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SCIENTIFIC OPINION

Re-evaluation of erythritol (E 968) as a food additive

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Abstract

This opinion addresses the re-evaluation of erythritol (E 968) as food additive and an application for its exemption from the laxative warning label requirement as established under Regulation (EU) No 1169/2011. Erythritol is a polyol obtained by fermentation with *Moniliella pollinis* BC or *Moniliella megachiliensis* KW3-6, followed by purifications and drying. Erythritol is readily and dose-dependently absorbed in humans and can be metabolised to erythronate to a small extent. Erythritol is then excreted unchanged in the urine. It does not raise concerns regarding genotoxicity. The dataset evaluated consisted of human interventional studies. The Panel considered that erythritol has the potential to cause diarrhoea in humans, which was considered adverse because its potential association with electrolyte and water imbalance. The lower bound of the range of no observed adverse effect levels (NOAELs) for diarrhoea of 0.5 g/kg body weight (bw) was identified as reference point. The Panel considered appropriate to set a numerical acceptable daily intake (ADI) at the level of the reference point. An ADI of 0.5 g/kg bw per day was considered by the Panel to be protective for the immediate laxative effect as well as potential chronic effects, secondary to diarrhoea. The highest mean and 95th percentile chronic exposure was in children (742 mg/kg bw per day) and adolescents (1532 mg/kg bw per day). Acute exposure was maximally 3531 mg/kg bw per meal for children at the 99th percentile. Overall, the Panel considered both dietary exposure assessments an overestimation. The Panel concluded that the exposure estimates for both acute and chronic dietary exposure to erythritol (E 968) were above the ADI, indicating that individuals with high intake may be at risk of experiencing adverse effects after single and repeated exposure. Concerning the new application, the Panel concluded that the available data do not support the proposal for exemption.

KEYWORDS

diarrhoea, E 968, erythritol, food additive, laxative, sweeteners

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SUMMARY

The present opinion deals with the re-evaluation of erythritol (E 968) when used as a food additive and with the evaluation for an application for exemption of erythritol (E 968) from the laxative warning label requirement as established under Regulation (EU) No 1169/2011.

Erythritol (E 968) is authorised as a food additive in the European Union (EU) in 66 different food categories (representing 83 uses) in accordance with Annex II, Part E, to Regulation (EC) No 1333/2008 at MPLs equal to *quantum satis* (QS) as a group I additive (for purposes other than sweetening). In addition, erythritol (E 968) belongs to the functional class of sweeteners and, being a 4-carbon sugar alcohol, is included in the group of polyols (group IV) specified in Regulation (EC) No 1333/2008.

Erythritol was previously assessed by the Scientific Commitee on Food (SCF) in 2003. In its opinion, after the evaluation of several human and animal data, the SCF considered it inappropriate to establish a numerical acceptable daily intake (ADI) for erythritol, in accordance with previous opinions issued on other polyols (SCF, 1985). The SCF also considered that erythritol had a laxative effect, but at higher doses than other polyols, and identified a no observed adverse effect level (NOAEL) for this effect in humans of 0.5 g/kg bw for a single dose. The use of erythritol as a food additive was considered acceptable, however the SCF expressed concerns that the laxative threshold may be exceeded, especially by young consumers through ingestion of erythritol in beverages. In 2010, the European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS) Panel issued an opinion following a request for the authorisation of use of erythritol for purposes other than sweetening at a maximum level of 2.5% in beverages (EFSA ANS Panel, 2010). New data were available in this application, i.e. a new paediatric study on the gastrointestinal tolerability of erythritol. The Panel concluded that the margin of safety (MOS) between the NOAEL set for laxation in children aged 4–7 years (0.71 g/kg bw) was too low to adequately protect this population and therefore, a safety concern was identified for the proposed extension of use of erythritol in beverages. Later, EFSA received two additional requests for extension of use (EFSA ANS Panel, 2013, 2015). For one, EFSA concluded that the acute bolus intake of erythritol via the consumption of non-alcoholic beverages at a maximum level of 1.6% would not raise concerns for laxation.

The current risk assessment was carried out based on structured protocols on hazard identification and characterisation (EFSA, 2020a and further revision) and on exposure assessment (EFSA, 2020b). The protocols defined upfront the strategy to be applied for collecting and selecting data, appraising the relevant evidence, analysing and integrating the evidence.

Erythritol (E 968) is a polyol and it corresponds to the *meso* diastereomer of butane-1,2,3,4-tetrol. According to Commission Regulation (EU) No 231/2012 definition, erythritol (E 968) is '*obtained by fermentation of carbohydrate source by safe and suitable food grade osmophilic yeasts such as Moniliella pollinis or Moniliella megachiliensis, followed by purification and drying*'. Based on the detailed information provided by the interested business operators (IBOs) on the characterisation of the microorganisms and the demonstration of the absence of viable cells in erythritol, the Panel considered that the manufacturing process of E 968 does not raise a safety concern. However, in order to better describe the manufacturing processes evaluated in the current assessment, the Panel recommended modifying the definition of the food additive in the Commission Regulation (EU) 231/2012 to specify that E 968 is obtained by fermentation of a carbohydrate source by non-genetically modified *M. pollinis* strain BC or *M. megachiliensis* strain KW3-6, followed by several purification steps and drying. In addition, the Panel emphasised that the present re-evaluation does not apply to erythritol (E 968) produced by other manufacturing processes (e.g. different microorganisms, strains). The reason is that this would be considered as significant changes in the production methods which would require an assessment in accordance with relevant legislation.

Based on the analytical data on the levels of lead (Pb) provided by the IBOs and the dietary exposure estimates to the food additive, the Panel calculated the potential exposure to this toxic element. The Panel noted that the presence of lead at the current specification limit (0.5 mg/kg) would result in a margin of exposure (MOE) below the target value of 1 for high consumers, while the presence of lead at the modulated value (0.25 mg/kg) would result in an MOE above the target value of 1. According to the information submitted, no other impurities from the evaluated manufacturing process were identified.

Based on the data submitted, the Panel considered that a microbiological contamination is unlikely and, therefore, it is not necessary to recommend inclusion of microbiological criteria in the EU specifications for E 968.

Regarding water solubility, solubility tests were submitted by the IBOs reporting a water solubility range of 352.6–426.6 g/L. The Panel noted that the ultrafiltration step recommended in the EFSA Guidance on Particle-Technical Requirements (TR) (EFSA Scientific Committee, 2021) was not included in the tests provided. Nonetheless, given the nature of this simple polyol, the Panel considered that the solubility of E 968 is substantially higher than the value of 33.3 g/L proposed as a criterion to decide whether an additional assessment for the fraction of small particles is needed. Therefore, the conventional risk assessment according to the EFSA Guidance on Food Additive (EFSA ANS Panel, 2012) can be followed.

The Panel noted that, based on the submitted information along with considerations of the structure and characteristics of erythritol, being a simple polyol, E 968 is expected to be stable in food over a wide range of temperatures and pH conditions.

Recently it has been shown that, in humans, erythritol can be formed endogenously through the pentose phosphate pathway (PPP) and that a small fraction can be metabolised to erythronate. No new absorption, distribution, metabolism and excretion (ADME) data were submitted by the IBOs or by the applicant in support of the re-evaluation. Nonetheless, several studies in animals and humans have been performed at the time of the first evaluation of this substance by the SCF in 2003. All studies demonstrated a high degree of absorption of ingested erythritol (60% to 90%) from the small intestine. Recent studies retrieved in the literature showed that absorption of erythritol is dose-dependent in humans (Bordier et al., 2022). In addition, it has been shown that erythritol can be metabolised to erythrose

and further to erythronate to a small extent (Bordier et al., 2022; Hootman et al., 2017). Erythritol is then excreted unchanged in the urine.

Regarding genotoxicity, the Panel concluded that erythritol (E 968) does not raise a concern.

The dataset evaluated by the Panel consisted of human interventional studies previously evaluated (EFSA ANS Panel, 2010, 2015; SCF, 2003) together with recent human studies retrieved in the literature. These studies were subjected to a risk of bias (RoB) evaluation and a weight of evidence (WoE) approach was applied for each relevant health outcome category (HOC). Based on the WoE analysis, it is very likely that erythritol (E 968) has the potential to cause diarrhoea in human, which was considered an adverse health effect because its potential association with electrolyte and water imbalance. Subjective gastrointestinal symptoms (abdominal pain, nausea, bloating, flatulence) have been also noted. Regarding glucose homeostasis, the Panel considered that the evidence available, albeit limited, consistently showed no short-term effect of erythritol on postprandial glucose homeostasis in human. Long-term studies addressing glucose homeostasis-related endpoints were not identified.

The Panel considered the human studies reporting on laxative effects, with diarrhoea as the critical endpoint, as the most appropriate data source for the hazard characterisation. The Panel considered the NOAELs for diarrhoea in human from the available interventional studies and identified 0.5 g/kg bw (500 mg/kg bw) as a reference point (lower bound of the range of NOAELs). The Panel considered that this value is sufficiently protective for all population groups.

Recent publications suggesting a possible association from human observational studies between higher circulating blood levels of erythritol and cardiovascular disease and related risk factors were retrieved in the literature (Rebholz et al., 2018; Wang et al., 2019; Witkowski et al., 2023). Overall, the Panel considered that the available evidence does not demonstrate a causal relationship between dietary intake of erythritol (E 968) as a food additive and increased risk for cardiovascular disease and related risk factors. Further studies might be helpful to clarify the nature of this association.

The Panel noted that no cardiovascular adverse effects were observed in the animal studies evaluated by the SCF (SCF, 2003). Based on the available data from human studies, the Panel considered diarrhoea to be the most sensitive endpoint for adverse effect of erythritol.

Following the 2014 ANS Panel conceptual framework approach for the re-evaluation of food additives, and since reliable information for both exposure and toxicity of erythritol (E 968) was available, the Panel considered it appropriate to set a numerical ADI at the level of the reference point identified from human interventional studies. A reference point for diarrhoea was identified by the Panel to be 0.5 g/kg bw (500 mg/kg bw). In this case, uncertainty factors are not needed since human data were used and the mechanism for laxation is not depending on the duration of the exposure. Furthermore, no other (e.g. systemic) effects were observed in animals at much higher chronic exposures. Therefore, the reference value corresponds to an ADI of 0.5 g/kg bw per day (500 mg/kg bw per day). The Panel acknowledged that this is the first time that an ADI is derived for a food additive based on an immediate adverse effect such as diarrhoea. In the case of erythritol, the reported laxative effects are mainly due to osmotic imbalance which may lead, in the chronic setting, to secondary adverse effects such as electrolyte imbalance. The Panel considered that this ADI of 0.5 g/kg bw per day (500 mg/kg bw per day) is protective for the immediate laxative effect as well as potential chronic effects secondary to the laxative effect (i.e. diarrhoea).

Dietary exposure to erythritol (E 968) was estimated according to different exposure scenarios based on consumers-only. IBOs provided EFSA with use level for 22 food categories (out of 66 in which erythritol is currently authorised) and analytical data were available for seven food categories.

A chronic as well as an acute exposure (per meal) to erythritol (E 968) were estimated. Regarding the chronic exposure to erythritol (E 968), for the *regulatory maximum level exposure assessment scenario*, the highest mean exposure to erythritol (E 968) was found in toddlers (798 mg/kg bw per day) and the highest 95th percentile (P95) in children (1638 mg/kg bw per day). In the *refined brand-loyal exposure assessment scenario*, the highest mean exposure to erythritol (E 968) was found in toddlers (742 mg/kg bw per day) and the highest P95 in children (1532 mg/kg bw per day). Acute exposure (per meal) to erythritol (E 968) was maximally 3531 mg/kg bw per meal at the 99th percentile (P99) for children. The acute scenario considered two maximum reported use levels, which is a conservative scenario. However, this is not an unreasonable scenario since erythritol (E 968) has a lower sweetening power than sugar (approximately 70% of its sweetening power) and can be used as a sugar replacement in many products. Overall, the Panel considered that the *refined brand-loyal* and the *regulatory maximum level exposure assessment scenarios* for chronic exposure as well as the acute exposure assessment scenario per meal overestimate the dietary exposure to erythritol.

The Panel noted that the 95th percentile exposure estimates for both acute and chronic exposure to erythritol (E 968) were at or above the ADI of 0.5 g/kg bw (500 mg/kg bw) (per meal for the acute scenario or per day for the chronic scenario) in all populations, indicating that individuals with high intake may be at risk of experiencing adverse effects after single and repeated exposure.

Jointly with the re-evaluation of the safety of erythritol (E 968) in its permitted uses as a food additive, the Panel was also requested by the European Commission to evaluate an application in support of the possible exemption for this food additive from the current laxative warning label requirement applicable to all foods containing more than 10% added polyols, which was considered by the applicant not to be justified in the case of erythritol. With diarrhoea being selected as the critical endpoint for the derivation of the ADI in the case of erythritol, the Panel considered that the current warning '*excessive consumption may produce laxative effects*' remains appropriate and concluded that the available data do not support the applicant's proposal for the exemption of erythritol from the current laxative warning requirement under Regulation (EU) 1169/2011 for food containing more than 10% erythritol (100,000 mg/L or mg/kg).

The Panel recommends the European Commission to consider:

- requesting more detailed occurrence data (use levels and analytical data) and label information, in order to be able to refine the exposure assessment;
- revising the definition of the food additive in the EU specifications as 'Obtained by fermentation of a carbohydrate source by non-genetically modified *Moniliella pollinis* strain BC or *Moniliella megachiliensis* strain KW3-6, followed by several purification steps and drying';
- including the CAS number 149–32-6 in the EU specifications;
- lowering the limit of lead (Pb) in the EU specifications.

1 | INTRODUCTION

The present opinion deals with the re-evaluation of erythritol (E 968) when used as a food additive and with the evaluation for an application for exemption of erythritol (E 968) from the laxative warning label requirement as established under Regulation (EU) No 1169/2011.[1]

1.1 | Background and Terms of Reference as provided by the requestor

1.1.1 | Background

1.1.1.1 | *Re-evaluation of erythritol (E 968) as a food additive under Regulation (EU) No 257/2010*

Regulation (EC) No 1333/2008[2] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union (EU). In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010.[3] This Regulation also foresees that food additives are re-evaluated whenever necessary in the light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU of 2001.[4] The report "Food additives in Europe 2000" submitted by the Nordic Council of Ministers to the Commission,[5] provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010, the 2003 Terms of References are replaced by those below (see Section 1.1.2.1).

1.1.1.2 | *Application for exemption of erythritol (E 968) from laxative warning under Regulation (EU) No 1169/2011*

Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers (hereinafter "the Regulation") establishes the general principles, requirements and responsibilities governing food information, and in particular food labelling. It lays down the means to guarantee the right of consumers to information and procedures for the provision of food information, while providing sufficient flexibility to respond to future developments and new information requirements.

Subject to the exceptions laid down in the Regulation, its Article 9(1) set up the list of mandatory particulars that have to be always provided on all foods. In addition to those particulars, Annex III to the Regulation establishes the list of foods for which the labelling must include one or more additional particulars. Point 2.4 of that Annex provides that the labelling of foods containing more than 10% added polyols authorised pursuant to Regulation (EC) No 1333/2008 must contain a statement that "*excessive consumption may produce laxative effects*". In accordance with Regulation (EC) No 1333/2008, the group of polyols currently permitted for use as food additives comprises: Sorbitols (E 420), Mannitol (E 421), Isomalt (E 953), Maltitols (E 965), Lactitol (E 966), Xylitol (E 967) and Erythritol (E 968).

Erythritol (E 968) is a 4-carbon polyol and currently an authorised food additive in the European Union under Annex II and III of Regulation (EU) 1333/2008.

Erythritol (E 968) is currently undergoing re-evaluation by EFSA under the frame of Regulation (EU) No 257/2010.

Article 10(2) of the Regulation empowers the Commission to amend Annex III to the Regulation by means of delegated acts, in order to ensure consumer information with respect to specific types or categories of foods and to take account of technical progress, scientific developments and the protection of consumers' health or the safe use of a food. To this end, the interested parties may communicate to the Commission studies substantiating such amendment.

[1]Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. OJ L 304, 22.11.2011, p. 18.

[2]Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

[3]Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19.

[4]Available online: https://op.europa.eu/en/publication-detail/-/publication/26105dba-6d8f-4515-a641-0e43fe3f5498/language-en

[5]Available online: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2007:0418:FIN:EN:PDF

Pursuant to Article 10(2) of the Regulation, the applicant Cargill R&D Centre Europe submitted an application requesting the European Commission to exempt erythritol from the laxative warning label requirement. Based on the scientific data, including an EFSA opinion (EFSA ANS Panel, 2015), which concludes that the acute bolus consumption of erythritol via non-alcoholic beverages at a maximum level of 1.6% would not raise concerns for laxation, the applicant claims that the above-mentioned laxative warning requirement is not justified for foods containing more than 10% erythritol.

1.1.2 | Terms of Reference

1.1.2.1 | *Re-evaluation of erythritol (E 968) as a food additive under Regulation (EU) No 257/2010*

The Commission asks the EFSA to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.1.2.2 | *Application for exemption of erythritol (E 968) from laxative warning under Regulation (EU) No 1169/2011*

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,[6] the European Commission requests the EFSA to evaluate the scientific data submitted by Cargill R&D Centre Europe. As stipulated in Article 10(2) of Regulation (EU) No 1169/2011, that scientific data was submitted in the context of a possible amendment of Annex III of the latter Regulation, in the light of new scientific developments.

In order to assess the need for an exemption of erythritol from the current laxative warning requirement for added polyols under Regulation (EU) 1169/2011, EFSA is requested to take into consideration, in the context of the ongoing re-evaluation of sweeteners under Regulation (EC) No 257/2010, data submitted by Cargill R&D Centre Europe. EFSA is requested to provide scientific advice on the basis of the information provided, on the laxative effect of food containing more than added 10% erythritol used in accordance with Regulation (EC) No 1333/2008. In this context, EFSA is kindly requested to evaluate the erythritol exposures by individuals and its absorption characteristics from the small intestine.

1.2 | Interpretation of the Terms of Reference

In accordance with the terms of reference in Section 1.1.2.2, this opinion evaluates the scientific data submitted by Cargill R&D Centre Europe, in order to reach a conclusion on the laxative effect of food containing more than added 10% erythritol, and if possible to derive a reference point.

Concerning the evaluation of erythritol exposures by individuals and its absorption characteristics from the small intestine, the Panel noted that published studies and unpublished study reports submitted by the applicant were already considered and evaluated by (SCF, 2003) and by EFSA (EFSA ANS Panel, 2015). Therefore, relevant data not previously considered, if any, will be taken into account in this evaluation.

1.3 | Information on existing authorisations and evaluations

Erythritol (E 968) is authorised as a food additive in the EU in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in Commission Regulation (EU) No 231/2012.[7]

In the EU, erythritol (E 968) was evaluated by the SCF in 2003 (SCF, 2003). The SCF reviewed several animal and human studies on erythritol and, in accordance with its earlier opinion on other polyols (SCF, 1985), considered inappropriate to establish a numerical acceptable daily intake (ADI) for erythritol. The SCF concluded that erythritol had a laxative effect, but at higher doses compared to other polyols. The SCF reported in its opinion that the laxative *'effect seen in the animal studies were attributable to physiological and adaptive responses to the rapid absorption and excretion of erythritol and to the osmotic activity of unabsorbed erythritol and its fermentation products in the gut'*. The SCF identified a no observed adverse effect level (NOAEL) for laxative effect in humans of 0.5 g/kg bw for a single dose. The SCF also noted that *'as with other polyols, this should not be interpreted as meaning the acceptance of unlimited use in all foods at any technological level, because the laxative effect should be borne in mind'*. At that time, a recommendation for a limit of not higher than 0.5 mg/kg of lead (Pb) in the specifications was also made.

[6]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1.

[7]Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1.

Based on this conclusion the use of erythritol as a food additive was considered acceptable, however the SCF expressed concerns that the laxative threshold may be exceeded, especially by young consumers through ingestion of erythritol in beverages.

In 2010, following a request for the authorisation of the use of erythritol (E 968) for purposes other than sweetening at a maximum level of 2.5% in beverages and in light of new data, including a paediatric study on the gastrointestinal tolerability of erythritol, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) issued a scientific opinion in relation to the safety of erythritol (E 968) (EFSA ANS Panel, 2010). In this opinion, the ANS Panel identified a NOAEL for laxation of 0.71 g/kg bw in children aged 4–6 years, when erythritol was consumed in a drink as a bolus dose. The ANS Panel noted that the margin of safety (MOS) between this NOAEL and the estimated daily intake of erythritol resulting from an incorporation rate of 2.5% in beverages (i.e. 0.59 g/kg bw in a single drinking occasion at the 97.5th percentile) was 1.24 and concluded that this MOS was too low to adequately protect children, taking into account that erythritol is also used in other food categories. Therefore, the ANS Panel concluded that '*based on the available data, there is a safety concern with respect to the gastrointestinal (GI) tolerability for the use of erythritol in beverages at a maximum use level of 2.5% for non-sweetening purposes*'.

In a subsequent statement on a refined dietary exposure assessment of erythritol (E 968), taking into account additional data provided by an applicant in support of an extension of the authorised uses to soft drinks at a use level of 2.5%, the ANS Panel concluded that the MOS of 1.54 was still too low to adequately protect the age group of children (3–9 years) from the laxative effect of erythritol (EFSA ANS Panel, 2013).

In 2015, EFSA issued another opinion on the safety of the proposed extension of use of erythritol (E 968) as a food additive based on an application for amending the permitted uses and use levels and proposing a maximum level of 1.6% erythritol as a flavour enhancer in non-alcoholic beverages (EFSA ANS Panel, 2015). The data from this new application combined with a new acute consumption scenario in the most relevant population group (children) resulted in an estimated bolus intake of 0.6 g/kg bw, which was lower than the previously identified NOAEL for laxation in children of 0.71 g/kg bw (EFSA ANS Panel, 2010). Therefore, the ANS Panel concluded that the acute bolus intake of erythritol via the consumption of non-alcoholic beverages at a maximum level of 1.6% would not raise concerns for laxation.

In 2000, erythritol was evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA, 2000) and was assigned an ADI 'not specified'. A single dose of 1 g/kg bw was considered by JECFA as having no laxative effect in humans.

In the context of the Regulation (EC) No 1907/2006[8] of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), a registration dossier[9] on erythritol is available. The dossier reports a study on biodegradability, according to OECD test guideline (TG) 301 D and GLP criteria.

2 | DATA AND METHODOLOGIES

The current risk assessment was carried out by the EFSA Panel on Food Additives and Flavourings (FAF Panel) in the context of Regulation (EU) No 257/2010. Structured protocols on hazard identification and characterisation (EFSA, 2020a and further revision) and on exposure assessment (EFSA, 2020b) were developed in line with the principles of the EFSA PROMETHEUS project (PROmoting METHods for Evidence Use in Scientific assessments) (EFSA, 2015a). The protocols define the strategy to be applied for collecting and selecting data, appraising the relevant evidence and analysing and integrating the evidence in order to draw conclusions that will form the basis for the scientific opinions.

The draft protocol for the hazard identification and characterisation of sweeteners was published on the EFSA's website for comments, and the online public consultation was made available until 19 September 2019. A technical report on the outcome of this public consultation with the overview of the comments received and the general responses from EFSA was published (EFSA, 2020a). During the implementation phase, some amendments and further elaborations to the original protocol were introduced. The changes introduced are documented in the revised version published in 2023[10] and followed for the preparation of the present opinion.

The draft protocol for assessing dietary exposure to sweeteners was published on the EFSA's website for comments, and the online public consultation was made available until 22 November 2019. A technical report on the outcome of this public consultation with the overview of the comments received and the general responses from EFSA was published (EFSA, 2020b).

[8]Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

[9]https://echa.europa.eu/it/registration-dossier/-/registered-dossier/23674/5/3/2

[10]Available online: https://doi.org/10.5281/zenodo.7788969

2.1 | Data

The FAF Panel was not provided with a newly submitted dossier for the re-evaluation of erythritol (E 968). In accordance with Regulation (EU) No 257/2010, EFSA launched public calls for data[11,12,13] and contacted interested parties that had replied to the calls for data to collect additional clarification or supplemental information (Documentation provided to EFSA No. 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14).

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to September 2023. The steps followed for the acquisition of data and their selection are documented in detail in Appendix A.

Food consumption data used to estimate the dietary exposure to erythritol (E 968) were derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database[14]). The Mintel's Global New Products Database (GNPD) was checked to identify the uses of erythritol (E 968) in food and beverage products and food supplements. The Mintel's GNPD is an online database that contains the compulsory ingredient information present on the label of numerous products.

For the application for exemption of erythritol (E 968) from laxative warning under Regulation (EU) No 1169/2011, the FAF Panel was provided with a newly submitted dossier (Documentation provided to EFSA No. 5). The applicant was invited to a hearing held at the 42nd meeting of the FAF Panel Working Group (WG) on sweeteners.[15] Additional information was provided during the assessment (Documentation provided to EFSA No. 13).

2.2 | Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee. In line with these principles, the current risk assessment was carried out based on structured protocols on hazard identification and characterisation of sweeteners (EFSA, 2020a and revised protocol) and on exposure assessment (EFSA, 2020b).

The FAF Panel assessed the safety of erythritol (E 968) as a food additive in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the Scientific Committee on Food (SCF, 2001) and the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

In animal studies, when the test substance is administered in the feed or in the drinking water, but doses are not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake is calculated by the Panel using the relevant default values. In case of rodents, the values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012) are applied. In the case of other animal species, the default values used by JECFA (2000) are used. In these cases, the dose was expressed as 'equivalent to mg/kg bw per day'. If a concentration in feed or drinking water was reported and the dose in mg/kg bw per day was calculated (by the authors of the study report or the Panel) based on these reported concentrations and on reported consumption data for feed or drinking water, the dose was expressed as 'equal to mg/kg bw per day'. When in adult human studies (aged above 18 years) the dose of the test substance administered was reported in mg/person per day, the dose in mg/kg bw per day is calculated by the Panel using a body weight of 70 kg as default for the adult population as described in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012).

For the genotoxicity assessment, an approach for assessing the relevance and reliability of genotoxicity studies and for weighing the evidence was developed and described in detail in the revised protocol. For the other toxicological endpoints, a systematic approach was used. The methods for hazard identification, including the assessment of internal validity for individual studies (risk of bias [RoB]) and the assessment of the body of evidence across all health outcomes, are described in the revised protocol and also detailed in Appendix A. In brief, following data retrieval and screening for relevance, RoB was performed and studies were classified into tiers from 1 to 3. In the current opinion, relevant studies retrieved from the literature with low to moderate RoB were considered and included in the weight of evidence (WoE) evaluation. In accordance with the revised protocol, human studies previously evaluated by the SCF in its 2003 opinion and by the EFSA ANS Panel in 2010, that constitute the body of evidence on which the conclusion for no numerical ADI was based, were subjected to a RoB evaluation. The Panel agreed to further consider all these studies in the WoE, independently of the outcome of the RoB, due to the fact that few new studies were available and that a WoE of the whole evidence was considered the most appropriate. In the case of erythritol (E 968), no new eligible animal studies were available, therefore only the evidence from human studies were weighted before being integrated to reach a conclusion on hazard identification. During this process, ratings of initial confidence (expressed as '*high*', '*moderate*',

[11]Call for technical and toxicological data on sweeteners authorised as food additives in the EU - Extended deadline for submitting data: 30 June 2018.

[12]Call for technical data on sweeteners authorised as food additives in the EU.

[13]Call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 7).

[14]https://www.efsa.europa.eu/en/food-consumption/comprehensive-database

[15]https://www.efsa.europa.eu/sites/default/files/wgs/food-ingredients-and-packaging/sweeteners-m.pdf

'*low*' or '*very low*') were assigned to all studies based on study design for each relevant, reported outcome. For each outcome across studies, the initial confidence rating could be downgraded based on either a concern for bias across studies, unexplained inconsistency, relevance of studies and/or imprecision; similarly, it could be upgraded based on the magnitude of effect, dose–response, consideration of residual confounding (human studies only) and consistency across study designs and experimental model systems (NTP-OHAT, 2019). The following terms were used to express the level of confidence in the body of evidence, irrespective of whether an association between exposure to the substance and adverse health outcome(s) were identified: '*high*', '*moderate*', '*low*' and '*very low/no evidence identified*'. For each level of confidence in the body of evidence, corresponding expressions for levels of evidence for adverse effects on health were denoted as '*high*', '*moderate*', '*low*' and '*inadequate*', respectively. Whereas when no adverse effects on health were identified, expressions for levels of evidence were denoted as '*high*', '*moderate*', '*inadequate*' and '*inadequate*', respectively. More details on the WoE procedure are outlined in step 1.14 of the revised protocol on hazard identification and characterisation and the US National Toxicology Program (NTP) Handbook for conducting a literature-based health assessment (NTP-OHAT, 2019), with some modifications. Integration of human data were based on the highest level of evidence rating for an adverse or no adverse effect on health. Hazard identification conclusions i.e. expressions of likelihood of an association between intake of erythritol (E 968) and adverse effect on health, were reached on groups of toxicological outcomes following a guidance developed by the FAF Panel (EFSA 2020a and revised version).

Dietary exposure to erythritol (E 968) from its use as a food additive was estimated combining food consumption data available within the EFSA Comprehensive Database with the maximum levels according to Annex II to Regulation (EC) No 1333/2008 and/or reported use levels and analytical data submitted to EFSA following a call for data. Different scenarios were used to calculate the exposure (see Section 3.4).

Finally, uncertainties in the hazard identification, characterisation and exposure assessment were identified and discussed.

3 | ASSESSMENT

3.1 | Technical data

3.1.1 | Identity of the substance and specifications

According to the definition given in Commission Regulation (EU) No 231/2012, erythritol (E 968) is '*obtained by fermentation of carbohydrate source by safe and suitable food grade osmophilic yeasts such as Moniliella pollinis* or *Moniliella megachiliensis*, *followed by purification and drying*'.

The Panel noted that the definition of the microorganisms used for the production of E 968 '*safe and suitable food grade osmophilic yeasts*' in the Commission Regulation (EU) No 231/2012 is not appropriate since *M. pollinis* and *M. megachiliensis* are filamentous fungi.

Erythritol (E 968) is a polyol, and it corresponds to the *meso* diastereomer of butane-1,2,3,4-tetrol.

