investigated in comparison to single substances.

Overall, it can be stated that in order to improve the informative value of future human studies on sweeteners, certain quality criteria should be given greater consideration. These include, for example, an adequate number of participants in intervention studies as well as the consideration of suitable control groups and longer exposure periods. The overall background (residual confounding) with regard to individual behaviour and dietary patterns of the study participants should also be taken into account in observational or experimental studies. In order to be able to test hypotheses on possible inherent effects of sweeteners that go beyond a reduction in calorie intake (e.g., the hypothesis that the consumption of non-nutritive sweeteners might maintain or increase a preference for confectionery and sweetened beverages due to their high sweetening power), controls without sugar, e.g., with water, should also be considered.

3.5 Data on non-nutritive sweetener consumption

3.5.1 Studies in Europe

Renwick et al. (2006) provided an overview of methods for estimating non-nutritive sweetener intake and results of previous exposure assessments of several non-nutritive sweeteners. Data on intake levels of non-nutritive sweeteners (acesulfame K, aspartame, cyclamate, saccharin, sucralose) in children and adults were compiled in this review and it was concluded that the average intake of the non-nutritive sweeteners in healthy children and adults was well below the ADI values of the respective non-nutritive sweeteners (Renwick et al., 2006).

For example, for the non-nutritive sweetener sucralose, with an ADI of 0–15 mg/kg bw/day, the estimated exposure in adults was between 1 and 3 % of the ADI for average consumers and between 6 and 15 % of the ADI for high consumers (95th percentile of consumption) (Renwick, 2006).

Only for the non-nutritive sweetener cyclamate the intake above the 95th intake percentile in children could exceed the maximum ADI value. In particular, children with T1DM were already identified in the study by Ilback et al. (2003) as displaying a high intake of cyclamate (317 % of the ADI value) and of saccharin (126 % of the ADI value).

Due to their lower body weight – compared to adults – children are more likely to exceed the ADI of non-nutritive sweeteners, as a higher intake per kg body weight is achieved.

Martyn et al. (2016) estimated dietary intakes of the four non-nutritive sweeteners acesulfame K, aspartame, saccharin and sucralose in 500 children aged 1-4 years using data from the *Irish National Preschool Nutrition Survey* (2010–11) and analysis data on non-nutritive sweetener concentrations in foods and beverages. Their analyses showed that the average daily intake levels of the non-nutritive sweeteners mentioned above were below the respective ADI values (17–31 % of the ADI value). Four different intake assessment methods were used. For example, the average intake of sucralose estimated using non-nutritive sweetener consumption and concentration data was 0.65 mg/kg bw/day for average consumers and 1.97 mg sucralose/kg bw/day for high consumers. The values were well below the maximum ADI of 15 mg/kg bw/day. Martyn et al. (2016) concluded that there was no health risk for Irish preschool children if current intake levels for acesulfame K, aspartame, saccharin and sucralose were maintained. Flavoured beverages were the main source of non-nutritive sweetener intake in young children.

Dewinter et al. (2016) assessed the intake of the non-nutritive sweeteners acesulfame K, aspartame, saccharin, steviol glycosides, neotame, neohesperidin and sucralose in 242 Bel-

gian children with T1DM following a tiered approach. The concept involving 3 tiers is explained in the *Report from the Commission on Dietary Food Additive Intake in the European Union*[18]: tier 1 is based on theoretical food consumption data and on the established maximum levels for the use of the respective non-nutritive sweetener; tier 2 incorporates up-to-date national food consumption data in combination with the maximum permitted use levels of the respective non-nutritive sweetener, and tier 3 combines the actual use levels of the respective non-nutritive sweetener with national food consumption data.

Food intake in children was estimated using a food frequency questionnaire specifically designed to assess consumption of foods sweetened with non-nutritive sweeteners. Tier 2 estimates of the consumption of steviol glycosides, neotame, neohesperidin and sucralose showed that the intake amounts were below the respective ADI value for all participants. A tier 3 estimation was also performed. For example, children with T1DM had a mean and a 95th percentile value of the estimated sucralose intake of 2.6 and 8.6 mg/kg bw/day when aged 4-6 years, 2.0 and 5.1 mg/kg bw/day when aged 7-12 years, and 1.1 and 4.9 mg/kg bw/day when aged 13-18 years. In all cases, the mean and high intake estimates were well below the maximum ADI for sucralose, indicating that there were no safety concerns regarding the consumption of sucralose-containing foods by this particular group of children with T1DM who may be considered high consumers. For the non-nutritive sweeteners acesulfame K and aspartame, however, the maximum ADI values were exceeded in the age group of 4- to 6-year-old children with T1DM above the 95th percentile (high consumers) in the tier 2 analysis. The consumer-only analysis showed that the maximum ADI values for the non-nutritive sweeteners acesulfame K, aspartame, saccharin and steviol glycosides were also exceeded in high consumers in the 4- to 6-year-old age group, as well as in the age group of 7- to 12-year-old children and 13- to 18-year-old adolescents for acesulfame K and aspartame (Dewinter et al., 2016).