Additional identification numbers and names for erythritol (E 968), currently not reported in Commission Regulation (EU) No 231/2012, are the following:

CAS number:	149-32-6
IUPAC name:	(2R,3S)-Butane-1,2,3,4-tetrol

The chemical structure of erythritol (E 968) is given in Figure 1.

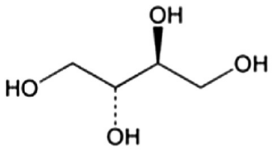


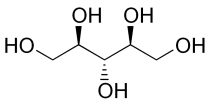
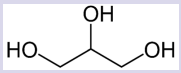
FIGURE 1 Chemical structure of erythritol (E 968) (Documentation provided to EFSA No. 1).

Structurally related polyol impurities, ribitol and glycerol, can be present in E 968 (Table 1). Both impurities are fermentation co-products.

The Panel noted that glycerol is an authorised food additive (E 422) and was re-evaluated by the EFSA ANS Panel and then by the EFSA FAF Panel in a follow-up of the re-evaluation (EFSA ANS Panel, 2017; EFSA FAF Panel, 2022).

One interested business operator (IBO) provided an analytical method based on the Food Chemical Codex (FCC) Monograph Method for erythritol assay testing for analysis of E 968 (Documentation provided to EFSA No. 1). High performance liquid chromatography (HPLC) with refractive index (RI) detector is used to quantify the impurities ribitol and glycerol present in erythritol (Table 1).

TABLE 1 Chemical structures of potential impurities in E 968.

Chemical name/IUPAC name	CAS No	Structure
Ribitol/D-erythro-pentitol	488-81-3	
Glycerol/propane-1,2,3-triol	56-81-5	

Specifications for erythritol (E 968), as laid down in the Commission Regulation (EU) No 231/201212, are listed in Table 2.

TABLE 2 Specifications for erythritol (E 968) according to Commission Regulation (EU) No 231/2012 and proposed by JECFA (2006).

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Synonyms	Meso-erythritol; Tetrahydroxybutane; Erythrite	Meso-erythritol; tetrahydroxybutane; erythrite
Definition	Obtained by fermentation of carbohydrate source by safe and suitable food grade osmophilic yeasts such as *Moniliella pollinis* or *Moniliella megachiliensis*, followed by purification and drying	Obtained by fermentation of starch enzyme hydrolysate (from starches such as wheat and corn) by safe and suitable food grade osmophilic yeasts such as Moniliella pollinis or Trichosporonoides megachiliensis. The heat-sterilised broth is filtered, purified by ion exchange resin, activated charcoal and ultrafiltration, crystallised washed and dried
Einecs	205-737-3	
Chemical name	1,2,3,4-Butanetetrol	1,2,3,4-Butanetetrol
Chemical formula	$C_4H_{10}O_4$	$C_4H_{10}O_4$
Molecular weight	122.12	122.12
Assay	Not less than 99% after drying	Not less than 99% after drying
Description	White, odourless, non-hygroscopic, heat-stable crystals with a sweetness of approximately 60%–80% that of sucrose	White, odourless, non-hygroscopic, heat-stable crystals. It has a sweetness approximately 60%–80% that of sucrose
Identification		
Solubility	Freely soluble in water, slightly soluble in ethanol, insoluble in diethyl ether	Freely soluble in water, slightly soluble in ethanol, insoluble in diethyl ether
Melting range	119–123°C	119–123°C
Main peak in HPLC	–	The retention time of the major peak in the chromatogram of the Assay Solution corresponds to that in the chromatogram of the Standard Solution obtained in the Assay
Purity		
Loss on drying	Not more than 0.2% (70°C, 6 h, in a vacuum desiccator)	Not more than 0.2% (70°C, 6 h, in a vacuum desiccator)
Sulphated ash	–	Not more than 0.1% Test 2 g of the sample (Method I)
Conductivity	Not more than 20 μS/cm (on 20% dry solids solution) at temperature 20°C	–
Reducing substances	Not more than 0.3% expressed as D-glucose	Not more than 0.3% calculated as D-glucose (Method I)
Ribitol and glycerol	Not more than 0.1%	Not more than 0.1%
Lead	Not more than 0.5 mg/kg	Not more than 0.5 mg/kg Determine using an atomic absorption technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the method described in Volume 4, 'Instrumental Methods'.

The Panel noted that according to Commission Regulation (EU) No 231/2012, no microbiological specifications are currently set and noted that the CAS number 149-32-6 is not included.

Following the EFSA calls for data[16,17], two IBOs provided data and information to support the re-evaluation of E 968 (Documentation provided to EFSA No. 1, 2, 3, 4, 7, 8). Technical data on commercial batches of E 968, and supported by certificates of analysis, were provided by both IBOs.

Both IBOs provided confidential data on analyses performed on commercial batches of E 968 supporting the microbiological quality of the food additive (Documentation provided to EFSA No. 1, 7, 8). Considering the various steps of the production process (see Section 3.1.2 Manufacturing process), the Panel considered that microbiological contamination is unlikely. This was confirmed by the microbiological data confidentially submitted by the IBOs. Hence, the Panel did not consider it necessary to recommend inclusion of microbiological criteria in the EU specifications for E 968.

One IBO provided information on purity, impurities, pH and water content (determined as loss on drying) supported by certificates of analysis, for 24 representative batches of erythritol coming from the same plant and process (Documentation provided to EFSA No. 7). The purity of the 24 analysed batches, determined by HPLC–RI detector, ranged from 99.96% to 100% (Documentation provided to EFSA No. 7). Regarding the impurities, the sum of glycerol and ribitol was up to 0.08% w/w for the 24 batches.

The other IBO provided information on purity, pH, water content (determined as loss on drying), sulphated ash/residue on ignition, reducing substances (as D-glucose) and glycerol and ribitol supported by certificates of analysis for 12 commercial batches of erythritol (Documentation provided to EFSA No. 8). The purity determined by HPLC-RI detector ranged from 99.5% to 100.1% w/w. Concerning the impurities glycerol and ribitol, they were not detected in all 12 analysed batches. The IBO explained the absence of the organic impurities by stating that they '*can be found during the fermentation and are eliminated in the purified erythritol product*' (Documentation provided to EFSA No. 8).

Since glycerol is known to be produced as a fermentation by-product during the production of erythritol E 968 and given the structural similarity between glycerol and erythritol, upon request from EFSA the two IBOs submitted information on potential impurities of glycerol since they may also be present in erythritol (Documentation provided to EFSA No. 7, 8).

Following this request, one IBO stated: '*There is no chlorine or chlorinated compounds used in the manufacturing process meaning there is no precursor for chlorinated by-products. Additionally, the temperature applied is not high enough to generate any of the chemical of concern listed by the EFSA*'. (Documentation provided to EFSA No. 7). Data were also submitted to support the statement. The concentrations of acrolein, 1,2,4-butantriol and the sum of 3-MCPDs derivatives (including free 3-MCPD and 3-MCPD esters) were below the limit of quantifications (LOQs), i.e. 0.03, 500 and 0.15 mg/kg, respectively, in all analysed samples (Documentation provided to EFSA No. 7). Similar information was also submitted by the other IBO stating that the erythritol production process is not prone to form impurities or by-products known to affect glycerol as the fermentation process is a natural process at ambient temperature and no chemical or catalytically steps are applied (Documentation provided to EFSA No. 8).

With regard to toxic elements, the IBOs provided analytical data on the levels of lead (Pb). Details of the analytical data provided are available in Appendix B. The Panel performed the risk assessment that would result if lead (Pb) was present in E 968 at: (i) the existing limit in EU specification (i.e. 0.5 mg/kg); (ii) the lowest reported LOQ by applying a factor[18] of 5 (i.e. resulting in 0.25 mg/kg). The outcome of the risk assessment for these two different scenarios is presented in Table B2, Appendix B. The presence of lead (Pb) at the current specification limit for high consumers would result in an MOE below the target value of 1, while the presence of lead (Pb) at the modulated value (ii) would result in an MOE above the target value of 1.

The Panel noted that the choice of a maximum limit for lead (Pb) in the EU specifications is in the remit of risk management.

Solubility

One IBO reported the solubility of E 968 as 610 g/L at 22°C (Documentation provided to EFSA No. 3). Further, in response to EFSA's request of data supporting the solubility value provided, the IBO submitted three solubility tests performed on three different batches of E 968 (Documentation provided to EFSA No. 7). Erythritol solubility was tested in-house following the Flask Method OECD TG 105. Then, the samples were analysed by HPLC–RI detector. The minimum and the maximum mean solubility results observed for the three analysed samples were 422.9 and 426.6 g/L respectively at 20 ± 0.5°C (1.1% relative standard deviation) (Documentation provided to EFSA No. 7).

Another IBO stated that erythritol '*will be in solution very short time < 1 min after application in aqueous solution*'. According to the IBO, this can be transferred on oral human consumption (Documentation provided to EFSA No. 4). Solubility was tested using one batch of E 968 according to Flask Method OECD TG 105 (1995) and the test substance in the aqueous phase was determined by an HPLC method. The solubility of erythritol at 23°C resulted to be 352.60 g/kg or 35.26% w/w (Documentation provided to EFSA No. 8).

The Panel noted that the ultrafiltration step recommended in the EFSA Guidance on Particle-TR (EFSA Scientific Committee, 2021) to remove any small particles from the solubilised fraction was not included in these tests for solubility from the two IBOs. Given the nature of this simple polyol, the Panel considered nonetheless that the solubility of E 968 is substantially higher than the value of 33.3 g/L proposed as a criterion to decide whether an additional assessment for the fraction of small particles is needed according to the EFSA Guidance on Particle-TR (EFSA Scientific Committee, 2021).

[16] https://www.efsa.europa.eu/en/data/call/170621

[17] https://www.efsa.europa.eu/en/consultations/call/call-technical-data-sweeteners-authorised-food-additives-eu

[18] To provide some 'headroom' (to account for representativeness, homogeneity and analytical measurement uncertainty).

Taking into account the water solubility range reported by the IBOs for E 968 (e.g. 352.6–610 g/L), the Panel noted that E 968 can be considered as fully dissolved when consumed as a food additive. Therefore, consumers would not be exposed to the material in particle form and the conventional risk assessment according to the EFSA Guidance on food additive (EFSA ANS Panel, 2012) can be followed.

Particle size

Information on particle size by laser diffraction (LD) was received from one IBO (Documentation provided to EFSA No. 4). Taking into account the high solubility of E 968 in water (see above), this information was not further considered.

3.1.2 | Manufacturing process

3.1.2.1 | *Description of the manufacturing process*

Two IBOs provided detailed information on the manufacturing process of erythritol (E 968) (Documentation provided to EFSA No. 1, 2).

Both manufacturing processes described by the IBOs are in line with the definition indicated in Commission Regulation (EU) No 231/2012. The manufacture of E 968 occurs in a dedicated closed production line (Documentation provided to EFSA No. 1, 2, 10).

The IBOs provided detailed information on the characterisation of two microorganisms (*M. pollinis* and *M. megachiliensis*) declared to be used in the manufacturing of erythritol (E 968) (Documentation provided to EFSA No. 7, 8).

The fermentation broth undergoes purification and drying. The purification may involve several steps such as filtration, double crystallisation, washing, chromatographic separation, carbon treatment, ion exchange and centrifugation.

3.1.2.2 | *Raw materials and processing aid*

Previously sterilised carbohydrate raw materials (corn steep liquor/powder, glucose, glucose syrup, sucrose) are converted to erythritol by *M. megachiliensis* (Documentation provided to EFSA No. 3, 7) or *M. pollinis* (Documentation provided to EFSA No. 2, 8) by aerobic, submerged fermentation with conventional controls in place. Information on the grade of the starting materials have been provided by both IBOs.

3.1.2.3 | *Characterisation of the microorganisms used in the manufacturing of E 968*

3.1.2.3.1 | *Moniliella megachiliensis KW3-6 and Moniliella pollinis BC*

Erythritol is obtained by fermentation using the filamentous fungus *M. megachiliensis* strain KW3-6, which is deposited at the Biological Resource Center of the National Institute of Technology and Evaluation (NITE, Japan) with deposition number NITE SD 00504. The strain was identified as *M. megachiliensis* by analysis of the 26S and ITS sequences of the ribosomal rRNA gene. *M. megachiliensis* KW3-6 is not genetically modified. It was derived by conventional mutagenesis from strain S1477, a wild type isolated from plant material. The species *M. megachiliensis* is not known to be pathogenic to humans (Documentation provided to EFSA No. 1, 7).

Based on the information provided by one IBO (Documentation provided to EFSA No. 7), the Panel noted that the strain KW3-6 was derived in 2010 by mutagenesis from ancestor strains (i.e. S1477 or 3AB). The same IBO has also claimed that the test material used in the unpublished toxicological studies performed before 2002 and submitted for the current assessment (Documentation provided to EFSA No. 1, 6) was produced by another variant of *M. pollinis* CBS461.67 (Documentation provided No. 14). According to the information provided this strain has no relationship with the production strain KW3-6.

Erythritol is also obtained by fermentation using the filamentous fungus *M. pollinis* strain BC, which is deposited at the German Collection of Microorganisms and Cell Cultures (DSMZ, Germany) [redacted]. The strain was identified as *M. pollinis* by analysis of the Internal transcribed spacer (ITS) sequence of the ribosomal DNA (rRNA). The species *M. pollinis* is not known to be pathogenic to humans (Documentation provided to EFSA No. 2, 8).

3.1.2.3.2 | *Absence of viable cells of the production strains in the end product*

No colonies of *M. megachiliensis* KW3-6 were found in nine independent batches of erythritol (each tested in duplicate), by plating 1 g of product on non-selective solid medium and incubating for 10 days. (Documentation provided to EFSA No. 7).

No colonies of *M. pollinis* were found in three independent batches of erythritol (each tested in triplicate), when 10 g of product were diluted to a final volume of 100 mL and filtered (ø 0.45 µm), then the filters were incubated on non-selective and selective solid media at 30°C for 6 and 10 days, respectively (Documentation provided to EFSA No. 11).

Based on the detailed information on the characterisation of the two microorganisms mentioned above and the demonstration of the absence of viable cells in erythritol, the Panel considered that the manufacturing process of E968 by non-genetically modified *M. megachiliensis* strain KW3-6 *or M. pollinis* strain BC does not raise a safety concern.

The Panel noted that in the peer-reviewed literature the manufacturing process of erythritol using other microorganisms is described. For example, researchers in China have reported that erythritol is produced commercially by fermentation using microorganisms giving high yields, such as *Aureobasidium* sp., *Torula corallina*, *Candida magnoliae*, *Moniliella* sp., *Pseudozyma tsukubaensis*, *Clavispora lusitaniae and Yarrowia lipolytica* (e.g. Eszterbauer & Nemeth, 2022; Huang et al., 2023; Jeya et al., 2009; Khatape et al., 2022; Lee et al., 2003; Moon et al., 2010; Seshadrinathan & Chakraborty, 2022; Shukla

et al., 2023). Alternative fermentation techniques, e.g. cell immobilisation, for the production of erythritol are also described in the literature (Hijosa-Valsero et al., 2022). However, no IBOs have indicated their use and, therefore, they have not been assessed by the Panel.

3.1.3 | Method of analysis in food

One IBO made reference to two published articles describing methods for the analysis of erythritol in a variety of food matrices (Documentation provided to EFSA No. 3). Shindou et al. (1988) described a method for the determination of erythritol in fermented foods by HPLC–RI. Sreenath and Venkatesh (2008) reported an analysis of erythritol in watermelon and red wine by polyclonal antibody based indirect competitive enzyme-linked immunosorbent assay (ELISA). The method was applied only to the two named food types and since neither the antibodies nor the ELISA are generally available, the method has limited general utility.

Further, the IBO reported analytical methods for quantification of erythritol 'naturally formed' in ripened cheese and pulp of various fruits (i.e. watermelon, melon, pears, grapes, apples, banana, cherry, peach) by HPLC-RI and by gas chromatography–mass spectrometry (GC–MS) following acetylation (Shindou et al., 1989; Shindou & Ishizuka, 1996).

The Panel noted that the above-mentioned methods are focused on the determination of '*naturally formed*' erythritol, for example in fermented foods, rather than on the quantification of E 968 used as a food additive.

Koh et al. (2018) described an analytical method for five sugars and eight sugar alcohols (including erythritol) using HPLC with evaporative light scattering detection (ELSD). The method was applied to the analysis of a limited number of commercial products of candy, chewing gum, jelly, chocolate, processed chocolate products and snacks. Erythritol was not detected in any of the 30 samples. The limit of detection (LOD) for erythritol was stated to be 0.01% but this was based only on the analysis of solvent-standards. Erythritol eluted very early in the HPLC chromatogram and ELSD is a non-specific detection method, so erythritol is likely to be prone to interferences in some food matrices when using this method.

Nojiri et al. (2000) developed a method to determine erythritol among other sugar alcohols applied as food additives in confectioneries by HPLC-UV following derivatisation with *p*-nitrobenzoyl chloride. The average recoveries of the sugar alcohols from four sugarless confectioneries spiked at 5% and 10% levels ranged from 73.2% to 109.0% with relative standard deviations ranging from 0.7% to 9.0%. The LOD of the developed method was 0.1% for the analysed sugar alcohols in the samples.

3.1.4 | Stability of the substance and reaction and fate in food

One IBO referred to two studies carried out with erythritol using HPLC–RI to monitor stability (Documentation provided to EFSA No. 3). E 968 was reported stable for 3 years at room temperature (Documentation provided to EFSA No. 9) and for 2 years temperature not reported, assumed to be room temperature (Documentation provided to EFSA No. 9). A second IBO reported a storage stability study on commercial samples of erythritol (E 968) over 3 years at room temperature in which no significant changes against the specification parameters were detected (Documentation provided to EFSA No. 2).

The stability of erythritol as a 10% w/w solution was examined under model conditions at pH 2, 4, 6, 8 and 10, at temperatures of 60, 100 and 120°C, and time intervals of 0, 30, 60, 180 and 300 min (Documentation provided to EFSA No. 1). The sample tubes were tightly sealed, but air was not specifically excluded. Decomposition was monitored by determining erythritol content by HPLC–RI and by measurement of colour development. No loss of erythritol was noted under any combination of the test conditions. There was minor colour development in the tests at 120°C when the pH was 6 or below and the heating time was 180 or 300 min. The IBO attributed this colour to the presence of small amounts of reducing sugars in erythritol (Documentation provided to EFSA No. 3).

One IBO reported a study where the content of erythritol was found to be stable in a low-calorie orange-flavoured beverage (pH 3.1–3.2) stored at room temperature for up to 9 months (Documentation provided to EFSA No. 1). The same IBO reported a study in which erythritol was used to make processed foods (candy, chewing gum and cookies) and the content of erythritol was then measured by HPLC–RI (Documentation provided to EFSA No. 9). The study authors concluded that erythritol is stable, but since the recovery from the different food types was in the range of 92%–143%, these tests were considered by the Panel to be inconclusive. In a study, lozenges formulated with erythritol were analysed by HPLC–RI after 4 years of storage and the erythritol content was stable (Documentation provided to EFSA No. 9).

The Panel noted that, based on the submitted information along with considerations of the structure and characteristics of erythritol, being a simple polyol, E 968 is expected to be stable in food over a wide range of temperatures and pH conditions.

3.2 | Authorised uses and use levels

Maximum levels of erythritol (E 968) have been defined in Annex II, Part E, to Regulation (EC) No 1333/2008 on food additives, as amended. In this document, these levels are called maximum permitted levels (MPLs).

Currently, erythritol (E 968) is an authorised food additive in the EU in 66 different food categories (representing 83 uses). It is authorised at MPLs equal to *quantum satis* (QS) as a group I additive (for purposes other than sweetening) and

as polyols group (group IV). Only one numerical MPL of 16,000 mg/kg has been set for use in food category (FC) 14.1.4 Flavoured drinks (in 'only energy reduced or with no added sugar, as flavour enhancer'). Table 3 lists the food categories with their restrictions/exceptions that are permitted to contain added erythritol (E 968) and the corresponding MPLs as defined in Annex II to Regulation (EC) No 1333/2008.

TABLE 3 MPLs of erythritol (E 968) in food categories according to Annex II to Regulation (EC) No 1333/2008.

Food category number	Food category name	Restrictions/exception	E-number	MPL (mg/L or mg/kg as appropriate)
01.3	Unflavoured fermented milk products, heat-treated after fermentation		Group I	QS
01.4	Flavoured fermented milk products including heat-treated products		Group I	QS
01.4	Flavoured fermented milk products including heat-treated products	Only energy-reduced products or with no added sugar	Group IV	QS
01.6.3	Other creams		Group I	QS
01.7.1	Unripened cheese excluding products falling in category 16	Except mozzarella	Group I	QS
01.7.5	Processed cheese		Group I	QS
01.7.6	Cheese products (excluding products falling in category 16)		Group I	QS
01.8	Dairy analogues, including beverage whiteners		Group I	QS
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions		Group I	QS
02.3	Vegetable oil pan spray		Group I	QS
03	Edible ices		Group I	QS
03	Edible ices	Only energy-reduced or with no added sugar	Group IV	QS
04.2.1	Dried fruit and vegetables		Group I	QS
04.2.2	Fruit and vegetables in vinegar, oil or brine		Group I	QS
04.2.4.1	Fruit and vegetable preparations excluding compote		Group I	QS
04.2.4.1	Fruit and vegetable preparations excluding compote	Only energy-reduced or with no added sugar, with the exception of those intended for the manufacture of fruit-juice based drinks	Group IV	QS
04.2.5.1	Extra jam and extra jelly as defined by Directive 2001/113/EC	Only energy-reduced jams, jellies, marmalades or with no added sugar	Group IV	QS
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut puree as defined by Directive 2001/113/EC	Only energy-reduced or with no added sugar	Group IV	QS
04.2.5.3	Other similar fruit or vegetable spreads	Only energy-reduced or with no added sugar	Group IV	QS
04.2.5.4	Nut butters and nut spreads		Group I	QS
04.2.6	Processed potato products		Group I	QS
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	Only energy-reduced or with no added sugar	Group I	QS
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	Only energy-reduced or with no added sugar	Group IV	QS
05.2	Other confectionery including breath refreshening microsweets		Group I	QS
05.2	Other confectionery including breath refreshening microsweets	Only with no added sugar	Group IV	QS
05.2	Other confectionery including breath refreshening microsweets	Only starch based confectionery energy reduced or with no added sugar	Group IV	QS

TABLE 3 (Continued)

Food category number	Food category name	Restrictions/exception	E-number	MPL (mg/L or mg/kg as appropriate)
05.2	Other confectionery including breath refreshening microsweets	Only cocoa or dried fruit based, milk or fat-based sandwich spreads, energy-reduced or with no added sugar	Group IV	QS
05.2	Other confectionery including breath refreshening microsweets	Only cocoa based or dried fruit based confectionery, energy reduced or with no added sugar	Group IV	QS
05.2	Other confectionery including breath refreshening microsweets	Only for crystallised fruit, energy reduced or with no added sugar	Group IV	QS
05.2	Other confectionery including breath refreshening microsweets	Only hard candies and lollies, chewy candies, fruit gums and foam sugar products/marshmallows, liquorice, nougat, marzipan, breath freshening microsweets and strongly flavoured freshening throat pastilles, energy-reduced or with no added sugar	Group IV	QS
05.3	Chewing gum		Group I	QS
05.3	Chewing gum	Only with no added sugar	Group IV	QS
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4		Group I	QS
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4	Only decorations, coatings and fillings with not added sugar	Group IV	QS
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4	Only sauces	Group IV	QS
06.2.2	Starches		Group I	QS
06.3	Breakfast cereals		Group I	QS
06.3	Breakfast cereals	Only breakfast cereals or cereal-based products, energy reduced or with no added sugar	Group IV	QS
06.4.2	Dry pasta	Only gluten free and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	Group I	QS
06.4.4	Potato Gnocchi	Except fresh refrigerated potato gnocchi	Group I	QS
06.4.5	Fillings of stuffed pasta (ravioli and similar)		Group I	QS
06.5	Noodles		Group I	QS
06.6	Batters		Group I	QS
06.7	Pre-cooked or processed cereals		Group I	QS
07.1	Bread and rolls	Except products in 7.1.1 and 7.1.2	Group I	QS
07.2	Fine bakery wares		Group I	QS
07.2	Fine bakery wares	Only energy reduced or with no added sugar	Group IV	QS
08.3.1	Non-heat-treated meat products		Group I	QS
08.3.2	Heat–treated meat products	Except *foie gras, foie gras entier, blocs de foie gras*, *Libamáj, libamáj egészben, libamáj tömbben*	Group I	QS
08.3.3	Casings and coatings and decorations for meat		Group I	QS
09.1.1	Unprocessed fish	Only frozen and deep-frozen unprocessed fish for purposes other than sweetening	Group IV	QS
09.1.2	Unprocessed molluscs and crustaceans	Only frozen and deep-frozen unprocessed crustaceans, molluscs and cephalopods; for purposes other than sweetening	Group IV	QS

(Continues)

TABLE 3 (Continued)

Food category number	Food category name	Restrictions/exception	E-number	MPL (mg/L or mg/kg as appropriate)
09.2	Processed fish and fishery products including molluscs and crustaceans		Group I	QS
09.3	Fish roe	Only processed fish roe	Group I	QS
10.2	Processed eggs and egg products		Group I	QS
11.2	Other sugars and syrups		Group I	QS
11.4.1	Table Top Sweeteners in liquid form		Group IV	QS
11.4.2	Table Top Sweeteners in powder form		Group IV	QS
11.4.3	Table Top Sweeteners in tablets		Group IV	QS
12.1.2	Salt substitutes		Group I	QS
12.2.2	Seasonings and condiments		Group I	QS
12.3	Vinegars		Group I	QS
12.4	Mustard		Group I	QS
12.4	Mustard		Group IV	QS
12.5	Soups and broths		Group I	QS
12.6	Sauces		Group I	QS
12.6	Sauces		Group IV	QS
12.7	Salads and savoury based sandwich spreads		Group I	QS
12.8	Yeast and yeast products		Group I	QS
12.9	Protein products, excluding products covered in category 1.8		Group I	QS
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)		Group I	QS
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)		Group IV	QS
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)		Group I	QS
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)		Group IV	QS
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Including dry pasta	Group I	QS
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009		Group IV	QS
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Only vegetable juices	Group I	QS
14.1.4	Flavoured drinks	Only energy reduced or with no added sugar, as flavour enhancer only	E 968	16,000
14.1.5.2	Other	Excluding unflavoured leaf tea; including flavoured instant coffee; E 420, E 421, E 953, E 965, E 966, E 967 and E 968 may not be used in drinks	Group I	QS
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Except whisky or whiskey; E 420, E 421, E 953, E 965, E 966, E 967 and E 968 may not be used except in liqueurs	Group I	QS

TABLE 3 (Continued)

Food category number	Food category name	Restrictions/exception	E-number	MPL (mg/L or mg/kg as appropriate)
15.1	Potato-, cereal-, flour- or starch-based snacks		Group I	QS
15.2	Processed nuts		Group I	QS
16	Desserts excluding products covered in category 1, 3 and 4		Group I	QS
16	Desserts excluding products covered in category 1, 3 and 4	Only energy-reduced or with no added sugar	Group IV	QS
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms		Group I	QS
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms		Group IV	QS
17.2	Food supplements supplied in a liquid form, excluding food supplements for infants and young children		Group I	QS
17.2	Food supplements supplied in a liquid form, excluding food supplements for infants and young children		Group IV	QS
18	Processed foods not covered by categories 1–17, excluding foods for infants and young children		Group I	QS

Abbreviation: MPL, maximum permitted level.

Use of erythritol (E 968) is authorised as carrier at QS in all food additives according to Part 1 to Annex III to Regulation (EC) No 1333/2008.

Erythritol (E 968) is also authorised as food additive in all food flavouring at QS for purposes other than sweetening, not as flavour enhancers, according to Part 4 to Annex III to Regulation (EC) No 1333/2008.

In addition, erythritol (E 968) is authorised in all nutrients, only as a carrier, at QS, according to Part 5, section A, to Annex III to Regulation (EC) No 1333/2008.

3.3 | Exposure data

3.3.1 | Concentration data

Erythritol (E 968) is authorised at QS in all but one food category (see Table 3). To assess the dietary exposure to this food additive, concentration data (use levels and/or analytical data) are required.

To obtain concentration data, EFSA issued a public call for data[19] (use levels and/or analytical data) on erythritol (E 968) in the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives.

In response to this public call, information on use levels of erythritol (E 968) in foods was made available to EFSA by six industry stakeholders by 2 October 2018 through the batch 7 call for data.

Analytical data on erythritol (E 968) in foods and beverages submitted to EFSA by two Member States and extracted in October 2022 were also considered for the present exposure assessment.

Reported use levels of erythritol (E 968)

Industry provided EFSA with 42 use levels of erythritol (E 968) in foods for 13 out of the 83 authorised uses or 12 out of 66 authorised food categories[20] according to Annex II to Regulation (EC) No 1333/2008 (Table 3).

[19] https://wayback.archiveit.org/12090/20180625074455/http://www.efsa.europa.eu/sites/default/files/engage/180122.pdf

[20] Term 'authorised uses' refers to each single use considering each restriction/exception. Term 'authorised food categories' refers to food categories authorised regardless the restriction/exception.

The use levels of erythritol (E 968) were provided by Food Drink Europe (FDE), the International Chewing Gum Association (ICGA), Produlce, Unione Italiana Food (AIDEPI), Cloetta Suomi Oy and Food Supplement Europe (FSE).

The Panel noted that industry indicated that eight use levels for four food categories referred to niche products. For two of these four food categories, these use levels on niche products (FC 05.1 Cocoa and Chocolate products as covered by Directive 2000/36/EC and FC 05.3 Chewing gum) were used in the exposure assessment in absence of use levels reported for non-niche products.

Additional use levels were submitted by the erythritol producer (Cargill R&D Centre Europe) based on a search in Mintel GNPD (see Section 3.3.2 for more details about this database) (Documentation provided to EFSA No. 13). The Mintel GNPD contains the required ingredient information on the label. From there, the erythritol use levels were extracted from the ingredients' list, when available. When this direct information was not available, the erythritol content was estimated based on the polyol content, the order of the ingredients or nutrition information, where this information was available in the Mintel GNPD. In this way, use levels of erythritol were provided for 836 products, on 20 authorised food categories (25 uses).

In total, data from industry were provided for 22 authorised food categories.

Annex A, Table A2 summarises the use levels of erythritol (E 968) in foods as reported.

Summarised data on analytical results of erythritol (E 968) provided by Member States

In total, 187 analytical results of erythritol (E 968) were reported to EFSA by two EU Member States: Austria ($n = 134$) and Germany ($n = 53$). These data were mainly for FC 14.1.4 'Flavoured drinks' and FC 14.1.2 'Fruit juices as defined by Directive 2001/112/EC and vegetable juices'. All foods were sampled in 2020 and 2021.

A total of 157 analytical results were either reported as non-detected or non-quantified. According to the protocol (EFSA, 2020b), these results were not considered in the exposure assessment. Therefore, only 30 quantified results remained, covering seven food categories with no results that can be used for FCs 14.1.4 and 14.1.2 because they were all non-detected or non-quantified.

Annex A, Table A3 lists the quantified analytical levels of erythritol (E 968) in foods as reported by Member States.

3.3.2 | Summarised data extracted from Mintel's Global New Products Database

Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 3.8 million food and beverage products of which more than 1200,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 24 out of its 27 member countries and Norway presented in the Mintel GNPD.[21]

For this opinion, Mintel's GNPD[22] was used for checking the labelling of food and beverage products and food supplements for erythritol (E 968) within the EU's food market as the database contains the required ingredient information on the label.

According to Mintel's GNPD, erythritol (E 968) was labelled on 1400 products between January 2018 and November 2022. These products belong mainly to 'Dairy Based Ice Cream & Frozen Yogurt' ($n = 206$), 'Other Natural Sweeteners' ($n = 157$, e.g. powder sweetening products), 'Snack/Cereal/Energy Bars' ($n = 137$, mainly protein bars), 'Chocolate Tablets' ($n = 103$) and different types of flavoured drinks ($n = 90$).

Annex A, Table A4 lists the percentages of the food products labelled to contain erythritol (E 968) out of the total number of food products per food subcategory according to Mintel's GNPD food classification. The percentages ranged from less than 0.1% in many food sub-categories to 29.1% in Mintel's GNPD food subcategory 'Other Natural Sweeteners'. The average percentage of foods labelled to contain erythritol (E 968) was 0.7%. However, these percentages do not consider the market share of the products listed per food category.

Table A4 in Annex A also contains the list of corresponding food categories according to Annex II to Regulation (EC) No 1333/2008. The information from Mintel's GNPD indicated uses of erythritol (E 968) in several authorised food categories (e.g. foods from the Mintel sub-categories 'Nutritional & Meal Replacement Drinks' (which should belong to FC 13.3), from 'Other Snacks' and 'Rice Snacks' (FC 15.1), from 'Coffee' (FC 14.1.5.1) and 'Tea' (FC 14.1.5.2), as well as from 'Nut Spreads' (FC 4.2.5.4) and 'Drinking yogurt & Liquid cultured milk' (FCs 1.3 or 1.4) for which no use levels/analytical data were reported to EFSA. The number of food items from FCs not considered should be around 5% of the total number of food items on which erythritol (E 968) is labelled. The Panel noted that for a few food categories in which the use of erythritol (E 968) is not authorised, foods were found labelled to contain erythritol (E 968) (e.g. nectars (FC 14.1.3) and gin (FC 14.2.6)). However, the number of non-authorised food products labelled to contain erythritol (E 968) is low (less than five products in total). As a one-to-one linkage between Mintel's GNPD food sub-categories and the food categories according to Annex II to Regulation No 1333/2008 was not possible, these results should be considered indicative.

[21] Missing Cyprus, Luxembourg and Malta.

[22] https://www.gnpd.com/sinatra/home/

3.3.3 | Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011). The version of the Comprehensive database taken into account in this assessment was published July 2021.[23] Data from EU Member States were considered for the estimations.

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

Food consumption data from infants, toddlers, children, adolescents, adults and the elderly were used in the exposure assessment. For the present assessment, food consumption data were available from 41 different dietary surveys carried out in 22 Member States (Table 4). Not all Member States provided consumption information for all population groups, and in some cases the same country provided food consumption data from more than one consumption survey. In most cases, when, for one country and age class, different dietary surveys were available, only the most recent was used. However, when two national surveys from the same country gave a better coverage of the age range than using only the most recent one, both surveys were kept. For details on each survey, see Annex A, Table A1.

TABLE 4 Population groups considered for the exposure estimates of erythritol (E 968).

Population	Age range	EU Member States with food consumption surveys covering more than 1 day
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Portugal, Slovenia
Toddlers[a]	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, the Netherlands, Portugal, Slovenia, Spain
Children[b]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, the Netherlands, Portugal, Spain, Sweden
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, the Netherlands, Portugal, Romania, Slovenia, Spain, Sweden
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Portugal, Romania, Slovenia, Spain, Sweden
The elderly[b]	From 65 years of age and older	Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Portugal, Romania, Slovenia, Spain, Sweden

[a]The term 'toddlers' in the Comprehensive Database (EFSA, 2011) corresponds to 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013.
[b]The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in Comprehensive Database (EFSA, 2011).

Since 2018, all consumption records in the Comprehensive Database are codified according to the FoodEx2 classification system (EFSA, 2015a, 2015b). Nomenclature from the FoodEx2 classification system has been linked to the food categorisation system of Annex II to Regulation (EC) No 1333/2008, part D, to perform exposure assessments of food additives. In practice, the FoodEx2 food codes were matched to the food categories. For a detailed description of the methodology used to link these codes and the food categories, see section 5.2.1 of EFSA (2020b). In FoodEx2, facets are used to provide further information about different properties and aspects of foods recorded in the Comprehensive Database. Facets have been used in the exposure assessment of erythritol (E 968) to further identify foods to be included in the assessment (e.g. sweetener-related facets for foods in relevant food categories, see details in Annex A, Table A5).

Food categories considered for the exposure assessment of erythritol (E 968)

Food categories for which concentration data of erythritol (E 968) were provided, were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx2 classification system), at the most detailed level possible (up to FoodEx2 Level 7) (EFSA, 2015b).

[23]https://www.efsa.europa.eu/en/data-report/food-consumption-data

Facets were used to identify eating events referring to foods reported to contain sweeteners (i.e. energy reduced or with no added sugar foods) and to foods related to the specific restrictions/exceptions defined in the legislation for the use of erythritol (E 968) (see details in Annex A, Table A5). As defined in the protocol (EFSA, 2020b), facets were not used to identify relevant eating events for FCs 11.4 Table-top sweeteners and 05.3 Chewing gum, and for gum drops in FC 05.2 Other confectionery including breath refreshening microsweets, for energy drinks in FC 14.1.4 Flavoured drinks, and for vitamin and mineral supplements in FC 17 Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children. These food categories and foods are expected to be major contributors to the exposure to sweeteners according to the literature and represent a relatively high percentage of products labelled to contain at least one sweetener. Thus, all eating events belonging to these food categories and foods were included in the dietary exposure assessment of erythritol (E 968).

As FC 17 Food supplements does not consider food supplements for infants and toddlers as defined in the legislation, the exposure to erythritol (E 968) for these two population groups does not include the exposure via food supplements.

Eating occasions belonging to FCs 13.2 Dietary foods for special medical purposes, 13.3 Dietary foods for weight control diets intended to replace total daily food intake or an individual meal and 18 Processed foods were reclassified under food categories in accordance with their main component (e.g. gluten-free pasta reclassified as pasta).

In addition, FC 04.2.5.1 Extra jam and extra jelly as defined by Directive 2001/113/EC cannot be distinguished from FC 04.2.5.2 Jam, jellies and marmalades and sweetened chestnut purée as defined by Directive 2001/113/EC in the Comprehensive Database. Therefore, consumption of foods belonging to these food categories was considered in the exposure assessment under the general category of jam.

Overall, considering the data available, out of the 66 food categories in which erythritol (E 968) is authorised, 15 food categories (corresponding to 31 uses) were included in both the *regulatory maximum level exposure scenario* and the *refined brand-loyal exposure assessment scenario*.

3.4 | Exposure estimates

3.4.1 | Chronic exposure to erythritol (E 968) from its use as a food additive

The Panel considered appropriate, in the remit of the re-evaluation of sweeteners, to estimate the chronic exposure to erythritol (E 986) (EFSA, 2020b). As suggested by the EFSA WG on Food Consumption and Exposure (EFSA, 2011), dietary surveys with only 1 day per subject were not considered as they are not adequate to assess repeated exposure. Similarly, subjects who participated only 1 day in the dietary studies, when the protocol prescribed more reporting days per individual, were also excluded for the chronic exposure assessment.

Exposure assessments of sweeteners under the re-evaluation programme are carried out by the Panel based on two different sets of concentration data: (a) MPLs set down in the EU legislation (in the *regulatory maximum level exposure assessment scenario*) and (b) use levels and/or analytical data provided through the calls for data (in the *refined brand-loyal exposure assessment scenario*).

To calculate the chronic dietary exposure to erythritol (E 968), food consumption and body weight data at the individual level were extracted from the Comprehensive Database and linked to the concentration data as described in Section 5.2.1 of the protocol (EFSA, 2020b).

Chronic dietary exposure was calculated by combining MPLs/concentration levels of erythritol (E 968) in each food with the average daily consumption for each food at individual level in each dietary survey and population group. Exposure estimates per individual were divided by the individual's body weight resulting in a distribution of daily individual average exposures per kilogram body weight. Based on these distributions, the mean and 95th percentile (P95) exposures were calculated per survey and per population group. Mean estimates based on dietary surveys/population groups with less than six consumers and P95 estimates with less than 60 observations are not presented (EFSA, 2011).

In this evaluation, as stated in Section 5.2.3 in the protocol (EFSA, 2020b), the dietary exposure was assessed for consumers-only of at least one food category that could contain erythritol (E 968)[24] for all scenarios. Exposure estimates for these population groups are assumed to be the best approximate reflecting the exposure levels in diabetics, which are considered to be the population with the highest exposure to sweeteners (EFSA, 2020b). Depending on the food categories considered in the exposure assessment, the exposure was estimated based on different numbers of consumers. Exposure estimates based on fewer food categories could be higher than those based on a larger number of food categories due to a higher number of non-consumers within certain food categories.

Consumers-only of a single food category may have a higher exposure than consumers-only of at least one food category. To evaluate this, the exposure to erythritol (E 968) for consumers-only of each single food category (but still considering their whole diet) was also calculated for the *refined brand-loyal exposure assessment scenario*. These exposure estimates are discussed if they are higher than the exposure estimates for consumers-only of at least one food category.

[24]Part of the survey population may have no exposure to the additive because they did not report eating a food from one of the food categories that could contain the additive (these are 'non-consumers'). The sub-group who report eating these foods are called consumers.

Regulatory maximum level exposure assessment scenario

The *regulatory maximum level exposure assessment scenario* is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008 and in case of QS, on maximum reported use level/the highest reliable percentile of the analytical level when available. For erythritol (E 968), all MPLs except for one (for FC 14.1.4 Flavoured drinks) are at QS. Therefore, this *regulatory maximum level exposure assessment scenario* is based on the MPL for flavoured drinks and on maximum use levels for the other food categories when available (Table A1 of Annex A).

When all MPLs are numerical, the *regulatory maximum level exposure assessment scenario* considers all food categories in which the additive is authorised, whereas the refined scenarios (see below) consider only the food categories for which concentration data have been submitted. These two scenarios may therefore be based on a different number of food categories, making a comparison between these scenarios not possible. To make such a comparison possible, also a *refined regulatory maximum level exposure assessment scenario* is usually performed taking into account, at the MPL, only the food categories for which data (use levels and/or analytical data) are available.

In case of erythritol (E 968) for which almost all MPLs are at QS, the number of food categories considered in the *regulatory maximum level exposure assessment scenario* depends on the availability of data (use levels and/or analytical data) and is the same as for the refined scenarios. Therefore, no *refined regulatory maximum level exposure assessment scenario* was performed for this additive.

Refined brand-loyal exposure assessment scenario

The *refined brand-loyal exposure assessment scenario* for erythritol (E 968) was based on use levels reported by food industry or analytical results reported by Member States. This exposure scenario considers only those food categories for which these data were provided to the Panel. In this brand-loyal consumers-only scenario, it was assumed that a consumer is exposed long-term to erythritol (E 968) present at the maximum reported use level/the highest reliable percentile of the analytical data for one food category and at the mean of typical use levels/mean of analytical data for the other authorised food categories as explained in the protocol (EFSA, 2020b).

Annex A, Table A5 summarises the concentration levels of erythritol (E 968) used in the *refined brand-loyal exposure assessment scenario*.

Additional exposure scenario for uncertainty analysis

In addition, to evaluate the uncertainty related to the use of facets, the *regulatory maximum level exposure assessment scenario* and *refined brand-loyal exposure assessment scenario* were also performed *without using facets* to select relevant foods. Results for these two scenarios are presented in Annex A (Table A9) and are considered in the uncertainty section.

Dietary exposure to erythritol (E 968)

Table 5 summarises the estimated dietary exposure to erythritol (E 968) from its use as food additive in six population groups (Table 3) according to two exposure scenarios among consumers-only of at least one food category containing erythritol (E 968).

TABLE 5 Summary of chronic dietary exposure to erythritol (E 968) from its use as a food additive in the *regulatory maximum level exposure assessment scenario* and in the *refined brand-loyal exposure scenario*, in six population groups among consumers-only of at least one food category containing erythritol (E 968) (minimum–maximum across the dietary surveys in mg/kg bw per day and number of surveys in bracket).

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Regulatory maximum level exposure assessment scenario						
Mean[a]	19–427 (12)	86–798 (16)	148–634 (20)	48–322 (22)	49–186 (23)	39–187 (24)
95th percentile[b]	247–1125 (7)	239–1512 (15)	428–1638 (20)	150–842 (21)	144–490 (23)	151–452 (22)
Refined brand-loyal exposure assessment scenario						
Mean[a]	19–426 (12)	82–742 (16)	137–579 (20)	43–300 (22)	44–170 (23)	38–179 (24)
95th percentile[b]	238–1125 (7)	225–1512 (15)	379–1532 (20)	134–796 (21)	126–472 (23)	117–452 (22)

[a]Mean estimates based on dietary surveys/population classes up to and including five consumers may not represent the population group and are thus not included in this table.

[b]95th percentile estimates based on dietary surveys/population classes up to and including 59 consumers may not be statistically robust (EFSA, 2011) and are thus not included in this table.

NB: A *refined regulatory maximum level exposure assessment scenario* was not performed since the food categories considered in such a scenario would have been the same as in the *regulatory maximum level exposure assessment scenario (see explanation above the table, in the Regulatory maximum level exposure assessment scenario paragraphs).*

For the *regulatory maximum level exposure assessment scenario*, the highest mean exposure to erythritol (E 968) was found in toddlers (798 mg/kg bw per day) and the highest P95 in children (1638 mg/kg bw per day).

In the *refined brand-loyal exposure assessment scenario*, the highest mean exposure to erythritol (E 968) was found in toddlers (742 mg/kg bw per day) and the highest P95 in children (1532 mg/kg bw per day).

Detailed results per population group and survey for both exposure scenarios are presented in Table A6 of Annex A.

Main food categories contributing to the exposure to erythritol (E 968)

For the two exposure scenarios presented in Table 5, the main food category contributing to the exposure to erythritol (E 968) was FC 7.2 Fine bakery wares for all population groups and almost all (except one) surveys. The second main food category was FC 03 Edible ices.

Dietary exposure for consumers of a single food category containing erythritol (E 968)

For consumers-only of a single food category while still considering their whole diet, in the *refined brand-loyal exposure assessment scenario*, Table A10 of Annex A lists the maximum exposure estimates that exceeded the highest overall exposure estimates of consumers-only of at least one food category.

For many food categories and population groups considering consumers of only one food category, the exposure estimates were higher than those considering consumers of at least one food category (i.e. one or more) containing erythritol (E 968). This can be explained by the high number of consumers considered in the latter case, which dilute the total exposure to the sweetener. The consumer only approach for only one food category can give an indication on the higher exposure in this population compared to the general population.

For most of the exposure estimates, mean exposure for consumers of one food category only was comparable to exposure for consumers of at least one food category (i.e. one or more, Table 5) in the refined brand-loyal exposure assessment scenario (less than two times), considering the uncertainties related to the exposure estimates (see Section 3.4.3). However, for two food categories, 'Fruit and vegetable preparations excluding compote' and 'Other confectionery including breath freshening microsweets', mean exposure of consumers-only could exceed the mean dietary exposure considering consumers of at least one food category by a factor of 2.5–5.6 (Table 4). It was noted that the consumers populations of these two food categories were small for each of the surveys (between 7 and 20 subjects).

3.4.2 | Acute exposure to erythritol (E 968) from its use as a food additive

Considering the laxative effect of polyols and the half-life of erythritol of 4 h (Section 3.5.3), an acute dietary exposure to erythritol (E 968) was calculated per meal.

Acute exposure per meal was assessed for each reporting meal by multiplying the total daily consumed amount for each relevant food by its concentration level (Table A5 of Annex A). The concentration levels considered were the maximum use level/highest percentile for the two food categories contributing most to the exposure (calculated with the mean concentration levels). For the remaining food categories, the mean level was used. For the acute exposure, it is more likely that the same person consumes foods from more than one food category with the highest level of sweetener on a single meal, than on two or more consecutive days for the chronic exposure. The exposures per food were then summed per meal and divided by the individual's body weight to obtain the acute exposure to erythritol (E 968) expressed in mg/kg bw per meal.

Information on the meal during which a food was consumed during a day was not always available. The exposure from these 'unclassified' foods was added to the exposure from the meal having the highest exposure on that day. After this, the two main food categories contributing to the exposure were recalculated as described above. When no information on meals was available for a certain day, the exposure to erythritol (E 968) on that day was not considered.

The 95th, 97.5th and 99th percentiles of exposure per meal were calculated to express a high level of acute exposure to erythritol (E 968) (Table 6).

TABLE 6 Summary of acute dietary exposure to erythritol (E 968) per meal, from its use as a food additive, in six population groups among consumers-only (minimum–maximum P95, P97.5 and P99 across the dietary surveys in mg/kg bw per meal and in g/person per meal and number of surveys in bracket).

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Acute exposure assessment scenario per kg bw per meal (in mg/kg bw per meal)						
95th percentile[a]	400–**1458** (6)	417–1426 (13)	477–1200 (16)	**168**–755 (21)	191–534 (24)	170–497 (24)
97.5th percentile[b]	500–1577 (4)	512–**1911** (12)	635–1625 (15)	228–1013 (20)	247–668 (24)	**202**–623 (23)
99th percentile[c]	1393 (1)	614–3400 (12)	813–**3531** (15)	296–1365 (19)	322–1121 (24)	**253**–863 (21)

TABLE 6 (Continued)

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Acute exposure assessment scenario per person and per meal (in g/person per meal)						
95th percentile[a]	**3.6**–14.2 (6)	4.0–17.6 (13)	8.7–26.6 (16)	8.5–39.0 (21)	14.3–37.7 (24)	12.4–37.3 (24)
97.5th percentile[b]	4.5–15.6 (4)	5.0–26.0 (12)	11.6–36.9 (15)	12.0–50.1 (20)	18.2–47.6 (24)	15.3–47.4 (23)
99th percentile[c]	12.0 (1)	6.0–36.5 (12)	15.0–**84.8** (15)	16.0–77.9 (19)	20.7–71.0 (24)	17.7–66.6 (21)

[a]95th percentile estimates based on dietary surveys/population classes up to and including 59 observations may not be statistically robust (EFSA, 2011) and were not included in this table.

[b]97.5th percentile estimates based on dietary surveys/population classes up to and including 118 observations may not be statistically robust (EFSA, 2011) and were not included in this table.

[c]99th percentile estimates based on dietary surveys/population classes up to and including 298 observations may not be statistically robust (EFSA, 2011) and were not included in this table.

These percentiles are only statistically robust if based on a sufficiently large number of observations, thus it was not possible to calculate these percentiles for all surveys. The 99th percentile of exposure was always the highest, except for infants. For this population group, surveys resulting in a high 97.5th percentile estimate were not included in the 99th percentile estimates due to an insufficient number of observations to calculate a 99th percentile (see Table 4).

The highest acute exposure estimate of erythritol (E 968) was 84.8 g/person per meal for children. This was a 99th percentile of exposure.

For all population groups, the food category contributing most to the acute exposure was fine bakery wares. Also edible ices and sauces were relevant food categories contributing to the acute exposure in all population groups, except infants.

3.4.3 | Uncertainty analysis related to the exposure assessment

In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties related to both chronic and acute exposure assessments have been considered and summarised in Table 7.

TABLE 7 Qualitative evaluation of influence of uncertainties on the chronic and acute dietary exposure estimates.

Sources of uncertainties	Direction[a]
Consumption data	
Different methodologies/representativeness/underreporting/misreporting/no portion size standard/only a few days	+/–
Underreporting of food descriptors (facets) concerning the presence or potential presence of sweeteners	–[b]
Use of the additive in table-top sweeteners added to home made products might not be captured for some surveys	–
Level of use of sweetener in home made products may differ from industrial counterpart	+/–
Use of the additive in table-top sweeteners regardless of the type of the sweetener consumed	+
Concentration data	
Correspondence of reported use levels and analytical data to the food items in the Comprehensive Database: uncertainties to which types of food the levels refer	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Acute exposure assessment scenario: 16 food categories out of the 66 authorised to contain erythritol (E 968) were considered	–
Regulatory maximum level and brand-loyal exposure assessment scenario: number of Mintel food sub-categories in which erythritol (E 968) was labelled were included in the current exposure assessment: 47 out of 65 food sub-categories, representing 94% of the products labelled with erythritol (E 968)	–
Use levels/MPLs considered applicable to all foods for some food categories a, while the percentage of foods labelled with erythritol (E 968) in a corresponding food subcategory labelled with erythritol (E 968) in Mintel was maximally 29% (FCs 11.1, 11.4)	+
Methodology	
Chronic exposure assessment scenario	
Regulatory maximum level exposure assessment scenario: – exposure calculations based on the MPL according to Annex II to Regulation (EC) No 1333/2008 for one FC (FC 14.1.4) and on the maximum for the other food categories	+
Refined brand-loyal exposure assessment scenario: – exposure calculations based on the maximum and mean levels	+/–
Use of data from food consumption survey covering only a few days to estimate high percentile (95th) of long-term (chronic) exposure	+

(Continues)

TABLE 7 (Continued)

Sources of uncertainties	Direction[a]
Acute exposure assessment scenario	
Acute exposure assessment scenario (per meal): – exposure calculations based on the maximum concentration data for two food categories and on the mean for the other food categories	+
Acute exposure assessment scenario per meal: – adding 'unclassified' foods' (with no information on the meal) to the meal having the highest exposure	+

[a]+, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.
[b]Direction of the uncertainty is based on the assumption that the underlying population of consumers does not change.

Erythritol (E 968) is a food additive belonging to the sweeteners category. It is also a group I food additive and as such can be used at QS for purposes other than sweetening. Furthermore, it belongs to the group IV polyols for which its use is also authorised at QS. Finally, erythritol is authorised in flavoured drinks (FC 14.1.4) at 16,000 mg/kg.

Uncertainties related to chronic exposure assessment

In the chronic *refined brand-loyal exposure assessment scenario*, the highest mean exposure to erythritol (E 968) was in toddlers (742 mg/kg bw per day) and the highest P95 in children (1532 mg/kg bw per day).

Chronic exposure results for the *refined brand-loyal exposure assessment scenario* are very similar to the ones for the *regulatory maximum level exposure assessment scenario*; this can be partly explained as the same food categories were considered in both scenarios.

In the *refined brand-loyal exposure assessment scenario*, facets were used to identify foods to be included in the assessment (e.g. sweetener-related facets for foods in relevant food categories). In a scenario in which these facets were not used, the exposure estimates were approximately two to four-fold higher in all population groups (fine bakery wares being still the most important contributor to the exposure). As it is likely that facets were underreported in the dietary surveys, the exposure estimates relying on the facets may underestimate the exposure to erythritol (E 968). However, this possible underestimation was more than compensated by the assumption that 100% of the foods in the food categories in which facets were not considered contained the sweetener such as FCs 11.4 Table-top sweeteners and 05.3 Chewing gum (see Section 3.4.1). According to Mintel GNPD, for the different food sub-categories, the percentage of food items containing the sweetener was maximally 24%.

The use of the maximum concentration data for the highest contributing food category has very likely also contributed to an overestimation of the total chronic exposure.

Overall, the Panel considered the chronic exposure to erythritol (E 968) from its use as food additive (excluding population groups under medical supervision), to be overestimated by the *regulatory maximum* and *refined brand-loyal exposure assessment scenario*.

Uncertainties related to acute exposure assessment

Erythritol (E 968) is part of the group of polyols which have a dose-dependent laxative effect and therefore acute exposure to the sweetener per meal was estimated. Acute exposure per meal could reach up to 3500 mg/kg bw for children, i.e. reaching 84.8 g/person per meal for children.

As in the chronic assessment, use of facets may have underestimated the exposure to erythritol (E 968), but this was more than compensated by the assumption that 100% of the foods within the considered food categories contain the sweetener.

Considering two food categories to contain erythritol (E 968) at the maximum level during the meal has also contributed to an overestimation of the total acute exposure (for 95th, 97.5th and 99th percentiles). Considering these maximum use levels is a conservative scenario. However, this is not an unreasonable scenario since erythritol (E 968) has a lower sweetening power than sugar (approximately 70% of its sweetening power) and can be used as a sugar replacement in many products.

In addition, adding the total exposure via foods not linked to a meal on a specific day to the exposure via the meal with the highest exposure will also have contributed to an overestimation of the acute exposure to erythritol (E 968).

If the 'unclassified' foods (those foods for which the information on the meal was missing) were not considered, acute exposure estimates per meal were similar.

Overall, the Panel considered the acute exposure to erythritol (E 968) from its use as food additive (excluding population group under medical supervision), to be overestimated in the *acute exposure assessment scenario per meal*.

3.4.4 | Literature on occurrence data and exposure assessment of erythritol

Based on the literature review related to publications on the occurrence and dietary exposure to erythritol (E 968), the Panel noted that no information relevant for the EU was found.

Some information on erythritol naturally occurring in foods was retrieved. Mushrooms, some fruits (melons, watermelons, pears, grapes), alcoholic beverages (wine, sake) or fermented products (soya sauce, miso bean paste) contain erythritol at levels from 22 to 1550 mg/kg. These few foods at levels lower than the use levels reported in processed foods would probably add 1%–2% to the exposure estimates in Table 5. In order to reach 10% of the estimated chronic exposure (up to 153 mg/kg bw per day at the 95th percentile of the *refined brand-loyal exposure assessment scenario*, for children, Table 5), consumption of more than 7 kg fruits, 6 kg cheese or around 270 g miso would be needed.

3.5 | Biological and toxicological data

The biological and toxicological data considered for this assessment consisted of an initial set of 5190 references comprising studies retrieved from the literature as well as data received by IBOs, following EFSA calls for data and subsequent additional data requests. After an initial screening at the level of title and abstract, 527 references were further screened based on full text, according to the criteria outlined in the revised protocol.

After screening for eligibility, a total of 114 references were considered eligible for this assessment. Most of these studies had previously been evaluated (EFSA ANS Panel, 2010, 2015; SCF, 2003).[25] Studies, on which previous conclusions were based (SCF, 2003), were considered in the current assessment together with relevant literature identified since the previous evaluation, using 2002 as cut-off date.

All human studies were subjected to a RoB evaluation, except observational studies with no information on dietary intake of erythritol, since these studies did not directly address the exposure to erythritol resulting from its currently permitted uses as a food additive. The detailed results of the RoB evaluations are reported in Tables A1 and A2 of Appendix A. For these studies, a WoE approach was applied for each relevant health outcome category. A narrative synthesis of the WoE analysis is reported in Section 3.5.4.2.

The Panel noted that the scientific data provided in the context of the new application for exemption of erythritol (E 968) from a laxative warning were human studies already considered and evaluated in previous opinions (EFSA ANS Panel, 2010, 2015; SCF, 2003).

Studies on absorption, distribution, metabolism and excretion (ADME) were not subjected to a RoB evaluation and are summarised narratively. In the case of genotoxicity, studies were evaluated according to the approach outlined in the revised protocol (EFSA 2020a and further revision). Human studies on sweetener mixtures, case-reports and studies in animal disease models were also summarised narratively (see Appendices F and G). In addition, studies concerning endogenous erythritol levels were considered by the Panel and summarised narratively (see Section 3.5.1 Biological data).

The list of studies that did not meet the inclusion criteria is provided in Annex B.

Concerning the manufacturing process of erythritol used as test item of the unpublished study reports sent by one IBO (Documentation provided to EFSA No. 1, 6), the Panel was informed that different production strains were used (see Section 3.1.2.3). Considering that the manufacturing process of erythritol (E 968) undergoes several purifications steps (see Section 3.1.2), the Panel considered it acceptable to use biological and toxicological studies performed with erythritol produced by *M. pollinis* CBS461.67 for the assessment of erythritol produced by the current microorganism in use (*M. megachiliensis* KW3-6) and to extend this option for the assessment of erythritol (E 968) produced also currently by *M. pollinis* BC. Uncertainty remains on the manufacturing process of the erythritol tested in peer reviewed articles.

3.5.1 | Biological data

3.5.1.1 | *Erythritol as an endogenously formed substance*

Evidence from the published literature, based on *in vitro*, *in vivo* and *ex vivo* studies, has recently accrued showing how erythritol is formed endogenously through the pentose phosphate pathway (PPP).

Hootman et al. (2017) investigated the potential metabolism of erythritol and metabolism of glucose to erythritol in humans in two ways: first, in an *in vivo* experiment in three healthy male volunteers, and second, in an *ex vivo-in vitro* experiment with blood from five healthy male volunteers. For the *in vivo* experiment the volunteers were given 2 g of [$U^{13}C$] glucose. Blood was taken at time 0, 5, 15, 30, 45, 60, 90, 120 and 180 min. Four baseline values were taken ($t = 0$, 5, 15 and 30 min) and 50 g erythritol was then orally given to the volunteers 2 min before taking the blood sample at 45 min. Glucose was measured by a commercial glucometer, and erythritol and erythronate were measured after extraction and derivation by GC–MS analysis. After intake of erythritol, the blood concentrations of erythritol increased to a maximum level of about 5000 μM at 90 min and the concentration of erythronate in blood also increased up to 225, 280 and 300 μM for the 3 volunteers at 180 min. The authors assumed that erythritol undergoes oxidative metabolism to erythrose and, in a second step, to erythronate. In the *in vitro* study, the authors incubated dipotassium ethylenediaminetetraacetic acid (K2EDTA) blood samples, taken from five healthy male volunteers, supplemented with [$U^{13}C$]glucose, [6-$^{13}C_1$]glucose, [1,2-$^{13}C_2$]glucose or [3,4-$^{13}C_2$]glucose, and measured the substances of interest by GC–MS after incubation for 120 min. The final total glucose (labelled + unlabeled) concentration was 15 mM. Mass isotopomer distributions (MIDs) of erythritol were determined. An

[25]For some of these studies, where available, original study reports were provided to EFSA by one IBO (Documentation provided to EFSA No. 1, 6).

increase of fully labelled erythritol was shown compared with the concentration of labelled erythritol before adding the [U^{13}C]glucose tracer indicating the metabolism of glucose to erythritol. In a further experiment, the authors provided evidence that erythritol is produced from glucose by the PPP pathway.