The exposure of children, adolescents and adults aged 3 to 97 years to five non-nutritive sweeteners (acesulfame K, aspartame, cyclamate, saccharin, sucralose) in Europe over a period from 1996 to 2007 was summarised by Logue et al. (2016) in their review. The results showed that the intake of the non-nutritive sweeteners mentioned was far below the respective ADI value. The average relative proportion of exposure (measured in % of the ADI value) ranged from 1–30 % for aspartame, for example. Only the average intake of cyclamate exceeded the permissible ADI value in the population group of children aged 1.5–4.5 years[19].

At the time of finalisation of the present opinion, current data on non-nutritive sweetener consumption in Germany was not available to the BfR, so that an estimate of the current possible utilisation of ADI values for individual non-nutritive sweeteners was not possible.

It should be noted that combinations of non-nutritive sweeteners are often used in products. It should also be taken into account that different foods containing different non-nutritive sweeteners may be consumed throughout the day. For a realistic estimation of the cumulative exposure to different non-nutritive sweeteners, current national data on non-nutritive sweetener consumption in connection with use levels of individual substances and substance combinations in products are therefore also required.

3.5.2 Worst-case estimates in children and adolescents using the current ADI values for selected non-nutritive sweeteners

In 2018, the Max Rubner-Institute (MRI) examined a total of 1,124 soft drinks in a non-representative sample for their added sugar and non-nutritive sweeteners, with 10.8 % containing

[18] https://publications.europa.eu/en/publication-detail/-/publication/26105dba-6d8f-4515-a641-0e43fe3f5498/language-de

[19] Food Standards Agency (UK) (2003) Diary survey of the intake of intense sweeteners by young children from soft drinks (No. 36/03) http://tna.europarchive.org/20110116 113217/http://www.food.gov.uk/science/surveillance/fsis2003/ fsis-200336soft-drink

non-nutritive sweeteners only and a further 10.5 % containing a combination of sugar and non-nutritive sweeteners. Forty-three drinks were identified as having an appearance appealing to children, four of which contained only non-nutritive sweeteners and eight of which contained sugar and non-nutritive sweeteners.

The analysis of the Mintel database query regarding foods and beverages in Germany with the addition of non-nutritive sweeteners that were newly launched in the period 2015-2018, revealed 989 solid foods and 1,055 beverages. Of these, 54 products were explicitly labelled as suitable for children, including teas for toddlers sweetened with stevia leaves, chewing gum, sweets, ketchup, throat lozenges, ice cream and toothpaste, as well as 39 drinks (soft drinks and milkshakes) with an appearance designed to appeal to children.

For children and adolescents, the relative proportion of the exhaustion of the ADI values for non-nutritive sweetener consumption from flavoured beverages was estimated using an example calculation. For this purpose, in the first part of the calculation it was determined how many mg of a non-nutritive sweetener children could consume per day as a maximum in order not to exceed the ADI value (Tab. 2). The corresponding percentile values of the body weight of children and adolescents aged 2, 4, 6, 8, 11, 12 and 15 years formed the basis of the calculation. For this purpose, the medians (P 50) as well as the values for the 3rd percentile (P 3) and the 97th percentile were used to cover 95 % of the children and adolescents in the age groups considered. Table 2 shows the maximum intake doses for each non-nutritive sweetener for P3 and P50.

This means, for example, that a four-year-old child with a median body weight of 16.6 kg could consume 664 mg of aspartame per day without exceeding the ADI. Aspartame may be added to flavoured beverages up to a maximum concentration of 600 mg/l. Accordingly, a four-year-old child (with a body weight of 16.6 kg) could consume more than one litre of this drink per day without exceeding the ADI value; whereas a four-year-old child with a body weight in P3 could consume about 200 ml less (about 900 ml).

Tab. 2: Calculation of non-nutritive sweetener intakes in children corresponding to the ADIs of the listed non-nutritive sweeteners (in mg per day; for non-nutritive sweetener-containing beverages in ml per day).

Age (P50, P3–P97 bw in kg)	**2 years (12.7 kg, 9.82–14.9)**	**4 years (16.6 kg, 13.4-21.7)**	**6 years (21.4 kg, 16.8-29.4)**	**8 years (27.0 kg, 20.4-40.0)**	**11 years (38.9 kg, 27.2-65.0)**	**12 years (44.9 kg, 31.1-73.2)**	**15 years (61.7 kg, 43.3-85.4)**
Aspartame, ADI: 40 mg/kg							
P3	393	534	671	816	1087	1242	1731
P50	508	664	854	1080	1555	1795	2468
Maximum amount/day, drink in ml; 600 mg/l of aspartame							
P3	655	890	1119	1360	1812	2071	2885
P50	847	1107	1423	1801	2592	2991	4113
Acesulfame K, ADI: 9 mg/kg							
P3	88.4	120	151	184	245	280	389
P50	114	149.4	192	243	350	404	555
Maximum amount/day, drink in ml; 350 mg/l of acesulfame K							
P3	253	343	431	525	699	799	1113
P50	327	427	549	695	1000	1154	1586
Saccharin, ADI: 5 mg/kg							
P3	49.1	66.8	83.9	102	136	155	216
P50	63.5	83	107	135	194	224	308
Maximum amount/day, drink in ml, 80 mg/l of saccharin							
P3	614	834	1049	1275	1699	1941	2704
P50	794	1038	1334	1688	2430	2804	3856
Sucralose, ADI: 15 mg/kg							
P3	147	200	252	306	408	466	649
P50	191	249	320	405	583	673	925
Maximum amount/day, drink in ml, 300 mg/l of sucralose							
P3	491	668	839	1020	1359	1553	2164
P50	635	830	1068	1351	1944	2244	3085
Cyclamate, ADI: 7 mg/kg							
P3	68.7	93.5	117	143	190	217	303
P50	88.9	116	149	189	272	314	432
Maximum amount/day, drink in ml, 250 mg/l of cyclamate							
P3	275	374	470	571	761	870	1212
P50	356	465	598	756	1089	1256	1727