3.5.1.2 | *Studies on circulating erythritol*

Recently, associations between increased erythritol blood levels and metabolic disorders and/or cardiovascular diseases have been reported (Rebholz et al., 2018; Wang et al., 2019; Witkowski et al., 2023). In addition, several metabolomic profiling studies reported that elevated circulating erythritol concentrations, together with other metabolites, were observed in patients with type II (T2) diabetes and related vascular and non-vascular complications (Chen et al., 2016; Duangkumpha et al., 2022; Menni et al., 2013; Moon et al., 2023; Shao et al., 2022) and/or cardiovascular disease (Fu et al., 2022).

Witkowski et al. (2023) examined the association between circulating blood erythritol levels and major adverse cardiovascular events (MACE): death, nonfatal myocardial infarction or nonfatal cerebrovascular accident (stroke) in one cohort (USA) consisting of 1157 stable patients aged 52–76 years and undergoing cardiac risk assessment for symptom evaluation. In this untargeted metabolomic study, circulating levels of multiple polyols, including erythritol, were associated with incident (3 years) risk for MACE.

The authors then validated their findings on erythritol in two independent cohorts from the USA and Europe. The USA cohort consisted of 2149 patients aged 51–76 years undergoing or having had a heart catheterisation within 1 year. The European cohort consisted of 833 patients aged 59–85 years, undergoing cardiac catheterisation. For both cohorts, baseline blood samples (fasting in the USA cohort) were collected at recruitment and MACE events were recorded over a follow-up period of 3 years. For all the three cohorts, circulating erythritol levels measured at baseline, varying between 1.4 μM and 134.6 μM, were associated with MACE when comparing the highest versus the lowest quartile of blood erythritol concentrations (adjusted hazard ratios (HR) 2.95, (95% confidence interval (CI) CI 1.70–5.12); HR 1.80, (95% CI, 1.18–2.77) and HR 2.21, (95% CI, 1.20–4.07)) in the discovery-, USA-validation and European-validation cohorts, respectively. Participants for all cohorts were recruited from a population with suspected chronic coronary syndromes and had high cardiovascular disease risk. Although confounders with a detailed sub-group analysis were reported, residual confounding may be present due to the lack of control in the multivariate analysis for socio-economic status, a detailed smoking history, duration of T2 diabetes and/or glycated haemoglobin levels and the use of drugs. The measurement of erythritol was done with an established quantitative method in the validation cohorts. No information was available on dietary intake. No distinction between endogenous and exogenous erythritol can be made, therefore the source of the measured levels could not be identified. The low circulating levels suggest that the main source for most participants was endogenic formation. Cardiovascular-specific mortality was not included as an outcome.

Additionally, Witkowski et al. (2023) performed *in vitro* studies to explore the biological plausibility of the findings described above. These studies showed that erythritol can activate platelets at minimal concentrations from 4.5 to 18 uM and increase platelet aggregation in platelet-rich plasma at 45 uM *in vitro* (see Appendix G). The Panel considered that these studies provided insufficient basis to predict what may occur in humans and thus cannot contribute to the current risk assessment of erythritol.

3.5.1.3 | *Absorption, distribution, metabolism and excretion (ADME)*

No new studies on ADME were submitted either by the interested parties or by the applicant.

As regards the data submitted through the call for data by one IBO, the Panel noted that the published studies and unpublished study reports were already considered and evaluated by the SCF in its 2003 opinion (Documentation provided No. 6). In addition, in the context of a new application on exemption for erythritol from a laxative warning label requirement, the applicant submitted some published studies (Bornet et al., 1996a, 1996b; Hiele et al., 1993; Noda et al., 1994, 1996; Noda & Oku, 1992; Van Ommen et al., 1996; Tetzloff et al., 1996. Til et al., 1996 in Documentation provided to EFSA No. 5). The Panel noted that the data received from the applicant had already been considered in previous opinions (EFSA ANS Panel, 2015; SCF, 2003).

In its 2003 opinion, the SCF reviewed many animal and human studies on ADME that demonstrated that 60%–90% of ingested erythritol is rapidly absorbed from the small intestine and excreted unchanged in the urine or fermented by the gut flora to short chain fatty acids (EFSA ANS Panel, 2010; SCF, 2003). A detailed summary of these studies is provided in Appendix C.

Six new relevant publications were identified in the literature (Arrigoni et al., 2005; Beards et al., 2010; Bordier et al., 2022; Maeng et al., 2019; Van Wijck et al., 2011; Witkowski et al., 2023), and are summarised below.

Human studies

In vivo studies

The publication of Van Wijck et al. (2011) describes a study in which 10 healthy volunteers (men and women aged 18–75 years) were given an oral bolus dose of 1 g erythritol (8.19 mmol). The urinary excretion and the plasma concentration of erythritol were measured for up to 5 h (urine) and 2 h (plasma) using a liquid chromatography mass spectrometry (LC–MS) assay. The peak concentration in plasma was 240 μmol/L (29.3 mg/L) and the cumulative urinary excretion was 3.4 mmol, which corresponds to 41.5% of the dose ingested.

Bordier et al. (2022) performed a pharmacokinetic cross over study in 12 healthy volunteers receiving a bolus dose of 10, 25 or 50 g of erythritol dissolved in 300 mL tap water. Following ingestion, blood was taken and erythritol and erythronate were

measured. The peak concentrations were 1810.6 ± 124.6 μM, 3676.9 ± 251.2 μM and 5404.3 ± 450.6 μM, for 10 g, 25 g or 50 g of erythritol, respectively. The area under the curve $(AUC)_{0–180\ min}$ of erythritol was 201.0 ± 12.7, 450.6 ± 29.3 and 707.1 ± 53.9 mM x min, following 10 g, 25 g and 50 g erythritol, respectively. The $AUC_{0\text{-}180\ min}$ of erythronate was 1034.4 ± 122.8, 2664.8 ± 241.6 and 5151.9 ± 763.2 μM x min, following 10 g, 25 g and 50 g erythritol, respectively. From this study it could be observed that the $AUC_{0\text{-}180\ min}$ of erythritol is not a linear increase with the dose administered, since a 5-fold increase in the dose administered corresponded to a 3.5 fold increase in the measured $AUC_{0\text{-}180\ min}$ for erythritol. This may indicate that absorption of erythritol is dose-dependent. Erythritol is metabolised to erythronate to a small extent (less than 1% of the dose).

Witkowski et al. (2023) performed a kinetic study[26] in eight volunteers that were given a single dose of 30 g erythritol in a drink (300 mL). Figure 5 of this publication shows that maximum concentrations of about 5000 μM in plasma were reached 30 min following ingestion and the concentrations remained elevated for over 2 days in all participants examined, compared to baseline plasma erythritol (3.84 μM). In the publication, the authors clarified that the study reporting pharmacokinetics data (Figure 5) were acquired as the first part of the clinical trial COSETTE (NCT04731363), to identify both the timing of peak plasma levels of erythritol after ingestion and the time course of erythritol elimination. The studies are on-going and detailed results were not reported in the current paper.

In vitro studies

Maeng et al. (2019) examined the metabolism of erythritol in human cryopreserved hepatocytes (pooled from 10 donors; five males and five females, overall age range 7–67 years, one African American and 9 Caucasians) and in pooled cryopreserved male IGS SD rat hepatocytes. Hepatocytes were thawed at 37°C, transferred to OptiThaw medium (XenoTech), centrifuged at 100 g for 5 min prior to re-suspension in incubation medium (OptiIncubate, XenoTech). The authors indicate that the glucose concentration in this medium was 11 mM and that the concentration did not significantly change over the 240 min incubation period. Hepatocytes (1 × 106 cells/mL) were incubated at 37°C in a humidified incubator with cells dispersed using an orbital shaker at 120 rpm. Incubations were terminated 0, 30, 60, 120 and 240 min. Erythritol (41 μM) was stable (no change in medium concentration after 240 min).

Arrigoni et al. (2005) examined the metabolism of erythritol in fresh human faeces collected and combined from four non-methanogenic donors. Incubations were performed under anaerobic conditions for up to 24 h and erythritol levels were determined by HPLC. No further details are provided. There was no metabolism of erythritol over the 24h period examined. No gas or hydrogen gas production was evident.

Beards et al. (2010) examined total gas production following addition of erythritol to fresh human faecal slurries (from healthy volunteers who had not taken antibiotics 3 months prior to sampling). The slurries were incubated at 37°C under anaerobic conditions for up to 24 h. Addition of erythritol resulted in gas production but there was no comparison to slurries in the absence of erythritol.

Summary and conclusions on ADME by the Panel

Human

Erythritol is a natural component of some foods, e.g. watermelon, melon, grape, pear (Sreenath & Venkatesh, 2008). In individuals unexposed to food containing erythritol as a food additive, mean urinary erythritol excretion rates have been shown to range between 75 and 118 mg/day. Erythritol is readily absorbed from the gastrointestinal tract in a dose-dependent manner and between 78% and 92% is excreted unchanged in the urine within 24 h, depending on the dose. Less than 1% of the dose is metabolised to erythronate. The half-life of excretion can be estimated to be about 4 h. Erythritol is subjected to negligible metabolism by the human gut microbiota.

Rat

Overall, studies in rats showed that at least 90% of erythritol is absorbed from the gastrointestinal tract and excreted, mainly in the urine as the parent compound. The half-life of excretion can be estimated to be approximately 4 h. When gut flora metabolism is excluded, no evidence of metabolism and resulting incorporation into cellular constituents is obtained. Gut flora metabolism of ^{14}C erythritol results in a proportion of erythritol ultimately appearing in expired air from the lungs as $^{14}CO_2$ (Appendix C).

Mice

Only one study was available in mice. Between at least 75%–95% of ingested erythritol is absorbed and excreted unchanged in the urine (Appendix C).

[26]The Panel noted that, according to a communication with the authors, Extended Data Figure 3 contains an error in that the Y axis scale is log_{10} when it should have scaled to ln. The error when using the log scale instead of the ln scale is considerable. For example, the highest erythritol concentrations in the European cohort would be between 10,000 and 100,000 μM with the log scale, whereas in reality they are 55 and 148 μM when using the ln scale.

Dog

Overall, considering the available studies in dogs, at least 90% of erythritol was absorbed from the gastrointestinal tract and excreted primarily in the urine unchanged (Appendix C).

In vitro

The *in vitro* study by Maeng et al., 2019, examining the metabolism of erythritol in human and rat hepatocytes, reported that erythritol is stable and not metabolised. This is in contrast with the evidence emerging from the recent *in vivo* study by Bordier et al., 2022, from which metabolic transformation to erythronate, although limited, is shown. The Panel noted that the *in vitro* study used a much lower concentration of erythritol (41 uM) than that of the *in vivo* study.

3.5.2 | Genotoxicity

Erythritol was previously evaluated by the SCF in 2003 (SCF, 2003). Concerning genotoxicity, the SCF noted that erythritol did not show evidence of mutagenic activity in two Ames tests (Nikken chemicals Co., Ltd., 1988; TNO-CIVO Industries 1990 in Documentation provided to EFSA No. 6) and did not produce a significant increase in the incidence of abnormal cells, polyploid cells, total chromosomal aberrations, break or exchange types in a cytogenetic test *in vitro* in Chinese hamster fibroblasts (Nikken Chemicals Co., Ltd., 1988 in Documentation provided No. 6), thus demonstrating no genotoxic activity. The Panel noted that the studies reported in the original study report provided by the IBO (Nikken Chemicals Co., Ltd., 1988 in Documentation provided to EFSA No. 6) were subsequently published in Kawamura et al., 1996.

An extensive literature search covering the period subsequent to the last SCF opinion identified a single paper addressing the genotoxicity of erythritol. The main findings from this paper are summarised below in Table 8 and in Appendix D.

Chung and Lee (2013) evaluated a commercial sample of erythritol in a battery of *in vitro* and *in vivo* assays. Erythritol was negative in the Ames test and in the *in vitro* chromosomal aberration and micronucleus assays. An increase in mean % Tail DNA was observed after extended (24 h) treatment at 2500 μg/mL and above in the *in vitro* comet assay in the absence of overt toxicity, as measured by trypan blue exclusion.

TABLE 8 Summary table of new genotoxicity studies on erythritol.

Test system (test object)	Exposure conditions (concentration/testing conditions)	Information on the characteristics of the test substance	Result	Reliability	Relevance of test system/ relevance of the result	Reference
Bacterial reversion assay (*Salmonella* typhimurium TA98, TA1537, TA100, TA1535 and *Escherichia coli* WP2 *uvrA*)	156, 312, 625, 1250, 2500 and 5000 μg/plate (+/− S9, plate incorporation)	Erythritol (commercial sample purchased at local marketplace (Korea))	Negative	Reliable without restriction	High/High	Chung and Lee (2013)
In vitro chromosomal aberration assay (Chinese hamster lung fibroblasts cells (CHL))	Experiment 1: 1250, 2500 and 5000 μg/mL (6h, +/− S9) Experiment 2: 1250, 2500 and 5000 μg/mL (24h, − S9)		Negative	Reliable with restriction	High/ Limited	
In vitro micronucleus test (L5178Y mouse lymphoma cells)	Experiment 1: 1250, 2500 and 5000 μg/mL (3 + 21h, +/− S9) Experiment 2: 1250, 2500 and 5000 μg/mL (24h, − S9)		Negative	Reliable without restriction	High/High	
In vitro comet assay (L5178Y mouse lymphoma cells)	Experiment 1: 1250, 2500 and 5000 μg/mL (3h, +/− S9) Experiment 2: 1250, 2500 and 5000 μg/mL (24h, − S9)		Positive	Reliable with restriction	Limited/ Limited	

Overall evaluation and conclusions based on weight of evidence

The Panel noted that the negative results reported by Chung and Lee (2013) in the Ames test and in the *in vitro* chromosomal aberration and micronucleus tests add to and confirm the results of previous studies evaluated by the SCF. The paper by Chung and Lee (2013) also reported negative results in the mouse bone marrow micronucleus test. However, due to the lack of demonstration of bone marrow exposure, this result is considered inconclusive.

Concerning the positive results in the *in vitro* comet assay, the Panel noted that the comet assay is an indicator test and considered the positive results in this test to be overruled by the negative findings obtained in the same concentration range in robust mutagenicity assays (Ames test, *in vitro* chromosomal aberrations and micronucleus). The Panel also noted that the statistical analysis of the comet assay results did not consider the hierarchical nature of data, with culture as experimental unit and slide as measurement unit and that the analysis at the cell level performed can lead to misinterpretations of results (Lovell et al., 1999). The Panel also noted that the concentrations the *in vitro* comet assay exceeded the maximum recommended in OECD document 'Overview of the set of OECD Genetic Toxicology TGs and updates performed in 2014-2015' (OECD, 2017) for *in vitro* assays in mammalian cells.

Overall, the Panel concluded that the new studies retrieved did not alter the previous conclusion (SCF, 2003) that erythritol is not genotoxic.

3.5.3 | Toxicity studies in animals

Since the last assessment (SCF, 2003), no newly generated toxicity data in animals were submitted by the interested parties through the calls for data nor by the applicant.

The extensive literature search, covering the period subsequent to the last SCF evaluation (SCF, 2003), allowing 1-year overlap, did not identify any new reliable repeated-dose toxicity study in animals that could be used to derive a health-based guidance value (HBGV). Nevertheless, several studies on animal disease models were retrieved in the literature. The Panel considered that these were of limited relevance to the risk assessment of erythritol. However, they have been described for completeness in Appendix G.

As previously reviewed (SCF, 2003), several studies have been conducted in rats, mice and dogs, including studies on acute, short-term, sub-chronic and chronic toxicity and carcinogenicity as well as developmental and reproductive toxicity. The most frequently occurring effects in rats and dogs, seen at high doses (i.e. ≥ 5% in the diet, ≥ 2500 mg/kg bw per day by gavage), were loose stool and/or diarrhoea, lower body weight gain, increase in water consumption and in urine volume. Some changes in urinalysis parameters were also observed, including increase in urinary excretion of electrolytes (sodium, potassium, calcium) and urinary enzymes, increase in serum alkaline phosphatase (AP) and in blood urea nitrogen (BUN) levels. Regarding the organ weights, increased absolute or relative caecum weight and increased absolute or relative kidney weight were observed. The kidney weight changes were accompanied by histopathological changes (i.e. dilatation of renal tubules, calcium deposits in kidneys/pelvic nephrocalcinosis). Minor isolated changes in haematological parameters or in blood chemistry were observed, however those were not consistent across sex and study design and there was no dose–response relationship (Documentation provided to EFSA No. 1, 6).

These effects are consistent with responses to increased osmolarity in gastrointestinal tract and of the blood. The laxative effect observed in oral toxicity studies in rodents at high doses is caused by increased osmolarity in the large intestine due to unabsorbed erythritol when high doses are applied. Decreased body weight gain was considered as an effect of loose stool/diarrhoea observed in the animals. The changes in kidney weight, observed in many studies, in rodents and dog, were attributed to the increased urine output recorded in these studies. Although this effect could be considered reversible and physiologically explained (WHO, 1987) due to osmotic diuresis, the loss of electrolytes by the increased diuresis is toxicologically relevant and is considered as adverse. Pelvic nephrocalcinosis was observed in a 2-year toxicity study in rat. This effect was likely associated with the measured increase in calcium excretion. Nephrocalcinosis was reported in other studies in rats administered with poorly absorbed or poorly metabolised carbohydrates (Bär, 1985).

No effects on developmental and reproductive endpoints were observed in the studies performed in rodents (Documentation provided to EFSA No. 6).

The Panel considered the data evaluated by the SCF in 2003 and agreed with their assessment of the studies. However, the Panel also considered that laxative effects – unless clinically recommended – should be considered adverse if sustained for more than a limited period of time and that continuous osmotic diuresis might lead to urinary loss of electrolytes with possible adverse effects. Whilst the available animal data were not considered for the derivation of a HBGV for erythritol with respect to a laxative effect, this effect, with diarrhoea as critical endpoint, was still considered by the Panel to be of significance for the identification of a reference point (RP) based on the available human data (see Section 3.6).

3.5.4 | Studies in humans

3.5.4.1 | *Studies included in the assessment*

A total of 22 eligible human studies were evaluated for the RoB. Detailed results of the RoB evaluation is reported in Tables A1 and A2 of Appendix A.

All human studies ($n = 12$) previously evaluated by the SCF in 2003 and by the EFSA ANS Panel in 2010 and 2015, that constitute the body of evidence on which the conclusions for no numerical ADI were based, were assessed by the FAF Panel (Documentation provided to EFSA No. 6, 12; Storey et al., 2007). These studies were considered regardless of the outcome of the RoB evaluation due to the fact that few new studies were available.

For studies retrieved in the literature, only those evaluated as having low to moderate risk of bias (tier 1 or tier 2) were considered further in the assessment ($n = 7$) (Kim et al., 2011; Meyer-Gerspach et al., 2021; Overduin et al., 2016; Teysseire et al., 2022, 2023; Wölnerhanssen et al., 2016, 2021).

Human data provided in the context of the new application for exemption of erythritol (E 968) from the current laxative warning requirement were also considered. However, the Panel noted that no new evidence was submitted by the applicant and that the human studies provided were already part of the current evaluated dataset for the reason explained above. Of note, one study out of the 12 previously evaluated (Biofortis, 2010 in Documentation provided to EFSA No. 6, 12) was submitted by the IBO as an unpublished study report. That report included one additional dose group (20 g), which was not included in the previous assessment (EFSA ANS Panel, 2010), and therefore considered in the current opinion.

A summary of all studies assessed and considered in the WoE ($n = 19$), including their RoB evaluation, is reported in Tables 10 and 11. All studies considered were human controlled trials (HCTs). Data extraction forms of these studies are also available in Appendix E.

3.5.4.2 | *Synthesis of systematically appraised evidence*

3.5.4.2.1 | *Weighing the body of evidence*

Annex C reports all the human studies evaluated, clustered by endpoint within the different health outcome categories (HOCs), for which a WoE analysis was performed.

The endpoints considered and evaluated in the WoE for the available human dataset are shown in Table 9.

TABLE 9 Health outcome categories (HOCs) and related endpoints.

Health outcome categories (HOCs)	Endpoints
Glucose homeostasis	Blood glucose levels, blood insulin levels, blood glucagon levels, haemoglobin A1c (HbA1c)
Gastrointestinal (GI) effects	Diarrhoea

GI endpoints other than diarrhoea were also investigated in several studies (e.g. abdominal pain, nausea, bloating, vomiting, flatulence, satiety, hunger, gut hormones levels). Those endpoints were not evaluated systematically using WoE approach as they were not considered relevant for the derivation of a possible HBGV. However, results reported in individual studies on these endpoints were considered when NOAELs for diarrhoea were extracted from the different studies.

Glucose homeostasis

Ten studies (cumulative sample size, 141; median sample size, 15) were identified assessing the effect of erythritol on glucose homeostasis (see Table 10). Only one study addressed glucose metabolism after exposure for 14 days and none of the studies addressed effects on glucose homeostasis after chronic intake. Three studies were randomised controlled trials and the remaining four were pre–post intervention studies, all measuring short-term changes in glucose homeostasis over few hours or few days. Four studies were conducted in Europe (France, $n = 2$; UK, $n = 1$; Switzerland, $n = 4$) while three studies were conducted in Japan. In two studies, the study populations consisted of T2 diabetic patients. Six studies assessed the effect on glucose metabolism up to 4 h after the ingestion of erythritol and the endpoints assessed were the postprandial glucose excursion ($n = 6$), insulin ($n = 6$), glucagon-like peptide 1 (GLP-1)/ peptide YY (PYY) ($n = 1$). Five studies implemented a single dose erythritol study arm using either fixed doses (50 g, 75 g, 8% wt/wt) or a dose adjusted to body weight (0.3 g/kg bw, 1 g/kg bw). One study assessed the erythritol effect implementing two erythritol study arms (0.4 g/kg bw, 0.8 g/bw kg). Finally, one study assessed the effect on glucose metabolism (fasting plasma glucose, haemoglobin A1c (HbA1c)) over 14 days of daily 20 g erythritol consumption.

TABLE 10 Summary of human studies considered under the glucose homeostasis HOC.

Authors (year) (RefID[a])	Type of HCT	Dose (g/person or g/kg bw)[b]	Administration	Number of subjects	Population (mean age in years)	RoB tier
Teysseire et al. (2023) (5111)	Cross-over trial	50 g	Single dose by a nasogastric tube	18 (5 M and 13 F)	Adults (24)	1
Meyer-Gerspach et al. (2021) (3859)	Cross-over trial	75 g	Single dose by a nasogastric tube	20 (10 M and 10 F)	Adults (27.7)	1
Wölnerhanssen et al. (2021) (3850)	Cross-over trial	10 g, 25 g, 50 g	Single dose, by a nasogastric tube	12 (7 M and 5 F)	Adults (21.7)	2

TABLE 10 (Continued)

Authors (year) (RefID[a])	Type of HCT	Dose (g/person or g/kg bw)[b]	Administration	Number of subjects	Population (mean age in years)	RoB tier
Wölnerhanssen et al. (2016) (3759)	Cross-over trial	75 g	Single dose, by a nasogastric tube	20 (10 M and 10 F)	Adults (25)	1
Overduin et al. (2016) (3756)	Cross-over trial	8 g	Single dose	20 (10 M and 10 F)	Adults (36)	1
Yokohama-shi Seibu Hospital (1993)[c] (Documentation provided to EFSA No. 6) (4299)	Single-arm intervention	20 g	Continuous, 14 days	11 (3 M and 8 F)	Adults (54)	3
Noda et al. (1994) (3808)	Single-arm intervention	0.3 g/kg bw	Single dose	5 (M)	Adults (51.5)	3
Bornet et al. (1996a) (3810)	Single-arm intervention	64 g[d]	Single dose	6 (3 M and 3 F)	Adults (32.6)	3
Bornet et al. (1996b) (3793)	3-arm intervention plus control	0.4 g/kg, 0.8 g/kg bw	Single dose	24 (12 M and 12 F)	Adults (33)	2
Yokohama-shi Seibu Hospital (1992)[e] (Documentation provided to EFSA No. 6) (4297)	Single-arm intervention	20 g	Single dose	5	Adults (52.4)	3

Abbreviations: HCT, human controlled trial; RoB, risk of bias.

[a]Numerical identifier generated by the DistillerSR tool.

[b]As reported by the study authors.

[c]This unpublished study report is referred as Miyashita M, Kawashina Y and Nakamura T, 1993 in SCF, 2003.

[d]64 g is the mean value reported in the study. A range of 56–78 g was also reported.

[e]This unpublished study report is referred as Ishikawa M, Hirose C, Tsujino D, Miyashita M, Kawashima Y and Nakamura T, 1992 in SCF, 2003.

Teysseire et al. (2023) conducted a randomised, cross-over, double-blind trial including 21 individuals (14% attrition) in Switzerland and assessed the effect of erythritol on glucose, insulin, ghrelin, blood lipids, uric acid and high-sensitive C-reactive protein (hsCRP). Participants received an intragastric administration of 25 g D-allulose or 50 g erythritol dissolved in 300 mL tap water or 300 mL tap water (placebo). An exploratory analysis showed that ghrelin concentrations were reduced after erythritol compared to tap water. No other statistically significant associations were observed for erythritol compared to tap water.

Meyer-Gerspach et al. (2021) assessed the effect of erythritol and xylitol on gut hormone release, in a randomised cross-over trial of 20 healthy subjects (10 males/10 females) in Switzerland. Erythritol (75 g), xylitol (50 g), glucose (75 g) dissolved in 300 mL tap water or 300 mL tap water (placebo) were administrated via intragastric tube. No significant differences in plasma insulin and glucose were observed between erythritol and tap water up to 1 h after ingestion. Increase in cholecystokinin (CCK) and PYY were observed for erythritol versus tap water.

Wölnerhanssen et al. (2021) conducted a randomised cross-over trial on 12 healthy subjects in Switzerland to examine the effect of erythritol on gastric emptying and on the release of CCK, active glucagon-like peptide-1 (aGLP-1) and PYY. Erythritol (10, 25 or 50 g) and 50 mg of ^{13}C-sodium acetate dissolved in 300 mL tap water or 300 mL tap water plus 50 mg of ^{13}C-sodium acetate (placebo) were administrated via nasogastric tube, and changes in these biomarkers were monitored for 240 min after administration. No effect was observed on plasma insulin, glucose-dependent insulinotropic polypeptide (GIP), motilin, insulin and glucagon. A statistically significant decrease of plasma glucose after 50 g erythritol compared to placebo was observed. Slowing of gastric emptying and a statistically significant increase in CCK, aGLP-1 and PYY secretion was also seen.

Wölnerhanssen et al. (2016) included 10 lean and 10 obese volunteers receiving 75 g of glucose, 50 g of xylitol or 75 g of erythritol in 300 mL of water or placebo (water) by a nasogastric tube. No effect on glucose or insulin were observed relative to water up to 3 h after ingestion.

In a randomised cross-over controlled clinical trial ($n = 20$, 50% obese, UK), Overduin et al. (2016) assessed the effect of 8% wt/wt erythritol plus 2% wt/wt sucrose compared to 10% wt/wt of sucrose on glucose metabolism up to 4 h after ingestion of a single meal. To adjust for sweetness, 0.4% wt/wt sucralose was added in the erythritol meal (13–16 mg sucralose per meal). There was a greater postprandial excursion in glucose and insulin levels after sucrose than after the erythritol meals; conversely, no statistically significant difference was observed for GLP-1/PYY levels.

In a before-after study ($n = 11$, T2 diabetic patients) in Japan assessed the effects of 20 g erythritol daily in food and drinks over 14 days on glucose metabolism were assessed (Yokohama-shi Seibu Hospital, 1993 in Documentation provided to EFSA No. 6). No significant changes were observed from baseline to endpoint for fasting blood glucose while a statistically significant decrease was observed for HbA1c.

Noda et al. (1994) in a pre-post single-arm cross-over study ($n = 5$) in Japan assessed the effect of oral 0.3 g/kg bw erythritol (average dose 17.3 g per subject) on glucose homeostasis compared to glucose. Peak blood glucose as well as blood insulin levels were statistically significantly lower shortly after erythritol ingestion than after glucose ingestion.

Bornet et al. (1996b) in a before-after (pre-post) study ($n = 6$) in France assessed the effect of oral 1 g/kg bw erythritol on the glucose metabolism. The authors reported that neither the plasma glucose nor the plasma insulin levels were affected up to 3 h after ingestion of erythritol.

Bornet et al. (1996a) assessed the effect of erythritol on glucose metabolism using a randomised controlled trial design ($n = 24$; 50% male; 20–46 years old; study arms, 0.4 g/kg bw snack (E4 group), 0.8 g erythritol/kg bw snack (E8 group), 0.8 g sucrose/kg bw snack, no snack; France). The authors reported no differences in the mean plasma glucose and insulin levels in the erythritol and negative control groups, measured for up to 3 h after ingestion.

In another before-after study ($n = 5$, treatment-naïve T2 diabetic patients) in Japan the effect of 20 g oral erythritol was assessed (Yokohama-shi Seibu Hospital, 1992 in Documentation provided to EFSA No. 6). The authors reported no statistically significant differences in plasma glucose or plasma insulin levels up to 3 h after ingestion of erythritol.

GI effects

For this HOC, 14 intervention studies conducted in adult volunteers (20–65 years) and one study in children (5–6 years) were available for the risk assessment (see Table 11). Many of the studies were designed to examine effects on post-prandial glucose response. These studies were generally of small sample size ($n < 20$), providing limited statistical power to assess effects on GI tract. Concerning the RoB, three out of the 15 studies were considered as having a high risk of bias (tier 3) and, although they were included in the WoE analysis, they were given less weight when assessing the overall body of evidence. The basic characteristics of these 15 interventional studies are summarised in Table 11.

TABLE 11 Summary of human studies considered under the GI effects HOC.

Authors (year) (RefID[a])	Type of HCT	Dose (g/person or g/kg bw)[b]	Administration	Number of subjects	Population (mean age in years)	RoB tier
Teysseire et al. (2022) (4355)	Cross-over trial	50 g	Single dose, by a nasogastric tube	18 (5 M and 13 F)	Adults (24)	2
Meyer-Gerspach et al. (2021) (3859)	Cross-over trial	75 g	Single dose, by a nasogastric tube	20 (10 M and 10 F)	Adults (27.7)	1
Wölnerhanssen et al. (2021) (3850)	Cross-over trial	10 g, 25 g, 50 g	Single dose, by a nasogastric tube	12 (7 M and 5 F)	Adults (21.7)	2
Wölnerhanssen et al. (2016) (3759)	Cross-over trial	75 g	Single dose, by a nasogastric tube	20 (10 M and 10 F)	Adults (25)	1
Kim et al. (2011) (1242)	Cross-over trial	33.3 g	Single dose	37 (13 M and 24 F)	Adults (23)	1
Biofortis (2010)[c] (Documentation provided to EFSA No. 6, 12) (4298)	Cross-over trial	5 g, 15 g, 20 g, 25 g	Single dose	172 (95 M and 77 F)	Children (5)	2
Storey et al. (2007) (759)	Cross-over trial	20 g, 35 g, 50 g	Single dose	70 (34 M and 36 F)	Adults	1
Tetzloff et al. (1996) (3789)	Cross-over trial	0.3, 0.6, 1 g/kg bw[d]	Continuous, 5 times a day, 7 days	12 (M)	Adults (34)	2
Bornet et al. (1996a) (3810)	Single-arm intervention	64 g[e]	Single dose	6 (3 M and 3 F)	Adults (32.6)	3
Bornet et al. (1996b) (3793)	3-arm intervention plus control	0.4, 0.8 g/kg bw	Single dose	24 (12 M and 12 F)	Adults (33)	2
Oku & Okazaki (1996) (3788)	Dose escalation	25 g, 37.5 g, 50 g, 62.5 g, 75 g	Single dose	38 (14 M and 24 F)	Adults (33)	2
Yokohama-shi Seibu Hospital (1993)[f] (Documentation provided to EFSA No. 6) (4299)	Single-arm intervention	20 g	Continuous, 14 days	11 (3 M and 8 F)	Adults (54)	3
Nikken Chemicals Co. Ltd. (1992a)[g] (Documentation provided to EFSA No. 6) (4301)	Dose escalation	30 g, 40 g, 50 g	Single dose	12 (8 M and 4 F)	Adults (32)	2
Mitsubishi Kasei Corporation (1992)[h] (Documentation provided to EFSA No. 6) (4302)	Dose escalation	30 g, 40 g, 50 g, 60 g	Single dose	6 (M)	Adults (35.5)	2

Authors (year) (RefID[a])	Type of HCT	Dose (g/person or g/kg bw)[b]	Administration	Number of subjects	Population (mean age in years)	RoB tier
Nikken Chemicals Co. Ltd. (1992b)[i] (Documentation provided to EFSA No. 6) (4300)	Single-arm intervention	20 g (40 g/day)	Single dose, twice a day, 5 days	10 (8 M and 2 F)	Adults (50.7)	3

Abbreviations: HCT, human controlled trial; RoB, risk of bias.

[a]Numerical identifier generated by the DistillerSR tool.

[b]As reported by the study authors.

[c]This unpublished study report was subsequently published in Jacqz-Aigrain et al. (2015).

[d]0.3 g/kg bw on the first day, 0.6 g/kg bw per day on the second day, 1 g/kg bw for the remaining 5 days.

[e]64 g is the mean value reported in the study. A range of 56 to 78 g was also reported.

[f]This unpublished study report is referred as Miyashita M, Kawashina Y and Nakamura T, 1993 in SCF, 2003.

[g]This unpublished study report is referred as Takahashi C, 1992a in SCF, 2003.

[h]This unpublished study report is referred as Umeki, 1992 in SCF, 2003.

[i]This unpublished study report is referred as Takahashi C, 1992b in SCF, 2003.

Teysseire et al. (2022) conducted a randomised double-blind cross-over trial aimed at examining the effect of D-allulose and erythritol on gastric emptying, appetite-related sensations and GI symptoms in 18 healthy subjects. The participants were randomly assigned to intragastric solutions 25 g D-allulose, 50 g erythritol or tap water, with or without 450 parts per million (ppm) lactisole. Participants were also asked to rate their GI symptoms with 30 min intervals over 4 h after ingestion. Diarrhoea was reported in 28% of the subjects (5 out 18) in the erythritol group alone and 17% (3 out of 18) in the group of the erythritol plus lactisole. No episodes of diarrhoea were observed in the tap water group. Other GI symptoms such as nausea, vomiting, borborygmus, abdominal bloating, eructation and flatulence were also observed in the erythritol groups.

In a randomised cross-over trial, aimed at examining the effect of erythritol and xylitol on gut hormone release, 20 healthy subjects received intragastrical erythritol (75 g), xylitol (50 g), glucose (75 g) dissolved in 300 mL tap water or 300 mL tap water (placebo). Erythritol lead to diarrhoea and bloating in 15% of subjects (3 out of 20) with no cases of diarrhoea being observed in the glucose and placebo (water) group (Meyer-Gerspach et al., 2021).

In a dose escalation trial, Wölnerhanssen et al. (2021) conducted a randomised cross-over trial on 12 healthy subjects to examine the effect of erythritol on gastric emptying and gut hormone secretion. The subjects received 10, 25 or 50 g erythritol or tap water enriched with ^{13}C-sodium acetate on four study days via a nasogastric tube. Bowel sounds were observed in all erythritol groups and bloating was observed at or above 25 g erythritol. Only one subject out of 12 (8.3%) reported diarrhoea in the 10 g erythritol group.

Wölnerhanssen et al. (2016) examined, in a randomised double-blind cross-over design, the possible effect of erythritol on incretin release and gastric emptying in 10 normal weight subjects randomly assigned to either a single dose solution of 75 g erythritol or water via intragastric tube. Glucose was used as positive control. After treatment with erythritol 60% of participants reported having experienced bloating and diarrhoea. No such episodes were observed in the placebo (water) group.

In a randomised, double-masked, controlled crossover study of 37 healthy volunteers of normal weight, Kim et al. (2011) examined the effect of 33.3 g of erythritol in 50 g glucose solution relative to a 50 g fructose solution alone. After ingestion, GI intolerance symptoms were recorded for all participants over 24 h post-prandially. Frequency of watery stools and signs of GI intolerance, including cramping and flatulence, were increased relatively to fructose alone.

In a dose escalation cross-over trial, a total of 172 children aged 4 to 6 years old were randomised over the study period to receive either 5, 15, 20 and 25 g solution (250 mL) of erythritol (Biofortis, 2010 in Documentation provided No. 6, 12). A 250 mL non-carbonated fruit drink, containing sucrose and maltodextrine, was used as placebo. According to the protocol the first dose tested was 5 g and children were randomised to receive first either dose or placebo. If no adverse effect occurred in the 10 g dose group the experiment would then proceed to the 15 g and then the 25 g dose group (different children in each dose group). During the study the authors made two amendments to their protocol. First, they increased the sample size from 14 children used in the 5 g dose group to 56–58 children in all higher dose groups. Then after completing the experiment (the 5, 15 and 25 g dose groups) another 20 g dose group was added. For all dose groups, treatment with erythritol or placebo occurred with at least a 5-day wash out period and GI tolerability (diarrhoea and other symptoms) were recorded until 48 h after administering the dose or placebo. The number of adverse events, defined as clinically relevant diarrhoea/GI symptoms, was significantly ($p < 0.0001$) increased in the 25 g dose group relative to placebo, while a similar but not formally significant increase ($p = 0.05$) was observed in the 20 g dose group. Stool consistency, reflecting more soft/watery stools, were significantly different from placebo treatment in both the 20 and 25 g dose groups. The authors concluded that *'the maximum tolerated dose of erythritol in children, in a single drinking occasion, is 15 g'*. Although well conducted, it is worth noting that sample size in the 5 g dose group was too small to allow for any robust conclusion on either presence or absence of an effect at that dose. Secondly the 5-day wash out period between dose and placebo is quite short which could have led to some spill over, inflating the number of adverse events during placebo testing.

In a double-blind cross-over study of 70 students aged 18–24 years, Storey et al. (2007) examined the tolerance of a single bolus dose of 20, 35 or 50 g of erythritol relative to placebo (45 g of sucrose). Subjects received each treatment in random order with wash out period of 7 days. The prevalence of watery faces was 14%, 8%, 17% and 29%, for the placebo, 20 g, 35 g and 50 g erythritol, respectively. Relative to placebo, the slightly higher prevalence in this 50 g erythritol treatment

was not significant for watery faeces. Significantly higher prevalence of nausea (10% vs. 31%) and borborygmi (23% vs. 38%) was observed at 50 g erythritol relative to placebo.

In a double-blind randomised cross over study in healthy males ($n = 12$), Tetzloff et al. (1996) examined the tolerability of 7-day erythritol treatment relative to 7-day sucrose treatment. Participants received a dose of 0.3 g/kg on the first day, 0.6 g/kg on the 2nd day after which the dose was 1.0 g/kg, divided into five portions, was consumed on the remaining 5 days. The study duration was 14 days meaning that there was no wash out period between treatments. No effect on GI tolerance was observed although some participants reported their faeces being '*softer than usual*" (14/60 vs. 8/60 observations) and their quantity being '*less than usual*" (13/60 vs. 5/60 observations) after erythritol relative to sucrose treatment.

Bornet et al. (1996b) randomised 24 adults to receive a single dose of either 0.4 or 0.8 g/kg bw erythritol, 0.8 g/kg bw sucrose in the form of snack or no treatment. GI symptoms such as nausea and flatulence were more frequently reported in both erythritol groups (more at the higher dose). Lack for formal significance compared to sucrose or control group needs to be interpreted in relation to the small number of subjects in each dose group ($n = 6$).

In a dose escalation trial conducted in 14 adults, Oku and Okazaki (1996) examined the GI tolerability of erythritol. Half of the participants were assigned to a dose escalation of 25, 50 and 75 g erythritol while the other half was assigned to 25, 37.5 and 62.5 g erythritol. Erythritol was ingested in cups of jelly from with lowest to highest dose with 1-day intervals with the highest dose and treatment was stopped on individual level if diarrhoea occurred. Each dose was tested with 1-day interval. Expressed in g/kg bw, as reported by the authors, the occurrence of diarrhoea showed clear dose-dependency with around 50% of female and male participants experiencing diarrhoea at doses of about 1.1 and 1.6 g/kg bw, respectively. The authors concluded that the laxative threshold for erythritol would be around 0.8 and 0.7 g/kg bw for females and males, respectively.

In a dose escalation study 12 healthy volunteers were treated in a non-random order with a single dose of 10 g sugar (control) then 30 g, 40 g or 50 g erythritol and 10 g sorbitol (in that order) dissolved in either coffee, tea or warm water (Nikken Chemicals Co. Ltd., 1992a in Documentation provided to EFSA No. 6). If 30 g of erythritol caused no diarrhoea symptoms, the dose was increased after 1–2 days to 40 and 50 g. If diarrhoeal symptoms occurred, the next substance was first ingested 3 days later. The median effective dose of erythritol (50% if subjects experiencing diarrhoea) was estimated to be 0.83 and at 1.30 g/kg bw for males and females, respectively. The corresponding NOAELs were 0.55 and 0.76 g/kg bw.

In a similarly designed but smaller ($n = 6$) dose escalation study, adult males were assigned in a non-random manner to a single dose of 60 g sucrose (negative control) and then 30, 40, 50 or 60 g of erythritol and finally 10 g sorbitol (in this order) (Mitsubishi Kasei Corporation, 1992 in Documentation provided to EFSA No. 6). The time between adjacent doses was 1–2 days or longer (3–4 days) if diarrhoea occurred. Two males experienced diarrhoetic symptoms for the 40 g dose, another two at the 50 g dose and the remaining two subjects had diarrhoetic symptoms at the highest dose (60 g).

Finally, three small ($n = 6$–11) studies ($n = 6$-11) assessed to be of high RoB (tier 3) evaluated the GI tolerance. One study gave single bolus dose (1 g/kg bw) of erythritol to six adults after which two subjects reported diarrhoea while the others reported cramping, discomfort and flatulence (Bornet et al., 1996a). In another study assigning 11 diabetic subjects to 14-day of treatment with 20 g erythritol the authors reported that '*No cases of diarrhoea and no specific subjective symptoms*' were observed (Yokohama-shi Seibu Hospital, 1993 in Documentation provided to EFSA No. 6). Finally, no GI effects were reported among 10 subjects (8M/2F) consuming 20 g erythritol twice a day over 5 days (Nikken Chemicals Co. Ltd., 1992b in Documentation provided to EFSA No. 6).

3.5.4.2.2 | *Evaluation of the confidence and level of evidence*

The body of evidence of human data assessed for quality is described in Table 12. The overall conclusion on the WoE, expressed as 'final confidence rating', was based on the outcome of the RoB (see Appendix A, Tables A1, A2), followed by upgrading and downgrading the confidence in each study, considering other study attributes (see Annex C). Then, the final confidence rating was reached by considering these elements across all studies within each HOC. The final confidence in the body of evidence was then translated into a level of evidence, as outlined in the revised protocol and in Section 2.2.

For the HOC 'glucose homeostasis', no adverse effects were identified in the included human studies. For those studies, the Panel considered the confidence in the body of evidence to be *'low'* (see Table 12). The reason for this conclusion was that most studies available for the assessment were of too short duration with few participants and a '*very serious*' concern on imprecision was identified. On the other hand, the consistent observation across all studies of no adverse effects on glucose homeostasis was considered enough to trigger an upgrade of the confidence in the body of evidence. The level of evidence for no adverse effects on health for the glucose homeostasis HOC was rated as '*inadequate*'.

The Panel considered the confidence in the body of evidence to be *'high'* for the association between oral intake of erythritol and the presence of laxative effects in humans. Therefore, the Panel considered that there is a high level of evidence that exposure to erythritol is associated with laxative effects, selecting diarrhoea as critical endpoint.

TABLE 12 Summary table of the final ratings of confidence in the body of evidence (n = 19 studies) for each HOC based on the WoE analysis.

		Elements for downgrading					Elements for upgrading				
Health outcome categories (HOCs)[a]	Initial rating (No. of studies)[a]	Concern for risk of bias	Concern for unexplained inconsistency	Concern related to relevance of studies	Concern for imprecision	Downgrading	Magnitude of effect	Dose–response	Consistency across study population/study design	Upgrading	Final rating of confidence
Glucose homeostasis	High (10)	Serious	Not serious	Serious	Very serious	Risk of bias, Relevance of studies, Imprecision	Not large (no effect)	No	Yes	Consistency	Low
GI effects	High (15)	Serious	Not serious	Not serious	Not serious	Risk of bias	Large	Yes	Yes	Magnitude of effect, Dose–response, Consistency	High

Abbreviation: N.A., not applicable.

[a]As defined in Table 9 (on HOC and related endpoints).

[b]The total number of studies assessed was 19. The number in parentheses refers to studies considered under the specific HOC.

3.5.4.2.3 | *Integration of evidence*

In the case of erythritol, for the reasons explained above, the integration of evidence consisted of the evaluation of human data that formed the basis for the possible derivation of HBGVs.

Regarding the glucose homeostasis related endpoints, the level of evidence was rated as '*inadequate*'. However, based on biological considerations, overall the Panel considered that the studies reviewed provided consistent evidence for no effect of erythritol on short-term postprandial glucose homeostasis. Studies addressing long-term effects were not identified.

Based on the WoE analysis, it is very likely that erythritol (E 968) has the potential to cause diarrhoea in human, which was considered an adverse health effect because its potential association with electrolyte and water imbalance. Subjective GI symptoms (abdominal pain, nausea, bloating, flatulence) have been also noted.

3.6 | Hazard characterisation and identification of a reference point

The Panel considered the human studies reporting on laxative effects, with diarrhoea as the critical endpoint, as the most appropriate data source for the hazard characterisation.

To identify a reference point for laxative effects, selecting diarrhoea as the critical endpoint, modelling of the human data was not considered appropriate given the limited number of doses and dose ranges tested (see Table 11). Therefore, the Panel decided to derive a reference point based on the observed NOAELs for diarrhoea reported in the studies. Only studies with at least two dose groups were considered suitable for the identification of a reference point. The NOAELs from these studies are shown in Figure 2. Based on a WoE approach, the Panel considered that erythritol has a laxative effect, even though in some studies the dose at which diarrhoea occurred was not clear. If a study did not show clearly diarrhoea at the highest dose tested, the latter was included in the analysis as a NOAEL.

The Panel agreed to use as reference point the lower bound of the range of the NOAELs reported in these studies i.e. 0.5 g/kg bw (500 mg/kg bw). This conservative approach was considered appropriate to account for small sample sizes and limited dose ranges in the available studies.

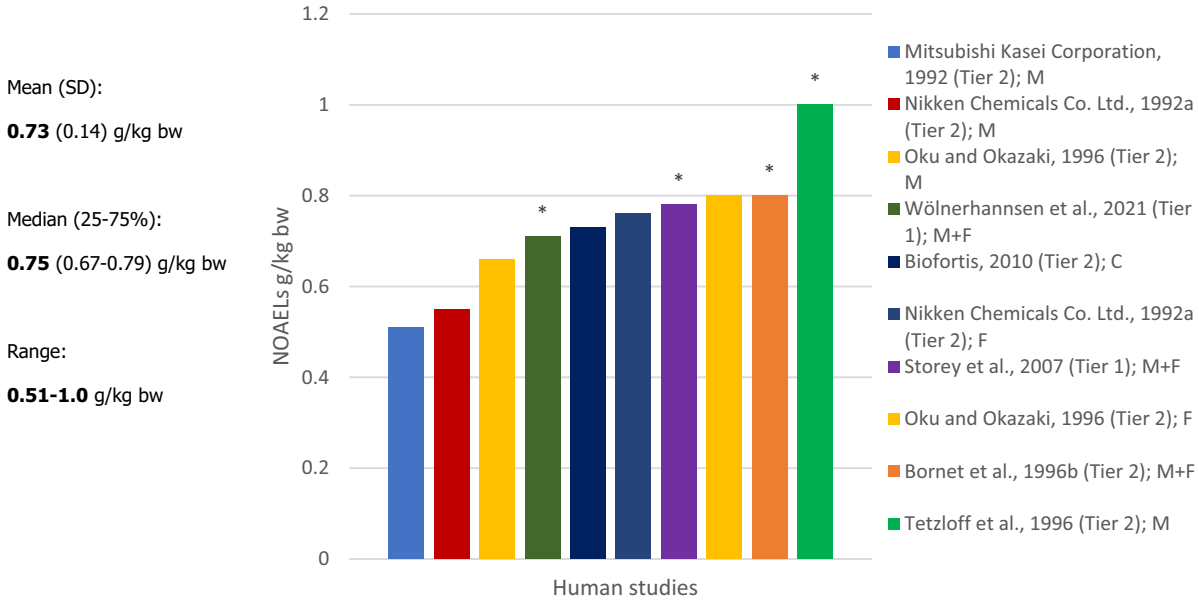


FIGURE 2 NOAELs for diarrhoea in human studies. M, males; F, females; C, Children. *Highest dose tested.

3.7 | Environmental considerations

A systematic review collating published data on polyols sweeteners, including erythritol (E 968), was performed to identify evidence of potential adverse effect on the environment (Agriculture and Environment Research Unit, University of Hertfordshire, 2021). In this review very limited information relating to the environmental impact of the polyols (including erythritol) has been identified. The review reports that, since polyols occur widely in nature, any environmental release would be expected to be *'short lived'*. The review also concluded that these substances do not appear to be toxic to the aquatic environment.

The conclusions from the above-described systematic review were confirmed in a follow-up update of the literature search, in which an additional publication dealing with the assessment of the biodegradability of several food additives, including erythritol, was retrieved; in this paper erythritol was reported to be readily biodegradable (Gatidou et al., 2020). This is also consistent with the results from a ready biodegradability study (OECD TG 301 D) (OECD, 1992) reported in the REACH registration dossier for erythritol.

In the literature, additional papers and reviews investigating the potential use of erythritol as an alternative to conventional insecticides were retrieved (Baker et al., 2023; Barrett et al., 2020; Baudier et al., 2014; Burgess & Geden, 2019; Burgess & King, 2017; Burgess et al., 2021; Caponera et al., 2020; Cha et al., 2023; Choi et al., 2019; Choi et al., 2017; Diaz-Fleischer et al., 2019; Fisher et al., 2017; Gilkey et al., 2018; Gullickson et al., 2019; Lee et al., 2021, 2023; Maestas et al., 2023; O'Donnell et al., 2018; O'Donnell et al., 2016; Pullmann-Lindsley et al., 2023; Sampson et al., 2017a; Sampson et al., 2017b; Schmidt-Jeffris et al., 2021; Sharma et al., 2020; Tang et al., 2017; Wentz et al., 2020; Zhang et al., 2017; Zheng et al., 2016). These papers focused on terrestrial insects. The hypothesised mechanisms behind the insecticidal properties e.g. osmotic imbalance, dehydration, starvation in insects feeding on erythritol (e.g. sucking insects) seems to be more relevant for the terrestrial environmental compartment/species rather than for the aquatic one, which is the main receiving environmental compartment in the case of erythritol.

A concern for the environment from the use of erythritol (E 968) as a food additive is not anticipated.

4 | DISCUSSION

The present opinion deals with the re-evaluation of erythritol (E 968) when used as a food additive and with an assessment of the laxative effects of foods containing more than 10% of added erythritol (E 968).

Erythritol (E 968) is authorised as a food additive in the European Union (EU) in accordance with Annex II, Part E, to Regulation (EC) No 1333/2008 at MPLs equal to QS as a group I additive (for purposes other than sweetening).

In addition, erythritol (E 968) belongs to the functional class of sweeteners and, being a 4-carbon sugar alcohol, is included in the group of polyols (group IV) specified in Regulation (EC) No 1333/2008.

Erythritol was previously assessed by the SCF in 2003. In its opinion, after the evaluation of several human and animal data, the SCF considered it inappropriate to establish a numerical ADI for erythritol, in accordance with previous opinions issued on other polyols (SCF, 1985). The SCF also considered that erythritol had a laxative effect, but at higher doses than other polyols, and identified a NOAEL for this effect in humans of 0.5 g/kg bw for a single dose. The use of erythritol as a food additive was considered acceptable, however the SCF expressed concerns that the laxative threshold may be

exceeded, especially by young consumers through ingestion of erythritol in beverages. In 2010, the EFSA ANS Panel issued an opinion following a request for the authorisation of use of erythritol for purposes other than sweetening at a maximum level of 2.5% in beverages (EFSA ANS Panel, 2010). New data were available in that application, i.e. a new paediatric study on the GI tolerability of erythritol. The Panel concluded that the MOS between the NOAEL set for laxation in children aged 4–7 years (0.71 g/kg bw) was too low to adequately protect this population and therefore, a safety concern was identified for the proposed extension of use of erythritol in beverages. Later, EFSA received two additional requests for extension of use (EFSA ANS Panel, 2013, 2015). For one, EFSA concluded that the acute bolus intake of erythritol via the consumption of non-alcoholic beverages at a maximum level of 1.6% would not raise concerns for laxation.

As specified in the Commission Regulation (EU) No 231/2012, erythritol (E 968) is defined as being '*obtained by fermentation of carbohydrate source by safe and suitable food grade osmophilic yeasts such as Moliniella pollinis* or *Moliniella megachiliensis*, *followed by purification and drying*'.

Information on the manufacturing process of erythritol (E 968) obtained by fermentation of carbohydrate source with non-genetically modified *M. pollinis* strain BC or *M. megachiliensis* strain KW3-6 was submitted and evaluated. Based on the detailed information on the characterisation of these microorganisms and the demonstration of the absence of viable cells in erythritol, the Panel considered that the manufacturing process of E 968 using these microorganisms does not raise a safety concern. However, in order to better describe the manufacturing processes evaluated in the current assessment for which no concern was identified, the Panel recommended modifying the definition of the food additive in the Commission Regulation (EU) 231/2012 to specify that the food additive erythritol (E 968) is obtained by fermentation of a carbohydrate source by non-genetically modified *M. pollinis* strain BC or *M. megachiliensis* strain KW3-6, followed by several purification steps and drying.

The Panel emphasised that the present re-evaluation does not apply to erythritol (E 968) produced by other manufacturing processes (e.g. different microorganisms, strains). The reason is that this would be considered as significant changes in the production methods which would require an assessment in accordance with relevant legislation.

Regarding toxic elements, the Panel noted that the presence of lead (Pb) at the current specification limit (0.5 mg/kg) would result in an MOE below the target value of 1 for high consumers, while the presence of lead (Pb) at the modulated value (0.25 mg/kg) would result in an MOE above the target value of 1. According to the information submitted, no other impurities from the evaluated manufacturing process were identified.

Considering microbiological data submitted and the various steps of the production process, the Panel considered that a microbiological contamination is unlikely and, therefore, it is not necessary to recommend inclusion of microbiological criteria in the EU specifications for E 968.

The Panel noted, based on the submitted information along with considerations of the structure and characteristics of erythritol, being a simple polyol, E 968 is expected to be stable in food over a wide range of temperatures and pH conditions.

The Panel noted it has been shown recently that, in humans, erythritol can be formed endogenously through the PPP and that a small fraction can be metabolised to erythronate.

No new studies on ADME were submitted by the IBOs or by the applicant in support of the re-evaluation. Nonetheless, several studies in animals and humans have been performed at the time of the first evaluation of this substance by the SCF in 2003. All studies demonstrated a high degree of absorption of ingested erythritol (60%–90%) from the small intestine. Recent studies retrieved in the literature showed that absorption of erythritol is dose-dependent in humans (Bordier et al., 2022). In addition, it has been shown that erythritol can be metabolised to erythrose and further to erythronate to a small extent (Bordier et al., 2022; Hootman et al., 2017). Erythritol is then excreted unchanged in the urine. More recent data from the literature showed negligible metabolism of erythritol by human gut microbiota (Arrigoni et al., 2005). This is also in agreement with earlier studies (Hiele et al., 1993). Both in rats and in humans, half-life of excretion was estimated to be about 4 h.

The Panel concluded that erythritol (E 968) does not raise a concern regarding genotoxicity.

The Panel considered (i.e. WoE analysis in accordance to the revised protocol: very likely) that erythritol (E 968) has the potential to cause diarrhoea in humans, which was considered an adverse health effect because its potential association with electrolyte and water imbalance. Subjective GI symptoms (abdominal pain, nausea, bloating, flatulence) have been also noted.

The Panel considered the NOAELs for diarrhoea in humans from the available interventional studies and identified 0.5 g/kg bw (500 mg/kg bw) as a reference point (lower bound of the range of NOAELs) (see Section 3.6). The Panel considered that this value is sufficiently protective for all population groups.

The Panel also considered that the evidence available, albeit limited, consistently showed no short-term effect of erythritol on post-prandial glucose homeostasis in humans. Long-term studies addressing glucose homeostasis-related endpoints were not identified.

The Panel is aware of recent publications suggesting a possible association from human observational studies between higher circulating blood levels of erythritol and cardiovascular disease and related risk factors (Rebholz et al., 2018; Wang et al., 2019; Witkowski et al., 2023). However, these preliminary results do not conclusively identify specific health concerns for the use of erythritol as a food additive. As also discussed in recent reviews (Ortiz & Field, 2020; Mazi and Stanhopee, 2023), the Panel considered that fasting erythritol serum levels may be a biomarker of metabolic disturbances (i.e. type 2 diabetes mellitus, central adiposity gain which are known risk factors for cardiovascular disease). However, it is highly uncertain whether this association is at all related to consumption of food containing erythritol (E 968). Overall, the Panel

considered that a causal relationship between dietary exposure to erythritol (E 968) and cardiovascular disease risk has not been demonstrated by the available studies. Further studies might be helpful to clarify the nature of the association between plasma erythritol level and incidence of cardiovascular disease. The Panel noted that no cardiovascular adverse effects were observed in the animal studies evaluated by the SCF (SCF, 2003). Based on the available data from human studies, the Panel considered diarrhoea to be the most sensitive endpoint for adverse effect of erythritol (E 968).

Following the 2014 ANS Panel conceptual framework approach for the re-evaluation of food additives, and since reliable information for both exposure and toxicity of erythritol (E 968) was available, the Panel considered it appropriate to set a numerical ADI at the level of the reference point identified from human interventional studies. A reference point for diarrhoea was identified by the Panel to be 0.5 g/kg bw (500 mg/kg bw). In this case, uncertainty factors are not needed since human data were used and the mechanism for laxation is not depending on the duration of the exposure. Furthermore, no other (e.g. systemic) effects were observed in animals at much higher chronic exposures. Therefore, the reference value corresponds to an ADI of 0.5 g/kg bw per day (500 mg/kg bw per day). The Panel acknowledged that this is the first time that an ADI is derived for a food additive based on an immediate adverse effect such as diarrhoea. In the case of erythritol (E 968), the reported laxative effects, with diarrhoea as the critical endpoint, are mainly due to osmotic imbalance which may lead, in the chronic setting, to secondary adverse effects such as electrolyte imbalance. The Panel considered that this ADI is protective for the immediate laxative effect as well as potential chronic effects secondary to the laxative effect (i.e. diarrhoea).

Dietary exposure to erythritol (E 968) was estimated according to different exposure scenarios based on consumers-only as described in Section 3.4. Currently, erythritol (E 968) is an authorised food additive in the EU in 66 different food categories (representing 83 uses), while IBOs provided EFSA with use level for 22 food categories and analytical data were available for seven food categories.

In addition to the chronic exposure assessment, acute exposure to erythritol (E 968) was also estimated because of its laxative effect (i.e. diarrhoea). Methodologies for both assessments are detailed above (see Sections 3.4.1 and 3.4.2).

The highest mean and 95th percentile chronic exposure among consumers of one or more food categories containing erythritol (E 968) was respectively in children (742 mg/kg bw per day) and adolescents (1532 mg/kg bw per day).