For the hypothetical case that the total daily fluid intake would be provided by a beverage sweetened with the maximum permissible concentration of a single non-nutritive sweetener, Table 3 shows the exhaustion of ADI (in %) for children and adolescents as a rough worst-case estimate. The daily fluid intake for a four-year-old child should be around 750 ml. With a median body weight of 16.6 kg, the maximum ADI for acesulfame K would be exceeded by

about 75 % and by about 60 % for cyclamate. Children with an exceptionally low body weight (P3) would significantly exceed the maximum ADI for acesulfame K and cyclamate in each age group.

Tab. 3: Estimation of the ADI exhaustion via consumption of non-nutritive sweetener-containing beverages by children (worst-case estimation).

Age	2 years	4 years	6 years	8 years	11 years	12 years	15 years
Recommended consumption for beverages in ml/day*	600	750	750	850	950	950	1,400
P50, % ADI (100 % = 1)							
Aspartame	0.71	0.68	0.53	0.47	0.37	0.32	0.34
Acesulfame K	**1.83**	**1.76**	**1.37**	**1.22**	0.95	0.82	0.88
Saccharin	0.76	0.72	0.56	0.50	0.39	0.34	0.36
Sucralose	0.94	0.90	0.70	0.63	0.49	0.42	0.45
Cyclamate	**1.69**	**1.61**	**1.25**	**1.12**	0.87	0.76	0.81
P3, % ADI (100 % = 1)							
Aspartame	0.92	0.84	0.67	0.63	0.52	0.46	0.49
Acesulfame K	**2.37**	**2.19**	**1.74**	**1.62**	**1.36**	**1.19**	**1.26**
Saccharin	0.98	0.90	0.71	0.67	0.56	0.49	0.52
Sucralose	**1.22**	**1.12**	0.89	0.83	0.70	0.61	0.65
Cyclamate	**2.18**	**2.01**	**1.60**	**1.49**	**1.25**	**1.09**	**1.16**

* Recommended consumption amounts for beverages by age, source: optimized mixed diet (Kersting et al., 2017)
Worst-case estimate: total beverage intake via non-nutritive sweetener-containing beverages.

In particular for toddlers and children up to the age of eight years with a body weight below the respective median (P50), it is theoretically possible to exhaust the ADI value for acesulfame K and cyclamate by consuming beverages sweetened with them, assuming that the recommended beverage consumption quantities would be covered exclusively by the consumption of such drinks and that these would be sweetened with the maximum permissible concentration of acesulfame K or cyclamate. In practice, however, it is rather unlikely that the ADI values will be exceeded, as the calculations were carried out under worst-case assumptions, which implies an overestimation of the actual intake.

For a realistic assessment of the intake of non-nutritive sweeteners, suitable studies should be carried out that also determine the non-nutritive sweetener consumption within the framework of the collection of national data on food consumption and combine it with the actual quantities of non-nutritive sweeteners used.

4 Framework for action/measures

The assessment of the currently available body of evidence does not allow to conclude on harmful effects of sweeteners in general with respect to the health-related endpoints examined in the present opinion. Accordingly, the BfR cannot give any further concrete recommendations for avoidance or reduction of the substances concerned.
The data situation is heterogeneous and also limited for some population groups (e.g., children, pregnant and breastfeeding women). In order to be able to derive well-founded conclusions on the (long-term) effects of non-nutritive sweeteners, further well-controlled intervention studies or experimental studies are necessary.

Further information on the subject of sweeteners is available on the BfR website:

Evaluation of sweeteners. BfR Background Information No 025/2014 of 1 July 2014* (in German) https://www.bfr.bund.de/cm/343/bewertung_von_suessstoffen.pdf

Harmful compounds might be formed when foods containing the sweetener Sucralose are heated. BfR Opinion No 012/2019 of 9 April 2019 https://www.bfr.bund.de/cm/349/harmful-compounds-might-be-formed-when-foods-containing-the-sweetener-sucralose-are-heated.pdf

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The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the federal states (“Länder”) on questions of food, chemicals, and product safety. The BfR conducts independent research on topics that are closely linked to its assessment tasks.

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