Overall, the Panel considered that the exposure to erythritol (E 968) from its use as a food additive according to Annex II was overestimated in the *refined brand-loyal exposure assessment scenario*, given that exposure calculations based on the reported use levels were considered applicable to all foods within each food category, while the percentage of the foods in a subcategory labelled with erythritol (E 968) in Mintel was maximally 29.1% (see Section 3.3.2).

In this special case, an acute exposure assessment scenario has been performed, for which the same reference point of 0.5 g/kg bw (500 mg/kg bw) applies. The Panel considered the exposure to erythritol (E 968) was maximally 3531 mg/kg bw per meal (at the 99th percentile) for children. The acute scenario considered two maximum reported use levels, which is a conservative scenario. However, this is not an unreasonable scenario since erythritol (E 968) has a lower sweetening power than sugar (approximately 70% of its sweetening power) and can be used as a sugar replacement in many products.

Overall, the Panel considered that the acute exposure per meal is overestimated.

The Panel noted that the 95th percentile exposure estimates for both acute and chronic exposure to erythritol (E 968) were at or above the ADI of 0.5 g/kg bw (500 mg/kg bw) (per meal for the acute scenario or per day for the chronic scenario) in all populations.

Jointly with the re-evaluation of the safety of erythritol (E 968) in its permitted uses as a food additive, the Panel was also requested by the European Commission to evaluate an application in support of the possible exemption for this food additive from the current laxative warning label requirement applicable to all foods containing more than 10% added polyols, which was considered by the applicant not to be justified in the case of erythritol.

With diarrhoea being selected as the critical endpoint for the derivation of the ADI, in the case of erythritol, the Panel considered that the current warning '*excessive consumption may produce laxative effects*' remains appropriate. The threshold for warning may need to be re-considered taking into account the use of erythritol in several food items. For example, consumption of 2 L of flavoured drinks (FC 14.1.4) containing 16 g erythritol/L (MPL of 1.6%) would lead to an exceedance of the ADI in a person with a body weight of 60 kg or less. Another example is the consumption of 100 g chocolate containing erythritol (E 968) which, at the typical level of 200,000 mg/kg, would lead to an exceedance of the ADI for a person of 40 kg or less. At the same typical level, the ADI would be exceeded for a consumption of 150 g chocolate for a 60 kg person.

5 | UNCERTAINTY

The uncertainties, and the direction of the uncertainty, related to the exposure assessments are summarised in Table 7 of Section 3.4.3. Overall, the Panel considers that the *refined brand-loyal* and the *regulatory maximum level exposure assessment scenarios* for chronic exposure as well as the acute exposure assessment scenario per meal overestimate the dietary exposure to erythritol (E 968).

Concerning the experimental human studies, there are some uncertainties. The studies, generally, had small numbers of participants and did not cover the whole age range of the population. In addition, there is no long-term interventional study that evaluated the association between dietary erythritol intake and adverse health effects. Some epidemiological

studies investigated the role of circulating erythritol on cardiovascular and metabolic diseases, but there is uncertainty whether the circulating levels of erythritol in these studies reflect dietary exposure from its use as a food additive.

These uncertainties were not considered to influence the conclusions on the safety.

6 | CONCLUSIONS

Based on the available human studies reporting a laxative effect following acute or short-term exposure to erythritol, the Panel derived an ADI of 0.5 g/kg bw per day (500 mg/kg bw per day) based on the identified reference point i.e. lower bound of the range of the NOAELs for diarrhoea of the considered human studies.

The estimates for both acute and chronic dietary exposure to erythritol (E 968) are above the newly established ADI, indicating that individuals with high intake may be at risk of experiencing adverse effects after single and repeated exposure.

With respect to the application for the exemption of erythritol from the current laxative warning requirement under Regulation (EU) 1169/2011 for food containing more than 10% erythritol (100,000 mg/L or mg/kg), the Panel concluded that the available data do not support such a proposal.

7 | RECOMMENDATION

The Panel recommends the European Commission to consider:

- requesting more detailed occurrence data (use levels and analytical data) and label information, in order to be able to refine the exposure assessment;
- revising the definition of the food additive in the EU specifications as 'Obtained by fermentation of a carbohydrate source by non-genetically modified *Moniliella pollinis* strain BC or *Moniliella megachiliensis* strain KW3-6, followed by several purification steps and drying'.;
- including the CAS number 149-32-6 in the EU specifications;
- lowering the limit of lead (Pb) in the EU specifications.

8 | DOCUMENTATION AS PROVIDED TO EFSA

1. European Association of Polyols production (EPA), June 2018. Reply to the EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500). Technical data on erythritol (E 968): Section 1 Technical data; Toxicological data on erythritol (E 968): Sections 2 and 3. The following unpublished study reports were submitted:

    - INRA, Station of Technology and Applied Nutrition, Nantes, France, 1992. In vitro fermentation of indigestible carbohydrates by human faecal flora. Unpublished study report.
    - Nikken Chemicals Co., Ltd., Japan. Division of metabolism, Omiya Research Lab, 1990a. Pharmacokinetics after single oral administration of NIK-242 to dogs. Unpublished study report. Data from this unpublished study report were subsequently published in Noda et al., 1996.
    - TNO Nutrition and Food Research Institute, 1998. Sub-acute (4-weeks) oral toxicity study of cell-free fermented broth 1 in rats. TNO Report no. V97.741. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report.
    - TNO Nutrition and Food Research Institute, 2002. Repeated-dose (28-day) oral toxicity study with erythritol fermentation broth from *Moniliella pollinis* in rats. Organization for Applied Scientific Research, Zeist, Netherlands TNO Report no. V 4736. Unpublished study report.

2. Jungbunzlauer International AG, June 2018. Reply to the EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500). Technical data on erythritol (E 968): Section 1 Technical data.
3. European Association of Polyols production (EPA), June 2019. Reply to the EFSA call for technical data on sweeteners authorised as food additive in the EU (EFSA-Q-2019-00318).
4. Jungbunzlauer International AG, June 2019. Reply to the EFSA call for technical data on sweeteners authorised as food additive in the EU (EFSA-Q-2019-00318).
5. Cargill R&D Centre Europe, June 2020. Dossier 'Application for exemption of erythritol from the current laxative warning requirement for added polyols under Regulation (EU) 1169/2011' (EFSA-Q-2022-00219).
6. Cargill R&D Centre Europe, February 2022. Reply to EFSA clarifications request on toxicological data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500). The following unpublished study reports were submitted:

- Nikken Chemicals Co., Ltd., Japan. Division of metabolism, Omiya Research Lab, 1990b. Blood cell incorporation, protein binding and excretions in urine, feces, expired air and bile after single oral administration of 14C-NIK-242 in rats. Unpublished study report. Data from this unpublished study report were subsequently published in Noda et al., 1996.
- Nikken Chemicals Co., Ltd., Japan. Division of metabolism, Omiya Research Lab, 1990c. Radioactivity distribution after single oral administration of C-NIK-242 in rats. Unpublished study report. Data from this unpublished study report were subsequently published in Noda et al., 1996.
- Nikken Chemicals Co., Ltd., Japan. Division of metabolism, Omiya Research Lab, 1990d. Blood radioactivity levels after single oral administration of C-NIK-242 in rats. Unpublished study report. Data from this unpublished study report were subsequently published in Noda et al., 1996.
- Nikken Chemicals Co., Ltd., Japan. Division of metabolism, Omiya Research Lab, 1994. Analysis of metabolites in urine after single oral administration of NIK-242 to dogs. Unpublished study report. Data from this unpublished study report were subsequently published in Noda et al., 1996.
- TNO-CIVO Industries, 1990. Disposition study with 14C-erythritol in rats. TNO Report No. V90.307, Organization for applied scientific research, Zeist, Netherlands. Unpublished study report.
- Nikken Chemicals Co., Ltd., Japan. Division of metabolism, Omiya Research Lab., 1988. Study on excretion of erythritol after oral administration to human subjects. Unpublished study report.
- TNO-CIVO Industries, 1994. Chronic (2-year) oral toxicity and carcinogenicity study with erythritol in rats. TNO Report No. V 93.059. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report. Data from this unpublished study report were subsequently published in Lina et al., 1996).
- Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Department of Metabolic Endocrinology and Department of Nutrition, 1992. The effect of erythritol on glucose tolerance in diabetes patients. Unpublished study report. Data from this unpublished study report were subsequently published in Ishikawa et al., 1996.
- Biofortis, 2010. Study of gastrointestinal tolerability of erythritol (polyol) in children. Cargill, Vilvoorde R&D Centre, Belgium. Report Ref. CER_TDEOH05. Unpublished study report. Data from this unpublished study report were subsequently published in Jacqz-Aigrain et al., 2015.
- TNO-CIVO Industries, 1992. Subchronic (13-week) feeding study with erythritol in mice (final report). TNO report No. V90.421. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report. Data from this unpublished study report were subsequently published in Til et al., 1996.
- Inveresk Research International (IRI), 1992. Erythritol: one-year oral (dietary) toxicity study in dogs. IRI Report no. 7900. Unpublished study report. Data from this unpublished study report were subsequently published in Dean et al., 1996.
- TNO-CIVO Industries, 1996. Dietary two-generation reproduction study with erythritol in rats. TNO report No. V92.552. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report. Data from this unpublished study report were subsequently published in Waalkens-Berendsen et al., 1996.
- Nikken Chemicals Co., Ltd., Japan, 1989. Omiya Research Laboratory. Oral reproduction study of erythritol (NIK-242) with mice prior to and in the early stage of pregnancy. Study No. 242040124. Unpublished study report.
- TNO Nutrition and Food Research, 1993. Oral embryotoxicity/teratogenicity study with erythritol in rats. Final Report. No. V 92.107. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report. Data from this unpublished study report were subsequently published in Smits-van Prooije et al., 1996.
- TNO-CIVO Industries, 1994. Chronic (78-week) oral toxicity study with erythritol in rats. Report No. V 93.367. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report.
- Nikken Chemicals Co., Ltd., Japan. A 13-week oral subacute toxicity study of NIK-242 in dogs with 4-week recovery period (PRL/35), 1990. Final report. Study No. 242020322. Division of Toxicology, Omiya Research Laboratory. Unpublished study report. Data from this unpublished study report were subsequently published in Eapen et al., 2017.
- Nikken Chemicals Co., Ltd., Japan, 1991. Study on increased BUN caused by repeated administration of erythritol in rats. Division of Toxicology, Omiya Research Laboratory. Unpublished study report.
- TNO-CIVO Industries, 1990. Sub-acute (28-day) oral toxicity study with erythritol in rats. TNO report No. V90.050. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report. Data from this unpublished study report were subsequently published in Til and Modderman, 1996.
- TNO-CIVO Industries, 1991. An exploratory subchronic feeding study with erythritol in adult male rats. TNO report No. V90.003. Organization for Applied Scientific Research, Zeist, Netherlands. Unpublished study report. Data from this unpublished study report were subsequently published in Til et al., 1996.
- TNO-CIVO Industries, 1992. Subchronic (13-week) feeding study with erythritol in mice. TNO report No. V90.421. Organization for Applied Scientific Research, Zeist, Netherlands. Data from this unpublished study report were subsequently published in Til et al., 1996.
- Nikken Chemicals Co., Ltd., Japan, 1989. 13-week oral subacute toxicity study of NIK-242 in rats with 4-week recovery period (PRL/34). Division of Toxicology, Omiya Research Laboratory (Internal report). Unpublished study report.
- TNO-CIVO Industries, 1990. Examination of erythritol for mutagenic activity in the Ames test. Report no. V 90.306, (1990). Organization for Applied Scientific Research, Netherlands. Unpublished study report.
- Nikken Chemicals Co., Ltd., Japan, 1988. Screening for mutagenicity of NIK-242 on reverse mutation test in Bacteria and Chromosome Aberration Test in Cultured Cells. Division of Toxicology, Omiya Research Laboratory. Unpublished study report. Data from this unpublished study report were subsequently published in Kawamura et al., 1996.

- Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Department of Metabolic Endocrinology and Department of Nutrition, 1993. The Effect of Continuous Administration of the Sweetener Erythritol on Diabetes Patients. Unpublished study report.
- Nikken Chemicals Co. Ltd., Japan, 1992a. Study on the maximum no-effect level of erythritol using transient diarrhoeal action as index. Unpublished study report.
- Mitsubishi Kasei Corporation, Food Business Department, 1992. Study concerning transient diarrhoea induces by erythritol. Unpublished study report.
- Nikken Chemicals Co. Ltd., Japan, 1992b. Effect of continuous injection of erythritol with laxative action serving as index. Unpublished study report.
- Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Department of Metabolic Endocrinology and Department of Nutrition, 1993. The effect of continuos administration of the sweetener erythritol on diabetes patients. Unpublished study report. Data from this unpublished study report were subsequently published in Ishikawa et al., 1996.

7. Cargill R&D Centre Europe, June 2022. Reply to EFSA clarifications request on technical data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500).
8. Jungbunzlauer International AG, May 2022. Reply to EFSA clarifications request on technical data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500).
9. Cargill R&D Centre Europe, September 2022. Reply to EFSA clarifications request on technical data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500).
10. Cargill R&D Centre Europe, February 2023. Reply to EFSA clarifications request on technical and toxicological data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500). The complete version of two unpublished study reports (IRI, 1992 and TNO-CIVO Industries, 1994) submitted in February 2022 (Documentation provided to EFSA No. 6) were requested and provided by Cargill R&D Centre Europe.
11. Jungbunzlauer International AG, March 2023. Reply to EFSA clarifications request on technical data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500) and to the response to EFSA clarifications request received in May 2022 (Documentation provided No. 7).
12. Cargill R&D Centre Europe, March 2023. Reply to EFSA clarifications request on technical and toxicological data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500). The complete version of the unpublished study report Biofortis, 2010 submitted in February 2022 (Documentation provided to EFSA No. 6) was requested and provided by Cargill R&D Centre Europe.
13. Cargill R&D Centre Europe, March 2023. Reply to EFSA clarifications request on the dietary exposure assessment data received for the application for exemption from mandatory labelling requirement under Regulation (EU) No 1169/2011 (EFSA-Q-2022-00219).
14. Cargill R&D Centre Europe, May 2023. Reply to EFSA clarifications request on technical and toxicological data provided in response to EFSA call for technical and toxicological data on sweeteners authorised as food additive in the EU (EFSA-Q-2017-00500).

ABBREVIATIONS

3-OHBA	3-hydroxybutyric acid
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
ADP	adenosine diphosphate
AE	adverse event
aGLP-1	active glucagon-like peptide-1
AIC	Akaike's Information Criterion
AIDEPI	Unione Italiana Food
ALT	alanine aminotransferase
ANS	EFSA Panel on Food Additives and Nutrient sources added to Food
AP	alkaline phosphatase
Ar	arsenic
AST	aspartate aminotransferase
AUC	area under the curve
b2M	b2-microglobulin
BAT	basophil activation test
BCRP	human breast cancer resistance protein
BMDL	benchmark dose lower bound
BMI	body mass index
bw	bodyweight
BUN	blood urea nitrogen

CaCo	case–control study
CAT	catalase
CCK	cholecystokinin
Cd	cadmium
CG	comparison group
CI	confidence interval
CK-MB	creatine kinase-myocardial band
Co	cohort study
CONTAM	EFSA Panel on Contaminants in Food Chain
CrSe	cross-sectional study
ED	effective dose
ELISA	enzyme-linked immunosorbent assay
ELSD	evaporative light-scattering detection
ERY	erythritol
eWAT	epididymal white adipose tissue
FAF	EFSA Panel on Food Additives and Flavourings
FBS	fasting blood sugar
FC	food category
FCC	Food Chemical Codex
FDE	Food Drink Europe
FFA	free fatty acids
FSE	Food Supplement Europe
GC–MS	Gas Chromatography–Mass Spectrometry
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GK	glucokinase
GLC	gas–liquid chromatography
GLP-1	glucagon-like peptide 1
Glut-4	glucose transporter type 4
GNPD	Global New Products Database
GOT	glutamic-oxaloacetic transaminase
GPL	Good Laboratory Practice
GPT	glutamic-pyruvic transaminase
GSH	glutathione
HBGV	health-based guidance value
HCT	human controlled trial
HDL	high-density lipoprotein
HFD	high-fat diet
Hg	mercury
HOC	Health Outcome Category
HPLC	high performance liquid chromatography
HPLC-RI	high performance liquid chromatography-refractive index
HPLC-UV	high-performance liquid chromatography with ultraviolet detection
HR	hazard ratio
HRT	histamine release test
hsCRP	high-sensitive C-reactive protein
IBO	interested business operator
ICGA	International Chewing Gum Association
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
ICP-OES	Inductively Coupled Plasma-Optical Emission Spectroscopy
IL	interleukin
IQ	intelligence quotient
IRI	immunoreactive insulin
IRS-1	insulinreceptor substrate-1
ITS	Internal transcribed spacer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LC–MS	liquid chromatography mass spectrometry
LD	Laser diffraction
LDL	low-density lipoprotein
LOD	Limit of detection

LOQ	Limit of quantification
MACE	major adverse cardiovascular events
MDA	malondialdehyde
MID	mass isotopomer distribution
MOE	Margin of exposure
MOS	Margin of safety
MPL(s)	maximum permitted level(s)
NAG	*N*-acetyl glucosaminidase
ND	normal diet
NEFA	non-esterified fatty acids
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NIDDM	non-insulin dependent diabetes mellitus
NTP	National Toxicology Program
OECD	TG Organisation for Economic Co-operation and Development Testing Guidelines
P95	95th percentile
Pb	lead
PEPCK	phosphoenolpyruvate carboxy-kinase
ppm	parts per million
PPP	pentose phosphate pathway
PRP	platelet-rich plasma
P-SG	partial substitute gummy
PYY	pancreatic peptide YY
QOL	quality of life
QS	*quantum satis*
rBOLD	resting blood oxigenation level-dependent
rCBF	resting cerebral blood flow
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RI	refractive index
RP	reference point
RoB	Risk of bias
rRNA	ribosomal RNA
ROS	reactive oxygen species
RT	retention time
SOD	superoxide dismutase
SPF	specific-pathogen-free
SPT	skin prick test
TC	total cholesterol
TG	triacylglycerol
TNF	tumour necrosis factor
TRAP6	thrombin receptor-activated peptide
T-SG	total substitute gummy
SCFA	short chain fatty acid
SCF	Scientific Committee on Food
SE	standard error
SEM	standard error mean
T2	type II
TG	test guideline
TLC	thin layer chromatography
UV	ultraviolet
VAS	visual analog scale
WG	working group
WoE	Weight of Evidence

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

QUESTION NUMBERS

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NOTE

The full opinion will be published in accordance with Article 12(3) of Regulation (EC) No 1331/2008 once the decision on confidentiality will be received from the European Commission.

REFERENCES

Agriculture and Environment Research Unit, University of Hertfordshire, Lewis, K. A., & Tzilivakis, J. (2021). Review and synthesis of data on the potential environmental impact of artificial sweeteners. *EFSA Supporting Publication 18*(10), EN-6918. https://doi.org/10.2903/sp.efsa.2021.EN-6918

Arrigoni, E., Brouns, F., & Amado, R. (2005). Human gut microbiota does not ferment erythritol. *British Journal of Nutrition*, *94*, 643–646. https://doi.org/10.1079/bjn20051546

Baker, K. A., White, G. S., Faraji, A., & Bibbs, C. S. (2023). Enhancing toxic sugar meals against Aedes aegypti (Diptera: Culicidae) by adulterating with erythritol in combination with other active ingredients. *Journal of Medical Entomology*, *60*(4), 833–836. https://doi.org/10.1093/jme/tjad041

Bär, A. (1985). Safety assessment of polyol sweeteners – Some aspects of toxicity. *Food Chemistry*, *16*(3–4), 231–241. https://doi.org/10.1016/0308-8146(85)90117-7

Barrett, M., Caponera, V., McNair, C., O'Donnell, S., & Marenda, D. R. (2020). Potential for use of erythritol as a socially transferrable ingested insecticide for ants (Hymenoptera: Formicidae). *Journal of Economic Entomology*, *113*(3), 1382–1388. https://doi.org/10.1093/jee/toaa019

Baudier, K. M., Kaschock-Marenda, S. D., Patel, N., Diangelus, K. L., O'Donnell, S., & Marenda, D. R. (2014). Erythritol, a non-nutritive sugar alcohol sweetener and the main component of truvia®, is a palatable ingested insecticide. *PLoS One*, *9*(6), e98949. https://doi.org/10.1371/journal.pone.0098949

Beards, E., Tuohy, K., & Gibson, G. (2010). Bacterial, SCFA, and gas profiles of a range of food ingredients following in vitro fermentation by human colonic microbiota. *Anaerobe*, *16*(4), 420–425. https://doi.org/10.1016/j.anaerobe.2010.05.006

Bordier, V., Teysseire, F., Schlotterbeck, G., Senner, F., Beglinger, C., Senner, C., Meyer-Gerspach, A. C., & Wolnerhanssen, B. K. (2021). Effect of a Chronic Intake of the Natural Sweeteners Xylitol and Erythritol on Glucose Absorption in Humans with Obesity. *Nutrients*, *13*(11), 3950–3960. https://doi.org/10.3390/nu13113950

Bordier, V., Teysseire, F., Senner, F., Schlotterbeck, G., Drewe, J., Beglinger, C., Wölnerhanssen, B. K., & Meyer-Gerspach, A. C. (2022). Absorption and metabolism of the natural sweeteners erythritol and xylitol in humans: A dose-ranging study. *International Journal of Molecular Sciences*, *23*(17), 9867. https://doi.org/10.3390/ijms23179867

Bornet, F., Blayo, A., Dauchy, F., & Slama, G. (1996a). Plasma and urine kinetics of erythritol after Oral ingestion by healthy humans. *Regulatory Toxicology and Pharmacology*, *24*(2 Pt. 2), 280–285. https://doi.org/10.1006/rtph.1996.0109

Bornet, F., Blayo, A., Dauchy, F., & Slama, G. (1996b). Gastrointestinal response and plasma and urine determination in human subjects given erythritol. *Regulatory Toxicology and Pharmacology*, *24*(2 Pt 2), 296–302. https://doi.org/10.1006/rtph.1996.0111

Burgess, E. R., & Geden, C. J. (2019). Larvicidal potential of the polyol sweeteners erythritol and xylitol in two filth fly species. *Journal of Vector Ecology*, *44*(1), 11–17. https://doi.org/10.1111/jvec.12324

Burgess, E. R., & King, B. H. (2017). Insecticidal potential of two sugar alcohols to Musca domestica (Diptera: Muscidae). *Journal of Economic Entomology*, *110*(5), 2252–2258. https://doi.org/10.1093/jee/tox190

Burgess, E. R., Taylor, E. E., Acevedo, A., Tworek, M., Nayduch, D., Khurana, N., Miller, J. S., & Geden, C. J. (2021). Diets of erythritol, xylitol, and sucrose affect the digestive activity and gut bacterial community in adult house flies. *Entomologia Experimentalis et Applicata*, *169*(10), 878–887. https://doi.org/10.1111/eea.13088

Caponera, V., Barrett, M., Marenda, D. R., & O'Donnell, S. (2020). Erythritol ingestion causes concentration-dependent mortality in eastern subterranean termites (Blattodea: Rhinotermitidae). *Journal of Economic Entomology*, *113*(1), 348–352. https://doi.org/10.1093/jee/toz260

Cha, D. H., Skabeikis, D., Kim, B. S., Lee, J. C., & Choi, M. Y. (2023). Insecticidal properties of erythritol on four tropical Tephritid fruit flies, Zeugodacus cucurbitae, Ceratitis capitata, Bactrocera dorsalis, and B. Latifrons (Diptera: Tephritidae). *Insects*, *14*(5), 472. https://doi.org/10.3390/insects14050472

Chen, L., Cheng, C. Y., Choi, H., Ikram, M. K., Sabanayagam, C., Tan, G. S. W., Tian, D., Zhang, L., Venkatesan, G., Tai, E. S., Wang, J. J., Mitchell, P., Cheung, C. M. G., Beuerman, R. W., Zhou, L., Chan, E. C. Y., & Won, T. Y. (2016). Plasma metabonomic profiling of diabetic retinopathy. *Diabetes*, *65*(4), 1099–1108. https://doi.org/10.2337/db15-0661

Choi, M. Y., Lucas, H., Sagili, R., Cha, D. H., & Lee, J. C. (2019). Effect of erythritol on Drosophila suzukii (Diptera: Drosophilidae) in the presence of naturally-occurring sugar sources, and on the survival of Apis mellifera (Hymenoptera: Apidae). *Journal of Economic Entomology*, *112*(2), 981–985. https://doi.org/10.1093/jee/toy362

Choi, M. Y., Tang, S. B., Ahn, S. J., Amarasekare, K. G., Shearer, P., & Lee, J. C. (2017). Effect of non-nutritive sugars to decrease the survivorship of spotted wing drosophila, Drosophila suzukii. *Journal of Insect Physiology*, *99*, 86–94. https://doi.org/10.1016/j.jinsphys.2017.04.001

Chukwuma, C. I., Mopuri, R., Nagiah, S., Chuturgoon, A. A., & Islam, M. S. (2018). Erythritol reduces small intestinal glucose absorption, increases muscle glucose uptake, improves glucose metabolic enzymes activities and increases expression of Glut-4 and IRS-1 in type 2 diabetic rats. *European Journal of Nutrition*, *57*(7), 2431–2444. https://doi.org/10.1007/s00394-017-1516-x

Chung, Y. M., Lee, J. H., Kim, D. Y., Hwang, S. H., Hong, Y. H., Kim, S. B., Lee, S. J., & Park, C. H. (2012). Dietary D-Psicose Reduced Visceral Fat Mass in High-Fat Diet-Induced Obese Rats. *Journal of Food Science*, *77*(2), H53–H58. https://doi.org/10.1111/j.1750-3841.2011.02571.x

Chung, Y. S., & Lee, M. (2013). Genotoxicity Assessment of Erythritol by Using Short-term Assay. *Toxicology Research*, *29*(4), 249–255.

Dean, I., Jackson, F., & Greenough, R. J. (1996). Chronic (1-year) oral toxicity study of erythritol in dogs. *Regulatory Toxicology and Pharmacology*, *24*, S254–S260. https://doi.org/10.1006/rtph.1996.0106

Diaz-Fleischer, F., Arredondo, J., Lasa, R., Bonilla, C., Debernardi, D., Perez-Staples, D., & Williams, T. (2019). Sickly sweet: Insecticidal polyols induce lethal regurgitation in dipteran pests. *Insects*, *10*(2), 53.

Duangkumpha, K., Jariyasopit, N., Wanichthanarak, K., Dhakal, E., Wisanpitayakorn, P., Thotsiri, S., Sirivatanauksorn, Y., Kitiyakara, C., Sathirapongsasuti, N., & Khoomrung, S. (2022). GC x GC-TOFMS metabolomics analysis identifies elevated levels of plasma sugars and sugar alcohols in diabetic mellitus patients with kidney failure. *The Journal of Biological Chemistry*, *298*(10), 12. https://doi.org/10.1016/j.jbc.2022.102445

Dong, X. H., Sun, X., Jiang, G. J., Chen, A. F., & Xie, H. H. (2015). Dietary Intake of Sugar Substitutes Aggravates Cerebral Ischemic Injury and Impairs Endothelial Progenitor Cells in Mice. *Stroke*, *46*(6), 1714. https://doi.org/10.1161/STROKEAHA.114.007308

Eapen, A. K., de Cock, P., Crincoli, C. M., Means, C., Wismer, T., & Pappas, C. (2017). Acute and sub-chronic oral toxicity studies of erythritol in beagle dogs. *Food and Chemical Toxicology.*, *105*, 448–455. https://doi.org/10.1016/j.fct.2017.04.049

EFSA (European Food Safety Authority). (2007). Opinion of the scientific committee related to uncertainties in dietary exposure assessment. *EFSA Journal*, *5*(1), 438. https://doi.org/10.2903/j.efsa.2007.438

EFSA (European Food Safety Authority). (2011). Use of the EFSA comprehensive European food consumption database in exposure assessment. *EFSA Journal*, *9*(3), 2097. https://doi.org/10.2903/j.efsa.2011.2097

EFSA (European Food Safety Authority). (2015a). Scientific report on principles and process for dealing with data and evidence in scientific assessments. *EFSA Journal*, *13*(5), 4121. https://doi.org/10.2903/j.efsa.2015.4121

EFSA (European Food Safety Authority). (2015b). The food classification and description system FoodEx2 (revision 2). *EFSA Supporting Publication*, *12*(5), EN-804. https://doi.org/10.2903/sp.efsa.2015.EN-804

EFSA (European Food Safety Authority). (2020a). Outcome of the public consultation on a draft protocol for the assessment of hazard identification and characterisation of sweeteners. *EFSA Supporting Publication*, *17*(2), EN-1803. https://doi.org/10.2903/sp.efsa.2020.EN-1803

EFSA (European Food Safety Authority). (2020b). Outcome of the public consultation on a draft protocol for assessing exposure to sweeteners as part of their safety assessment under the food additives re-evaluation programme. *EFSA Supporting Publication*, *17*(8), EN-1913. https://doi.org/10.2903/sp.efsa.2020.EN-1913

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), Mortensen, A., Aguilar, F., Crebelli, R., Di Domenico, A., Dusemund, B., Frutos, M. J., Galtier, P., Gott, D., Gundert-Remy, U., Leblanc, J. C., Lindtner, O., Moldeus, P., Mosesso, P., Parent-Massin, D., Oskarsson, A., Stankovic, I., Waalkens-Berendsen, I., Woutersen, R. A., … Lambré, C. (2017). Scientific opinion on the Re-evaluation of glycerol (E 422) as a food additive. *EFSA Journal*, *15*(3), 4720. https://doi.org/10.2903/j.efsa.2017.4720

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources). (2010). Statement in relation to the safety of erythritol (E 968) in light of new data, including a new paediatric study on the gastrointestinal tolerability of erythritol. *EFSA Journal*, *8*(7), 1650. https://doi.org/10.2903/j.efsa.2010.1650

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources). (2012). Guidance for submission for food additive evaluations. *EFSA Journal*, *10*(7), 2760. https://doi.org/10.2903/j.efsa.2012.2760

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources). (2013). Statement on a refined dietary exposure assessment of erythritol (E 968) taking into account additional data provided. *EFSA Journal*, *11*(3), 3121. https://doi.org/10.2903/j.efsa.2013.3121

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources). (2015). Scientific opinion on the safety of the proposed extension of use of erythritol (E 968) as a food additive. *EFSA Journal*, *13*(3), 4033. https://doi.org/10.2903/j.efsa.2015.4033

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes, M., Aquilina, G., Castle, L., Engel, K., Fowler, P., Frutos Fernandez, M. J., Gundert-Remy, U., Gürtler, R., Husøy, T., Manco, M., Mennes, W., Moldeus, P., Passamonti, S., Shah, R., Waalkens-Berendsen, I., Wölfle, D., Wright, M., Cheyns, K., … Fürst, P. (2022). Scientific opinion on the follow-up of the Re-evaluation of glycerol (E 422) as a food additive. *EFSA Journal*, *20*(6), 7353. https://doi.org/10.2903/j.efsa.2022.7353

EFSA Scientific Committee. (2009). Guidance of the scientific committee on transparency in the scientific aspects of risk assessment carried out by EFSA. Part 2: General principles. *EFSA Journal*, *7*(4), 1051. https://doi.org/10.2903/j.efsa.2009.1051

EFSA Scientific Committee. (2012). Guidance on selected default values to be used by the EFSA scientific committee, scientific panels and units in the absence of actual measured data. *EFSA Journal*, *10*(3), 2579. https://doi.org/10.2903/j.efsa.2012.2579

EFSA Scientific Committee, More, S., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T., Hernández-Jerez, A., Bennekou, S. H., Koutsoumanis, K., Lambré, C., Machera, K., Naegeli, H., Nielsen, S., Schlatter, J., Schrenk, D., Silano (deceased), V., Turck, D., Younes, M., Castenmiller, J., … Schoonjans, R. (2021). Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles. *EFSA Journal*, *19*(8), 6769. https://doi.org/10.2903/j.efsa.2021.6769

Eszterbauer, E., & Nemeth, A. (2022). Optimization of erythritol fermentation by high-throughput screening assays. *Hungarian Journal of Industry and Chemistry*, *50*(2), 7–10. https://doi.org/10.33927/hjic-2022-11

Fisher, M. L., Fowler, F. E., Denning, S. S., & Watson, D. W. (2017). Survival of the house Fly (Diptera: Muscidae) on Truvia and other sweeteners. *Journal of Medical Entomology*, *54*(4), 999–1005. https://doi.org/10.1093/jme/tjw241

Flint, N., Hamburg, N. M., Holbrook, M., Dorsey, P. G., Dorsey, P. G., LeLeiko, R. M., Berger, A., de Cock, P., de Cock, P., Bosscher, D., & Vita, J. A. (2014). Effects of erythritol on endothelial function in patients with type 2 diabetes mellitus: a pilot study. *Acta diabetologica*, *51*(3), 513–516. https://doi.org/10.1007/s00592-013-0534-2

Fu, B., Wang, J., Wang, L., Wang, Q., Guo, Z., Xu, M., & Jiang, N. (2022). Integrated proteomic and metabolomic profile analyses of cardiac valves revealed molecular mechanisms and targets in calcific aortic valve disease. *Frontiers in Cardiovascular Medicine*, *9*, 15. https://doi.org/10.3389/fcvm.2022.944521

Fukuda, M., Terata, T., Tsuda, K., Sugawara, M., Kitatani, N., & Seino, Y. (2010). Aspartame-acesulfame K-containing low-energy erythritol sweetener markedly suppresses postprandial hyperglycemia in mild and borderline diabetics. *Food Science and Technology Research*, *16*(5), 457–466. https://doi.org/10.3136/fstr.16.457

Gan, D., Xu, M., Chen, L., Cui, S., Deng, C., Qiao, Q., Guan, R., & Zhong, F. (2022). Intake of sugar substitute gummy candies benefits the glycemic response in healthy adults: A prospective crossover clinical trial. *Gels*, *8*(10), 642. https://doi.org/10.3390/gels8100642

Gatidou, G., Vazaiou, N., Thomaidis, N. S., & Stasinakis, A. S. (2020). Biodegradability assessment of food additives using OECD 301F respirometric test. *Chemosphere*, *241*, 125071. https://doi.org/10.1016/j.chemosphere.2019.125071

Gilkey, P. L., Bolshakov, D. T., Kowala, J. G., Taylor, L. A., O'Donnell, S., Marenda, D. R., & Sirot, L. K. (2018). Lethal effects of erythritol on the mosquito Aedes aegypti Linnaeus (Diptera: Culicidae). *Journal of Applied Entomology*, *142*(9), 878–881. https://doi.org/10.1111/jen.12538

Gullickson, M. G., Rogers, M. A., Burkness, E. C., & Hutchison, W. D. (2019). Efficacy of organic and conventional insecticides for Drosophila suzukii when combined with erythritol, a non-nutritive feeding stimulant. *Crop Protection*, *125*, 104878. https://doi.org/10.1016/j.cropro.2019.104878

Han, Y., Kwon, E. Y., & Choi, M. S. (2020). Anti-diabetic effects of allulose in diet-induced obese mice via regulation of mRNA expression and alteration of the microbiome composition. *Nutrients*, *12*(7), 2113. https://doi.org/10.3390/nu12072113

Han, Y., Park, H., Choi, B. R., Ji, Y., Kwon, E. Y., & Choi, M. S. (2020). Alteration of microbiome profile by D-allulose in amelioration of high-fat-diet-induced obesity in mice. *Nutrients*, *12*(2), 352. https://doi.org/10.3390/nu12020352

Harada, N., Hiragun, M., Mizuno, M., Kawaguchi, T., Ishii, K., Yanase, Y., Hiragun, T., Sugita, Y., & Hide, M. (2016). A case of erythritol allergy studied by basophil histamine release and CD203c expression in vitro in addition to a challenge test in vivo. *Journal of Investigational Allergology & Clinical Immunology*, *26*(2), 135–136. https://doi.org/10.18176/jiaci.0032

Hiele, M., Ghoos, Y., Rutgeerts, P., & Vantrappen, G. (1993). Metabolism of erythritol in humans: Comparison with glucose and lactitol. *British Journal of Nutrition*, *69*(1), 169–176. https://doi.org/10.1079/bjn19930019

Hijosa-Valsero, M., Paniagua-García, A. I., & Díez-Antolínez, R. (2022). Cell immobilization for erythritol production. *Journal of Fungi*, *8*(12), 1286–1289. https://doi.org/10.3390/jof8121286

Hootman, K. C., Trezzi, J. P., Kraemer, L., Burwell, L. S., Dong, X. Y., Guertin, K. A., Jaeger, C., Stover, P. J., Hiller, K., & Cassano, P. A. (2017). Erythritol is a pentose-phosphate pathway metabolite and associated with adiposity gain in young adults. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(21), 4233–4240. https://doi.org/10.1073/pnas.1620079114

Huang, L.-g., Xiao, B.-w., Wang, W.-j., Nian, L., Wang, H.-y., Yang, W.-l., Zhou, J.-p., Zhang, B., Liu, Z.-q., & Zheng, Y.-G. (2023). Multiplex modification of *Yarrowia lipolytica* for enhanced erythritol biosynthesis from glycerol through modularized metabolic engineering. *Bioprocess and Biosystems Engineering*, *46*, 1351–1363. https://doi.org/10.1007/s00449-023-02906-0

Ishikawa, M., Miyashita, M., Kawashima, Y., Nakamura, T., Saitou, N., & Modderman, J. (1996). Effects of Oral Administration of Erythritol on patients with diabetes. *Regulatory Toxicology and Pharmacology*, *24*, S303–S308. https://doi.org/10.1006/rtph.1996.0112

Jacqz-Aigrain, E., Kassai, B., Cornu, C., Cazaubiel, J.-M., Housez, B., Cazaubiel, M., Prével, J.-M., Bell, M., Boileau, A., & de Cock, P. (2015). Gastrointestinal tolerance of erythritol-containing beverage in young children: A double-blind, randomised controlled trial. *European Journal of Clinical Nutrition*, *69*, 746–751. https://doi.org/10.1038/ejcn.2015.4

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2000). Safety evaluation of certain food additives and contaminants: Fifty-third report of the joint FAO/WHO expert committee on food additives. *WHO Technical Report Series*, *896*, 128. ISBN: 92-4-120896-1. https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf?sequence=1&isAllowed=y

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2006). Combined compendium of food additive specifications. All specifications monographs from the 1st to the 65th meeting (1956–2005), Volume 4, 331. ISBN 92–5–105569-6. https://www.fao.org/3/a0691e/a0691e.pdf

Jeya, M., Lee, K. M., Tiwari, M. K., Kim, J. S., Gunasekaran, P., Kim, S. Y., Kim, I. W., & Lee, J. K. (2009). Isolation of a novel high erythritol-producing Pseudozyma tsukubaensis and scale-up of erythritol fermentation to industrial level. *Applied Microbiology and Biotechnology*, *83*(2), 225–231. https://doi.org/10.1007/s00253-009-1871-5

Juskiewicz, J., Zdunczyk, Z., Klewicki, R., & Gomez-Villalva, E., (2004). Physiological effects of dietary inulin, xylitol and β-galactosyl-derivatives of sugar alcohols in rat. *Acta Alimenteria*, *33*(3), 303–311. https://doi.org/10.1556/AALIM.33.2004.3.11

Katsue, H., Higashi, Y., Baba, N., Aoki, M., Sakanoue, M., Matsushita, S., & Kanekura, T. (2014). Allergic reaction caused by acesulfame potassium in foods. *Contact Dermatitis*, *71*(4), 251–252. https://doi.org/10.1111/cod.12252

Kawamura, Y., Saito, Y., Imamura, M., & Modderman, J. P. (1996). Mutagenicity studies on erythritol in bacterial reversion assay systems and in Chinese hamster fibroblast cells. *Regulatory Toxicology and Pharmacology*, *24*(2), 261–263. https://doi.org/10.1006/rtph.1996.0107

Kawano, R., Okamura, T., Hashimoto, Y., Majima, S., Senmaru, T., Ushigome, E., Asano, M., Yamazaki, M., Takakuwa, H., Sasano, R., Nakanishi, N., Hamaguchi, M., & Fukui, M. (2021). Erythritol ameliorates small intestinal inflammation induced by high-fat diets and improves glucose tolerance. *International Journal of Molecular Sciences*, *22*(11), 5558. https://doi.org/10.3390/ijms22115558v

Khatape, A. B., Dastager, S. G., & Rangaswamy, V. (2022). An overview of erythritol production by yeast strains. *FEMS Microbiology Letters*, *369*(1), 1–12. https://doi.org/10.1093/femsle/fnac107

Kim, S., Yoo, W., Park, H. K., & Jo, E. J. (2022). The first case of erythritol-induced anaphylaxis in Korea. *Journal of Korean Medical Science*, *37*(10), 6. https://doi.org/10.3346/jkms.2022.37.e83

Kim, Y., Park, S. C., Wolf, B. W., & Hertzler, S. R. (2011). Combination of erythritol and fructose increases gastrointestinal symptoms in healthy adults. *Nutrition Research*, *31*(11), 836–841. https://doi.org/10.1016/j.nutres.2011.09.025

Koh, D. W., Park, J. W., Lim, J. H., Yea, M. J., & Bang, D. Y. (2018). A rapid method for simultaneous quantification of 13 sugars and sugar alcohols in food products by UPLC-ELSD. *Food Chemistry*, *240*, 694–700. https://doi.org/10.1016/j.foodchem.2017.07.142

Lee, J. C., Price, B. E., Adams, C. G., Rutkowski, E., & Choi, M. Y. (2023). Erythritol sprays reduce *Drosophila suzukii* infestation without impacting honey bee visitation nor fruit quality. *Pest Management Science*, *79*, 4990–5002. https://doi.org/10.1002/ps.7701

Lee, J. K., Jung, H. M., & Kim, S. Y. (2003). 1,8-Dihydroxynaphthalene (DHN)-melanin biosynthesis inhibitors increase erythritol production in torula corallina, and DHN-melanin inhibits erythrose reductase. *Applied and Environmental Microbiology*, *69*(6), 3427–3434.

Lee, S. H., Choe, D. H., & Lee, C. Y. (2021). The impact of artificial sweeteners on insects. *Journal of Economic Entomology*, *114*(1), 1–13. https://doi.org/10.1093/jee/toaa244

Lee, D., Han, Y., Kwon, E. Y., & Choi, M. S. (2020). D-allulose Ameliorates Metabolic Dysfunction in C57BL/KsJ-db/db Mice. *Molecules*, *25*(16), 3656. https://doi.org/10.3390/molecules25163656

Lina, B., Bos-Kuipers, M. H. M., Til, H. P., & Bär, A. (1996). Chronic toxicity and carcinogenicity study of erythritol in rats. *Regulatory Toxicology and Pharmacology*, *24*, S264–S279.

Lovell, D. P., Thomas, G., & Dubow, R. (1999). Issues related to the experimental design and subsequent statistical analysis of in vivo and in vitro comet studies. *Teratogenesis, Carcinogenesis, and Mutagenesis*, *19*(2), 109–119. https://doi.org/10.1002/(SICI)1520-6866(1999)19:2%3C109::AID-TCM4%3E3.0.CO;2-5

Maeng, H. J., Yoon, J. H., Chun, K. H., Kim, S. T., Jang, D. J., Park, J. E., Kim, Y. H., Kim, S. B., & Kim, Y. C. (2019). Metabolic stability of D-allulose in biorelevant media and hepatocytes: Comparison with fructose and erythritol. *Food*, *8*(10), 448. https://doi.org/10.3390/foods8100448

Maestas, L., Lee, J. C., & Choi, M. Y. (2023). Effect of erythritol and sucralose formulation on the survivorship of the mosquito *Aedes aegypti*. *Florida Entomologist*, *106*(2), 129–132. https://doi.org/10.1653/024.106.0210

Mazi, T. A.., & Stanhope, K. L. (2023). Erythritol: An In-Depth Discussion of Its Potential to Be a Beneficial Dietary Component). *Nutrients*, *15*(1), 2072–6643. https://doi.org/10.3390/nu15010204

Menni, C., Fauman, E., Erte, I., Perry, J. R. B., Kastenmüller, G., Shin, S. Y., Petersen, A. K., Hyde, C., Psatha, M., Ward, K. J., Yuan, W., Milburn, M., Palmer, C. N. A., Frayling, T. M., Trimmer, J., Bell, J. T., Gieger, C., Mohney, R. P., Brosnan, M. J., … Spector, T. D. (2013). Biomarkers for type 2 diabetes and impaired fasting glucose using a nontargeted metabolomics approach. *Diabetes*, *62*(12), 4270–4276. https://doi.org/10.2337/db13-0570

Meyer-Gerspach, A. C., Wingrove, J. O., Beglinger, C., Rehfeld, J. F., Le Roux, C. W., Peterli, R., Dupont, P., O'Daly, O., Van Oudenhove, L., & Wölnerhanssen, B. K. (2021). Erythritol and xylitol differentially impact brain networks involved in appetite regulation in healthy volunteers. *Nutritional Neuroscience*, *25*(11), 2344–2358. https://doi.org/10.1080/1028415x.2021.1965787

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., the PRISMA Group, (2009). Preferred reporting items forsystematicreviews and meta-analyses: the PRISMA statement. *PLoS Medicine*, *6*, 6. https://doi.org/10.1371/journal.pmed.1000097

Mohsenpour, M. A., Kaseb, F., Nazemian, R., Mozaffari-Khosravi, H., Fallahzadeh, H., & Salehi-Abargouei, A. (2019). The effect of a new mixture of sugar and sugar-alcohols compared to sucrose and glucose on blood glucose increase and the possible adverse reactions: A phase I double-blind, three-way randomized cross-over clinical trial. *Endocrinologia, Diabetes y Nutricion*, *66*(10), 647–653. https://doi.org/10.1016/j.endinu.2018.12.008

Moon, H. J., Jeya, M., Kim, I. W., & Lee, J. K. (2010). Biotechnological production of erythritol and its applications. *Applied Microbiology and Biotechnology*, *86*(4), 1017–1025. https://doi.org/10.1007/s00253-010-2496-4

Moon, J. Y., Chai, J. C., Yu, B., Song, R. J., Chen, G. C., Graff, M., Daviglus, M. L., Chan, Q., Thyagarajan, B., Castaneda, S. F., Grove, M. L., Cai, J., Xue, X., Mossavar-Rahmani, Y., Vasan, R. S., Boerwinkle, E., Kaplan, R. C., & Qi, Q. (2023). Metabolomic signatures of sedentary behavior and cardiometabolic traits in US Hispanics/Latinos: Results from HCHS/SOL. *Medicine and Science in Sports and Exercise*, *55*(10), 1781–1791. https://doi.org/10.1249/mss.0000000000003205v

Mori, S., Kurihara, K., & Inuo, C. (2022). Case of a 6-year-old boy with anaphylaxis induced by erythritol with positive skin prick test and negative basophil activation test. *Allergy, Asthma and Clinical Immunology*, *18*(1), 28. https://doi.org/10.1186/s13223-022-00670-6

Msomi, N. Z., Erukainure, O. L., Salau, V. F., Olofinsan, K. A., & Islam, M. S. (2023). Comparative effects of xylitol and erythritol on modulating blood glucose; inducing insulin secretion; reducing dyslipidemia and redox imbalance in a type 2 diabetes rat model. *Food Science and Human Wellness*, *12*(6), 2052–2060. https://doi.org/10.1016/j.fshw.2023.03.023

Noda, K., Nakayama, K., & Modderman, J. (1996). Fate of erythritol after single Oral administration to rats and dogs. *Regulatory Toxicology and Pharmacology*, *24*(2 Pt 2), 206–213. https://doi.org/10.1006/rtph.1996.0100

Noda, K., Nakayama, K., & Oku, T. (1994). Serum glucose and insulin levels and erythritol balance after Oral Administration of Erythritol in healthy subjects. *European Journal of Clinical Nutrition*, *48*(4), 286–292.

Noda, K., & Oku, T. (1992). Metabolism and disposition of erythritol after Oral Administration in Rats. *Journal of Nutrition*, *122*(6), 1266–1272. https://doi.org/10.1093/jn/122.6.1266

Nojiri, S., Taguchi, N., Oishi, M., & Suzuki, S. (2000). Determination of sugar alcohols in confectioneries by high-performance liquid chromatography after Nitrobenzoylation. *Journal of Chromatography A*, *893*(1), 195–200. https://doi.org/10.1016/s0021-9673(00)00694-4

NTP-OHAT (National Toxicology Program- Office of Health Assessment and Translation). (2019). *Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. 101 pp*. https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf

O'Donnell, S., Baudier, K., Fiocca, K., & Marenda, D. R. (2018). Erythritol ingestion impairs adult reproduction and causes larval mortality in Drosophila melanogaster fruit flies (Diptera: Drosophilidae). *Journal of Applied Entomology*, *142*(1–2), 37–42. https://doi.org/10.1111/jen.12409

O'Donnell, S., Baudier, K., & Marenda, D. R. (2016). Non-nutritive polyol sweeteners differ in insecticidal activity when ingested by adult Drosophila melanogaster (Diptera: Drosophilidae). *Journal of Insect Science (Online)*, *16*(1), 47. 10.1093%2Fjisesa%2Fiew031

OECD (Organisation for Economic Co-operation and Development). (1992). *Test No. 301: Ready biodegradability. OECD guidelines for the testing of chemicals, Section 3* (p. 62). OECD Publishing, Paris. https://doi.org/10.1787/9789264070349-en

OECD (Organisation for Economic Co-operation and Development). (1995). *Test No. 105: Water solubility. OECD guidelines for the testing of chemicals, Section 1* (p. 7). OECD Publishing, Paris. https://doi.org/10.1787/9789264069589-en

OECD (Organisation for Economic Co-operation and Development). (2017). *Overview on genetic toxicology TGs. OECD series on testing and assessment, No. 238* (p. 60). OECD Publishing, Paris. https://doi.org/10.1787/9789264274761-en

Oku, T., & Noda, K. (1990a). Erythritol balance study and estimation of metabolizable energy of erythritol. *Proceedings of the International Symposium on Caloric Evaluation of Carbohydrates*, 66–75.

Oku, T., & Noda, K. (1990b). Influence of chronic ingestion of newly developed sweetener, erythritol, on growth and gastrointestinal function of the rat. *Nutrition Research*, *10*(9), 987–996. https://doi.org/10.1016/S0271-5317(05)80040-5

Oku, T., & Okazaki, M. (1996). Laxative threshold of sugar alcohol erythritol in human subjects. *Nutrition Research*, *16*(4), 577–589. https://doi.org/10.1016/0271-5317(96)00036-X

Oku, T., & Sadako, N. (2007). Threshold for transitory diarrhea induced by ingestion of xylitol and lactitol in young male and female adults. *Journal of Nutritional Science and Vitaminology*, *53*(1), 13–20. https://doi.org/10.3177/jnsv.53.13

Ortiz, S. R., & Field, M. S. (2020). Mammalian metabolism of erythritol: A predictive biomarker of metabolic dysfunction. *Current Opinion in Clinical Nutrition and Metabolic Care*, *23*(5), 296–301. https://doi.org/10.1097/mco.0000000000000665

Ortiz, S. R., & Field, M. S. (2021). Chronic dietary erythritol exposure elevates plasma erythritol concentration in mice but does not cause weight gain or modify glucose homeostasis. *The Journal of Nutrition*, *151*(8), 2114–2124. https://doi.org/10.1093/jn/nxab130

Ortiz, S. R., & Field, M. S. (2023). Sucrose intake elevates erythritol in plasma and urine in male mice. *The Journal of Nutrition*, *153*(7), 1889–1902. https://doi.org/10.1016/j.tjnut.2023.05.022

Overduin, J., Collet, T. H., Medic, N., Henning, E., Keogh, J. M., Forsyth, F., Stephenson, C., Kanning, M. W., Ruijschop, R. M., Farooqi, I. S., & van der Klaauw, A. A. (2016). Failure of sucrose replacement with the non-nutritive sweetener erythritol to alter GLP-1 or PYY release or test meal size in lean or obese people. *Appetite*, *107*, 596–603. https://doi.org/10.1016/j.appet.2016.09.009

Pullmann-Lindsley, H., Bartlett-Miller, A., & Pitts, R. J. (2023). Diols and sugar substitutes in attractive toxic sugar baits targeting *Aedes aegypti* and *Aedes albopictus* (Diptera: *Culicidae*) mosquitoes. *Journal of Medical Entomology*, *60*(5), 1022–1029. https://doi.org/10.1093/jme/tjad072

Rebholz, C. M., Yu, B., Zheng, Z., Chang, P., Tin, A., Köttgen, A., Wagenknecht, L. E., Coresh, J., Boerwinkle, E., & Selvin, E. (2018). Serum metabolomic profile of incident diabetes. *Diabetologia*, *61*(5), 1046–1054. https://doi.org/10.1007/s00125-018-4573-7

Sampson, B. J., Marshall, D. A., Smith, B. J., Stringer, S. J., Werle, C. T., Magee, D. J., & Adamczyk, J. J. (2017). Erythritol and lufenuron detrimentally Alter age structure of wild Drosophila suzukii (Diptera: Drosophilidae) populations in blueberry and blackberry. *Journal of Economic Entomology*, *110*(2), 530–534. https://doi.org/10.1093/jee/tow307

Sampson, B. J., Werle, C. T., Stringer, S. J., & Adamczyk, J. J. (2017). Ingestible insecticides for spotted wing drosophila control: A polyol, erythritol, and an insect growth regulator, Lufenuron. *Journal of Applied Entomology*, *141*(1–2), 8–18. https://doi.org/10.1111/jen.12350

SCF (Scientific Committee for Food), (1985). *Reports of the scientific committee for foods 16th series. EU Commission*. https://ec.europa.eu/food/system/files/2020-12/sci-com_scf_reports_16.pdf

SCF (Scientific Committee on Food). (2001). *Guidance on submissions for food additive evaluations by the Scientific Committee on Food. 42 pp*. https://ec.europa.eu/food/fs/sc/scf/out98_en.pdf

SCF (Scientific Committee on Food). (2003). *Opinion of the Scientific Committee on Food on Erythritol*. 25 pp. https://ec.europa.eu/food/fs/sc/scf/out175_en.pdf

Schmidt-Jeffris, R. A., Beers, E. H., Smytheman, P., & Rehfield-Ray, L. (2021). Erythritol, an artificial sweetener, is acaricidal against Pest mites and minimally harmful to a predatory mite. *Journal of Economic Entomology*, *114*(4), 1701–1708. https://doi.org/10.1093/jee/toab101

Seshadrinathan, S., & Chakraborty, S. (2022). Fermentative production of erythritol from cane molasses using *Candida magnoliae*: Media optimization, purification, and characterization. *Sustainability*, *14*(16), 10342–10357. https://doi.org/10.3390/su141610342

Shao, M. M., Xiang, H. J., Lu, H., Yin, P. H., Li, G. W., Wang, Y. M., Chen, L., Chen, Q. G., Zhao, C., Lu, Q., Wu, T., & Ji, G. (2022). Candidate metabolite markers of peripheral neuropathy in Chinese patients with type 2 diabetes. *American Journal of Translational Research*, *14*(8), 5420–5440.

Sharma, A., Reyes, J., Borgmeyer, D., Ayala-Chavez, C., Snow, K., Arshad, F., Nuss, A., & Gulia-Nuss, M. (2020). The sugar substitute erythritol shortens the lifespan of Aedes aegypti potentially by N-linked protein glycosylation. *Scientific Reports*, *10*(1), 6195. https://doi.org/10.1038/s41598-020-63050-3

Shin, D. H., Lee, J. H., Kang, M. S., Kim, T. H., Jeong, S. J., Kim, C. H., Kim, S. S., & Kim, I. J. (2016). Glycemic effects of Rebaudioside a and erythritol in people with glucose intolerance. *Diabetes and Metabolism Journal*, *40*(4), 283–289.

Shindou, T., & Ishizuka, H. (1996). Quantitative determination of erythritol from various natural cheeses by HPLC. *Food Science and Technology International, Tokyo*, *2*(2), 82–83. https://doi.org/10.3136/fsti9596t9798.2.82

Shindou, T., Sasaki, Y., Eguchi, T., Euguchi, T., Hagiwara, K., & Ichikawa, T. (1989). Identification of erythritol by HPLC and GC-MS and quantitative measurement in pulps of various fruits. *Journal of Agricultural and Food Chemistry*, *37*(6), 1474–1476. https://doi.org/10.1021/jf00090a004

Shindou, T., Sasaki, Y., Miki, H., Eguchi, T., Hagiwara, K., & Ichikawa, T. (1988). Determination of erythritol in fermented foods by high performance liquid chromatography. *Food Hygiene and Safety Science*, *29*(6), 419–422. https://doi.org/10.3358/shokueishi.29.419

Shirao, K., Inoue, M., Tokuda, R., Nagao, M., Yamaguchi, M., Okahata, H., & Fujisawa, T. (2013). "bitter sweet": A child case of erythritol-induced anaphylaxis. *Allergology International: Official Journal of the Japanese Society of Allergology*, *62*(2), 269–271. https://doi.org/10.2332/allergolint.12-LE-0517

Shukla, R., Hemansi, K., Gaurav, S., Shraddha, S., Jitendra, K., & Kuhad, R. C. (2023). Biorefinery potential of newly isolated yeast Clavispora lusitaniae for co-production of erythritol and ethanol. *Biomass Conversion and Biorefinery*, *13*, 8061–8073. https://doi.org/10.1007/s13399-021-02073-w

Smits-van Prooije, A. E., Waalkens-Berendsen, D. H., & Bär, A. (1996). Embryotoxicity and teratogenicity study with erythritol in rats. *Regulatory Toxicology and Pharmacology*, *24*(2), S232–S236. https://doi.org/10.1006/rtph.1996.0103

Sreenath, K., & Venkatesh, Y. P. (2008). Analysis of erythritol in foods by polyclonal antibody-based indirect competitive ELISA. *Analytical and Bioanalytical Chemistry*, *391*(2), 609–615. https://doi.org/10.1007/s00216-008-2016-x

Storey, D., Lee, A., Bornet, F., & Brouns, F. (2007). Gastrointestinal tolerance of erythritol and xylitol ingested in a liquid. *European Journal of Clinical Nutrition*, *61*(3), 349–354. https://doi.org/10.1038/sj.ejcn.1602532

Sugiura, S., Kondo, Y., Ito, K., Hashiguchi, A., Takeuchi, M., & Koyama, N. (2013). A case of anaphylaxis to erythritol diagnosed by CD203c expression-based basophil activation test. *Annals of Allergy, Asthma and Immunology*, *111*(3), 222–223. https://doi.org/10.1016/j.anai.2013.06.007

Tang, S. B., Lee, J. C., Jung, J. K., & Choi, M. Y. (2017). Effect of erythritol formulation on the mortality, fecundity, and physiological excretion in Drosophila suzukii. *Journal of Insect Physiology*, *101*, 178–184. https://doi.org/10.1016/j.jinsphys.2017.07.015

Tetzloff, W., Dauchy, F., Medimagh, S., Carr, D., & Bär, A. (1996). Tolerance to subchronic, high-dose ingestion of erythritol in human volunteers. *Regulatory Toxicology and Pharmacology*, *24*(2), 286–295. https://doi.org/10.1006/rtph.1996.0110

Teysseire, F., Bordier, V., Budzinska, A., Van Oudenhove, L., Weltens, N., Beglinger, C., Wölnerhanssen, B. K., & Meyer-Gerspach, A. C. (2023). Metabolic effects and safety aspects of acute D-allulose and erythritol Administration in Healthy Subjects. *Nutrients*, *15*(2), 1228–1238. https://doi.org/10.1093/jn/nxac026

Til, H. P., Kuper, C. F., Falke, H. E., & Bär, A. (1996). Subchronic Oral toxicity studies with erythritol in mice and rats. *Regulatory Toxicology and Pharmacology*, *24*(2 Pt 2), 221–231. https://doi.org/10.1006/rtph.1996.0102

Til, H. P., & Modderman, J. (1996). Four-week Oral toxicity study with erythritol in rats. *Regulatory Toxicology and Pharmacology*, *24*(2 Pt 2), 214–220. https://doi.org/10.1006/rtph.1996.0101

Van Ommen, B., de Bie, B., & Bär, A. (1996). Disposition of 14C-erythritol in germfree and conventional rats. *Regulatory Toxicology and Pharmacology*, *24*(2 Pt 2), 198–205. https://doi.org/10.1006/rtph.1996.0099

Van Wijck, K., van Eijk, H. M. H., Buurman, W. A., Dejong, C. H. C., & Lenaerts, K. (2011). Novel analytical approach to a multi-sugar whole gut permeability assay. *Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences*, *879*(26), 2794–2801. https://doi.org/10.1016/j.jchromb.2011.08.002

Waalkens-Berendsen, D. H., Smits-van Prooije, A. E., Wijnands, M. V. M., & Bär, A. (1996). Two-generation reproduction study of erythritol in rats. *Regulatory Toxicology and Pharmacology*, *24*(2), S237–S246. https://doi.org/10.1006/rtph.1996.0104

Wang, Z., Zhu, C., Nambi, V., Morrison, A. C., Folsom, A. R., Ballantyne, C. M., Boerwinkle, E., & Yu, B. (2019). Metabolomic pattern predicts incident coronary heart disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *39*(7), 1475–1482. https://doi.org/10.1161/atvbaha.118.312236

Wen, H., Tang, B., Stewart, A. J., Tao, Y., Shao, Y., Cui, Y., Yue, H., Pei, J., Liu, Z., Mei, L., Yu, R., & Jiang, L. (2018). Erythritol attenuates postprandial blood glucose by inhibiting α-glucosidase. *Journal of Agricultural and Food Chemistry*, *66*(6), 1401–1407. https://doi.org/10.1021/acs.jafc.7b05033

Wentz, K., Cooper, W. R., Horton, D. R., Kao, R., & Nottingham, L. B. (2020). The artificial sweetener, erythritol, has insecticidal properties against pear psylla (Hemiptera: Psyllidae). *Journal of Economic Entomology*, *113*(5), 2293–2299. https://doi.org/10.1093/jee/toaa124

WHO (World Health Organization). (1987). Principles for the safety assessment of food additives and contaminants in foods. In *Environmental health criteria 70. IPCS international Programme on chemical safety in cooperation with the joint FAO/WHO expert committee on food additives (JECFA). World Health Organization, Geneva*. ISBN 92 4 154270 5. https://apps.who.int/iris/bitstream/handle/10665/37578/9241542705-eng.pdf?sequence=1&isAllowed=y

Witkowski, M., Nemet, I., Alamri, H., Wilcox, J., Gupta, N., Nimer, N., Haghikia, A., Li, X. S., Wu, Y., Saha, P. P., Demuth, I., König, M., Steinhagen-Thiessen, E., Cajka, T., Fiehn, O., Landmesser, U., Tang, W. H. W., & Hazen, S. L. (2023). The artificial sweetener erythritol and cardiovascular event risk. *Nature Medicine*, *29*(3), 710–718. https://doi.org/10.1038/s41591-023-02223-9

Wölnerhanssen, B. K., Cajacob, L., Keller, N., Doody, A., Drewe, J., Rehfeld, J. F., Peterli, R., Beglinger, C., & Meyer-Gerspach, A. C. (2016). Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects. *American Journal of Physiology-Endocrinology and Metabolism*, *310*(11), 1053–1061. https://doi.org/10.1152/ajpendo.00037.2016

Wölnerhanssen, B. K., Drewe, J., Verbeure, W., le Roux, C. W., Dellatorre-Teixeira, L., Rehfeld, J. F., Holst, J. J., Hartmann, B., Tack, J., Peterli, R., Beglinger, C., & Meyer-Gerspach, A. C. (2021). Gastric emptying of solutions containing the natural sweetener erythritol and effects on gut hormone secretion in humans: A pilot dose-ranging study. *Diabetes Obesity Metabolism*, *23*(6), 1311–1321. https://doi.org/10.1111/dom.14342

Zhang, X., Chen, S., Li, Z., & Xu, Y. (2017). Effect of sweeteners on the survival of Solenopsis invicta (Hymenoptera: Formicidae). *Journal of Economic Entomology*, *110*(2), 593–597. https://doi.org/10.1093/jee/tox038

Zheng, C., Zeng, L., & Xu, Y. (2016). Effect of sweeteners on the survival and behavior of Bactrocera dorsalis (Hendel) (Diptera: Tephritidae). *Pest Management Science*, *72*(5), 990–996. https://doi.org/10.1002/ps.4079

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APPENDIX A

Tailored protocol and its implementation for the assessment of hazard identification and characterisation of erythritol (E 968)

Please refer to steps **1.11–1.15** of the revised protocol for hazard identification and characterisation of sweeteners.[9]

Extensive literature search

Methodology

For step **1.11**, open-ended literature searches were conducted in the three selected databases with the search strings and criteria applied as follow:

1. **Web of Science**: TOPIC: (erythritol OR E968 OR "E 968" OR "149–32-6") AND LANGUAGE: (English) Timespan: 2002–2023.[27] Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.
2. **Pubmed**: ((erythritol OR E968) AND (("2002"[Date - Publication]: "2023[27]"[Date - Publication]))) AND ("english"[Language])
3. **SciFinder**: Substance Identifier "149–32-6 ">substances (1) > get references (12851) > refine "2002–2023[27]" (9718) > refine "English" (5158) > refine "Clinical Trial Journal Preprin..."

Additional data were submitted by the I through the call for biological and toxicological data on sweeteners and through an application dossier (see Section 2.1).

Results

The final number of references that were screened, after removal of duplicates (based on title, year, author, journal, volume, issue and page numbers) was 5190.

For step **1.11.1** (Screening of the studies for relevance), the general principles reported in the protocol applied. 527 papers were included at the level of title and abstract screening, whereas 4662 papers were excluded. From the 527 papers included for the full text screening, 114 were considered as possibly relevant, whereas 413 were either excluded at the level of full text screening, or preliminarily categorised into technical data (227), exposure data (25), environmental data (49) or toxicological review (25), and further screened for confirmation of their relevance (see Figure A1).

[27]Until September 2023.

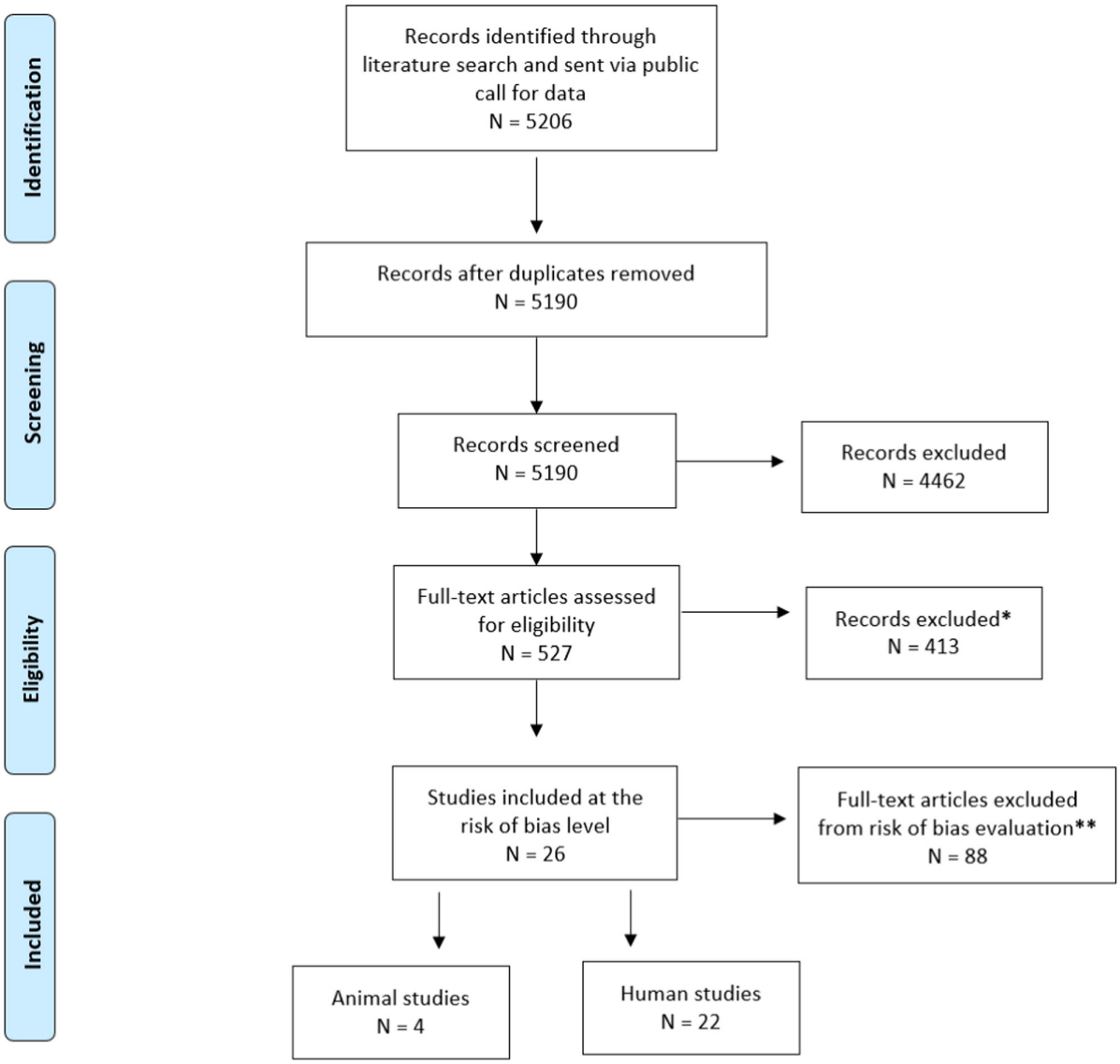

FIGURE A1 PRISMA flow chart (adapted from Moher et al., 2009).

Evaluation of the risk of bias (RoB)

Methodology

For step 1.12, the criteria outlined in the revised protocol for the risk of bias evaluation of studies have been applied (NTP-OHAT, 2019), including the rules for tier allocation.

The studies evaluated for the RoB were allocated to a tier (from 1 to 3 corresponding to decreasing levels of internal validity11) based on the rules as reported in step 1.12 of the revised protocol.

The evaluation of the RoB was conducted in parallel independently by two reviewers and, in case a conflict on tier allocation of a study was identified, *ad hoc* discussion between the reviewers took place prior to a final agreed tier allocation that was reached by consensus.

The tier was automatically generated by the DistillerSR tool, after input of the ratings for the individual elements of the study considered for the RoB. At the end of the evaluation, the reviewers were requested to express their agreement or disagreement on the tier generated by the tool based on their expert judgement. In case of disagreement, a clear justification should have been provided.

As prescribed by the revised protocol, studies on which the derivation of the ADI was based or studies used for identification of a NOAEL/no observed effect level (NOEL) (in case of ADI not specified) were included and evaluated according to the protocol together with any relevant literature published since the previous evaluation by the SCF, allowing 1 year of overlap. If studies that were previously considered as critical were evaluated as having moderate or low RoB, other

non-critical studies from previous assessments, including those received by the interested business operators, would not have to be re-evaluated and subjected to the different steps of the protocol (e.g. RoB, WoE).

Results

In the case of erythritol (E 968), the studies on which the conclusions for no numerical ADI were based were human studies. These studies were subjected to the RoB evaluation and the results are shown in Table A1. No disagreements with the tier generated by the tool were identified (see last two columns on the right of Table A1).

TABLE A1 Results of the RoB evaluation of human studies previously considered (EFSA ANS Panel, 2010; SCF, 2003).

RefID[a]	Authors (year)	Study type	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Confidence in exposure to the interventions (detection bias)	Confidence in outcome assessment (detection bias)	Selective reporting (reporting bias)	Appropriateness of statistical methods (other source of bias)	Tier (based on rules)	Tier (agreement with expert judgement)
4301	Nikken Chemicals Co. Ltd. (1992a)[b] (Documentation provided to EFSA No. 6)	HCT	−	+	+	+	++	+	+	−	2	Yes
					−			++				
4300	Nikken Chemicals Co. Ltd. (1992b)[c] (Documentation provided to EFSA No. 6)	HCT	−	+	+	++	+	+	+	+	3	Yes
			+		−−	+	++			−		
4302	Mitsubishi Kasei Corporation (1992)[d] (Documentation provided to EFSA No. 6)	HCT	−	−	−	+	+	+	+	−	2	Yes
						++						
4297	Yokohama-shi Seibu Hospital (1992)[e] (Documentation provided to EFSA No. 6)	HCT	−−	+	+	+	+	+	+	+	3	Yes
				−	−	+			++	−−		
4299	Yokohama-shi Seibu Hospital (1993)[f] (Documentation provided to EFSA No. 6)	HCT	−−	+	+	−−	+	+	+	−	3	Yes
				−	−			−	++			
3808	Noda et al. (1994)	HCT	−−	+	−	+	+	+	+	+	3	Yes
						++	++	++	++	++		
3810	Bornet et al. (1996a)	HCT	−	+	+	+	+	−	+	+	3	Yes
			−−	−−	−−	++	++	++	++	−		
3793	Bornet et al. (1996b)	HCT	+	−	−	++	++	++	++	++	2	Yes
						+	+			+		
3788	Oku & Okazaki (1996)	HCT	−	+	−	+	++	+	+	+	2	Yes
						++			++	−		
3789	Tetzloff et al. (1996)	HCT	−	+	++	++	+	++	++	++	2	Yes
					+		++					
759	Storey et al. (2007)	HCT	++	+	+	+	++	+	+	+	1	Yes
						++		++	++			
4298	Biofortis (2010)[g] (Documentation provided to EFSA No. 6, 12)	HCT	++	++	++	+	−	+	++	+	2	Yes
				+					+			

(Continues)

TABLE A1 (Continued)

Abbreviation: HCT, human controlled trial.

Notes: Definitely low risk of bias (++), Probably low risk of bias (+), Probably high risk of bias (–), Definitely high risk of bias (––). Split cells reporting two different scorings for the same risk of bias question express the view of the two independent reviewers.

[a]Numerical identifier generated by the DistillerSR tool.

[b]This unpublished study report is referred as Takahashi C, 1992a in SCF, 2003.

[c]This unpublished study report is referred as Takahashi C, 1992b in SCF, 2003.

[d]This unpublished study report is referred as Umeki, 1992 in SCF, 2003.

[e]This unpublished study report is referred as Ishikawa M, Hirose C, Tsujino D, Miyashita M, Kawashima Y and Nakamura T, 1992 in SCF, 2003.

[f]This unpublished study report is referred as Miyashita M, Kawashina Y and Nakamura T, 1993 in SCF, 2003.

[g]This unpublished study report was subsequently published in Jacqz-Aigrain et al., 2015.

After having evaluated the critical studies, the Panel agreed to further considered the whole body of evidence in the current assessment, regardless the outcome of the RoB. The reason why was that only few new reliable studies (see Table A2) were available for the assessment. Nevertheless, the Panel did not consider necessary to re-evaluate other non-critical studies i.e. repeated-dose toxicity studies in animals previously considered by the SCF in 2003 and received by the IBOs through the call for data. These studies were not considered further in the assessment but a narrative synthesis of the previous evaluation was reported in the opinion (see Section 3.5.3).

Relevant studies retrieved from the literature, either in humans or in animals, were also considered and evaluated for the RoB. The results of these studies are shown in Tables A2 and A3. Disagreements with the tier generated by the tool were identified by the reviewers and the tier was adjusted based on expert judgement, including the reasoning behind (see last two columns on the right of Table A2).

TABLE A2 Results of the RoB evaluation of human studies retrieved from the literature.

RefID	Authors (year)	Study type	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Confidence in exposure to the interventions (detection bias)	Confidence in outcome assessment (detection bias)	Selective reporting (reporting bias)	Appropriateness of statistical methods (other source of bias)	Tier (based on rules)	Tier (agreement with expert judgement)	Tier based on expert judgement and reasoning for disagreement
595	Oku and Sadako (2007)	HCT	--	+	+	+	+	+	+	–	3	Yes	
				–	–		++	++	++	++			
1242	Kim et al. (2011)	HCT	+	+	+	+	+	++	+	+	1	Yes	
			++	++	++			+	++				
1882	Flint et al. (2014)	HCT	--	–	–	+	+	+	+	+	3	Yes	
				--	--	++	++	++	++	++			
3756	Overduin et al. (2016)	HCT	+	++	+	+	+	+	+	+	1	Yes	
			++	+	++	++	++	++	++	++			
3759	Wölnerhanssen et al. (2016)	HCT	++	++	++	++	++	++	++	++	1	Yes	
				+	–								
3850	Wölnerhanssen et al. (2021)	HCT	+	+	+	–	+	+	+	+	2	Yes	
					++	+	++		++		1	No	2 Missing results and only 7 subjects in the placebo group
3859	Meyer-Gerspach et al. (2021)	HCT	+	+	+	+	+	+	+	+	1	Yes	
			++		++	++	++	++					
3946	Bordier et al. (2021)	HCT	–	--	–	+	+	+	+	+	3	Yes	
			+	–	+	+	+	++	++	–	2	No	3 No double-blind in the control group

TABLE A2 (Continued)

RefID	Authors (year)	Study type	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Confidence in exposure to the interventions (detection bias)	Confidence in outcome assessment (detection bias)	Selective reporting (reporting bias)	Appropriateness of statistical methods (other source of bias)	Tier (based on rules)	Tier (agreement with expert judgement)	Tier based on expert judgement and reasoning for disagreement
4355	Teysseire et al. (2022)	HCT	+	+	+ ++	– +	+ ++	– +	+	+ ++	3 1	No No	2 Drop-out is a borderline issue Missing results regarding glycaemic control
5111	Teysseire et al. (2023)	HCT	+	+	+ ++	+ +	+ ++	+ ++	+ ++	+ ++	1	Yes	

Notes: Definitely low risk of bias (++), Probably low risk of bias (+), Probably high risk of bias (–), Definitely high risk of bias (––). Split cells reporting two different scorings for the same risk of bias question express the view of the two independent reviewers.

TABLE A3 Results of the RoB evaluation of animal studies retrieved from the literature.

RefID	Authors (year)	Study type	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Experimental conditions (performance bias)	Blinding of research personnel (performance bias)	Incomplete outcome data (attrition bias)	Confidence in exposure characterisation (detection bias)	Confidence in outcome assessment (detection bias)	Selective reporting (reporting bias)	Appropriateness of statistical methods (other source of bias)	Tier (based on rules)	Tier (agreement with expert judgement)
372	Juskiewicz et al. (2004)	Short-term toxicity	–	+ +	+ ++	–	++ –	+ --	– +	+ ++	+ ++	3	Yes
1015	Chung et al. (2012)	Short-term toxicity	–	+ _[a]	+ –	+ _[a]	++ +	–	– ++	++	– ++	3	Yes
1852	Dong et al. (2015)	Short-term toxicity	–	+	+	+	–	– +	– –	++	+ ++	3	Yes
3488	Lee et al. (2020)	Sub-chronic toxicity	+	+[b]	+ ++	+	+ –	+	+	++ +	--	3	Yes

Notes: Definitely low risk of bias (++), Probably low risk of bias (+), Probably high risk of bias (–), Definitely high risk of bias (––). Split cells reporting two different scorings for the same risk of bias question express the view of the two independent reviewers.

[a]This question was cloned for some endpoints (total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL), liver histopathology) and scored as of probably low risk of bias (+). The tier allocation for this study, related to this specific endpoint, was also tier 3.

[b]This question was cloned for some endpoints (intraperitoneal glucose tolerance test, adipose tissue weight) and scored, by one reviewer, as of definitely high risk of bias (––). The tier allocation for this study, related to this specific endpoint, was also tier 3.

Eight human studies were evaluated as having moderate or low risk of bias and therefore considered further in the assessment, while those having a high RoB were not included. All relevant animal studies retrieved from the literature were considered of high RoB and therefore not included in the assessment.

Data extraction

Methodology

For step **1.13**, information and data from the assessed human studies as well as from the included genotoxicity studies were extracted and reported in tabular form. The data extraction forms outlined in the revised protocol were used.

Results

The data extraction forms of the studies are reported in Appendices D and E of the current opinion.

Weighing the body of evidence and synthesis of the evidence

Methodology

For step **1.14** (Weighing the body of evidence), a WoE analysis for different health outcome categories, grouped by endpoint as appropriate, was performed on the considered human studies. The WoE analysis was performed using Excel tables. The detailed methodology is reported in the revised protocol.

Results

The result of the WoE analysis for erythritol is presented in Annex C and summarised in Section 3.5.4.2 on 'Synthesis of systematically appraised evidence'.

APPENDIX B

Exposure calculation to lead (Pb) from the use of erythritol (E 968) as a food additive

One IBO provided results for the analysis of lead (Pb) by Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) in 24 samples (different batches) of erythritol. 22 of the 24 samples were below the LOQ of 0.24 mg/kg. Two batches had quantifiable concentrations, at 0.28 and 0.33 mg/kg (Documentation provided to EFSA No. 7).

The other IBO submitted data for 12 batches of E 968 analysed by inductively coupled plasma-mass spectrometry (ICP–MS). The level of lead (Pb) for all batches was below the LOQ of 0.05 mg/kg Documentation provided to EFSA No. 8).

Additionally, the IBO submitted results for three samples of E 968 tested for additional elements. The methods used were; for nickel (ICP–MS or ICP–OES); for lead (Pb), cadmium (Cd), arsenic (Ar) and mercury (Hg) (ICP–MS or AAS). In all analysed samples the concentration of the above-mentioned elements was below the LOQs (i.e. for Ni: ICP-OES < 0.1 mg/kg and ICP-MS < 0.1 mg/kg; for Pb: ICP-MS < 0.05 mg/kg and AAS < 0.5 mg/kg; for Cd: ICP-MS < 0.01 mg/kg and AAS < 0.1 mg/kg; for As: ICP-MS < 0.1 mg/kg and AAS < 0.5 mg/kg; for Hg ICP-MS < 0.005 mg/kg and AAS < 0.01 mg/kg) (Documentation provided to EFSA No. 2). The Panel noted that the number of analysed samples for these additional toxic elements is low. However, considering the manufacturing process, the presence of these impurities in erythritol is unlikely. Therefore, the Panel considered that there is no need for additional limits for other toxic elements apart from lead (Pb) in the EU specifications for E968.

The Panel noted that no information on the lowest technologically achievable levels for lead (Pb) in E 968 was provided by neither of the two IBOs.

The potential exposure to lead (Pb) from the use of erythritol (E 968) can be calculated by assuming that the impurity is present in the food additive up to a certain limit value, and then by calculation pro-rata to the estimates of exposure to the food additive itself.

With regard to the dietary exposure to E 968, the Panel considered the refined brand-loyal exposure assessment scenario (Table 5). For the current assessment, the highest exposure levels for the mean and 95th percentile among the different population groups were considered, i.e. 742 and 1532 mg/kg bw per day, for toddler and children, respectively.

The level of lead (Pb) in the food additive combined with the estimated intakes of E 968, presented in Table 5, could result in an exposure which can be compared with the reference point for lead (Pb) (Table B1).

TABLE B1 Reference point for lead (Pb).

Element/RP	Basis/reference
Lead (Pb) 0.5 µg/kg bw per day ($BMDL_{01}$)	The reference point is based on a study demonstrating perturbation of intellectual development in children with the critical response size of 1 point reduction in IQ. The EFSA CONTAM Panel mentioned that a 1 point reduction in IQ is related to a 4.5% increase in the risk of failure to graduate from high school and that a 1 point reduction in IQ in children can be associated with a decrease of later productivity of about 2%. A risk cannot be excluded if the exposure exceeds the $BMDL_{01}$ (MOE lower than 1) (EFSA CONTAM Panel, 2010)

The risk assessment of lead (Pb) helps determine whether there could be a possible health concern if it would be present at the limit value in the food additive. The assessment is performed by calculating the MOE by dividing the reference point (BMDL Table B1) by the exposure estimate (Table 5).

The IBOs provided analytical data on the levels of lead (Pb), in commercial batches of erythritol (E 968) (see Section 3.1.1). No proposal for the lowest achievable levels for lead (Pb) in E 968 was provided by neither of the two IBOs. Concentration data were reported in some samples up to 0.33 mg/kg (LOQ 0.24 mg/kg), corresponding to 66% of the limit in the EU specifications. The Panel noted the differences in the two sets of data submitted by the IBOs. In one set, levels were measured up to 0.33 mg/kg with a LOQ 0.24 mg/kg, and in the other data submission, all results were reported below the LOQ of 0.05 mg/kg.

The Panel performed the risk assessment that would result if lead (Pb)was present in E 968 at (i) the current limit in the EU specification and (ii) the lowest reported LOQ modulated by the Panel by applying a factor of 5, to account for uncertainty in representativeness, homogeneity and analytical measurement. The outcome of the risk assessment is presented in Table B2.

The Panel emphasises that the choice of the factor, as well as other considerations such as on multiple sources of exposure, to conclude on the maximum limit for lead (Pb) in the specifications is in the remit of risk management. The numbers used here are merely taken to support the risk assessment of these toxic element as presented below.

TABLE B2 Risk assessment for lead (Pb).

Exposure to E 968 (mg/kg bw per day)	MOE for Pb at (i) considering the presence of lead (Pb) at the current limit in the EU specifications for E 968 (Commission Regulation (EU) No 231/2012) (0.5 mg/kg)
742[a]	1.3
1532[b]	0.6
	MOE for Pb at (ii) considering the presence of lead (Pb) at the lowest reported LOQ by applying a factor of 5 (0.25 mg/kg)
742[a]	2.7
1532[b]	1.3

[a]Highest exposure level among the different population groups (refined brand-loyal scenario – toddlers – mean (Table 5).

[b]Highest exposure level among the different population groups (refined brand-loyal scenario – children – 95th percentile (Table 5).

APPENDIX C

ADME studies

Studies on ADME already considered and evaluated in SCF, 2003

Human

Healthy male volunteers were given 0.159 g/kg bw (10 g per person) and 0.336 g/kg bw (20 g per person) erythritol by oral administration. Four volunteers received both doses and for each dose an additional volunteer took part so that the total number was five volunteers per doses (age 53.8 ± 3.1 and 50.4 ± 3.0 respectively). Urine was sampled in intervals (0–3 h, 3–8 h, 8–24 h and for the 20 g dose 24–48 h). The concentration of erythritol was measured by GC (reference for the method is given, but not available). Cumulative urinary excretion was 41.0 ± 2.1%, 66.9 ± 2.2% and 91.8 ± 2.1% of the dose up to 3 h, up to 8 h and up to 24 h in the 10 g group, and 39.0 ± 3.6%, 66.1 ± 5.1%, 86.7 ± 3.9% of the dose up to 3 h, up to 8 h, up to 24 h and 90.5 ± 3.8% up to 48 h in the 20 g group. In summary, in humans erythritol is absorbed to at last 90% and rapidly excreted, mainly in the urine as the parent compound. The half-life of excretion can be estimated as about 4 h (Nikken Chemicals Co., Ltd, 1988 in Documentation provided to EFSA No. 6).

Oku and Noda (1990a) stated that erythritol is naturally present in urine in people unexposed to food containing erythritol as a food additive. They examined the urine collected from six adult males (age range 20–23 years), three boys (age range 11–15 years) and an adult female (39 years old) and determined mean and standard error urinary erythritol excretion rates of 118 ± 10, 98 ± 22 and 75 mg/day respectively. Six fasted healthy non-medicated volunteers (age range: 44–58 years old; bw range 55–71 kg) were also orally administered 50 mL (10 g, approximately 0.17g/kg bw) or on a separate occasion, 100 mL (20 g, approximately 0.34 g/kg bw) of a 20% w/v erythritol solution at 9.00 am. Subjects were subsequently allowed lunch and dinner but no alcohol. Individuals' pooled urine was collected 24 and 48 h after erythritol administration. At both dose levels, about 40% and more than 70% of ingested erythritol was excreted into urine within 3 and 8 h, respectively. Total urinary excretion of erythritol was 92% after 24 h for those administered 10 g of erythritol and 91% after 48 h for those administered 20 g. It was also reported that when approximately 0.3 g of erythritol per kg bw was orally administered to male human subjects, the decrease in serum concentrations of erythritol closely corresponded to the increase of urinary erythritol and that the half-life of erythritol in blood was 3.4 h. No further information is provided.

Five non-insulin dependent diabetes mellitus (NIDDM) hospitalised patients (mean age 52.4 years), only on dietary therapy, received orally 20 g erythritol dissolved in water in fasting state and were allowed to eat 3 h following ingestion. Venous blood was taken in intervals, before and 0.5, 1., 1.5, 2, 3, 4, 6, 8 and 24 h, and urine was collected before and 0–24, 24–48 and 48–72 h, following ingestion, respectively. Erythritol concentration was measured by GC (no further details given). Peak concentration in blood was reached 1 h following ingestion and a rapid decline was observed. The mean urinary excretion of erythritol was 82 (SE 3.7) %, 87.8 (SE 3.3) % and 88.5 (SE 3.3) % after 24, 48 and 72 h, respectively (Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Department of Metabolic Endocrinology and Department of Nutrition, 1992 in Documentation provided to EFSA No. 6, subsequently published in Ishikawa et al., 1996).

Six healthy volunteers (4 males, 2 females, aged 21–25 years) ingested 25 g ^{13}C-glucose, ^{13}C-lactitol and ^{13}C- erythritol, respectively, in a random order, at least 3 days apart. Breath samples were taken for analysis of ^{13}CO2 and H^2 before and every 30 min until 6 h following ingestion. Urine was collected from 0 to 6 h and from 6 to 24 h. To maintain the basic metabolic rate constant the volunteers rested for the duration of the test. Whereas the $^{13}CO_2$ breath concentration increased following ^{13}C-glucose and ^{13}C-lactitol ingestion $^{13}CO_2$ breath concentration did not increase following ^{13}C- erythritol ingestion. From 2 to 6 h the H_2 breath excretion was increased compared to baseline following ingestion of lactitol, however not following ingestion of glucose and erythritol. After 6 h 52.2 (SE 2.5) % and after 24 h 84.1 (SE 3.3) % of the erythritol dose, respectively, were excreted in the urine. Faecal samples from the six healthy volunteers were incubated with glucose, lactitol and erythritol for 6 h, under anaerobic conditions and H_2 production was measured by means of the GM1 H2-monitor. The amount of H_2 formed within 6 h was not higher than in the control when incubation was done with erythritol and was significantly higher with glucose and lactitol. The results of the in vivo and the *in vitro* experiments indicate that glucose and lactitol, however not erythritol is metabolised endogenously or by the microbiome in humans (Hiele et al., 1993).

In a study with the primary aim to investigate the effect of an oral administration of erythritol on serum glucose and insulin levels in healthy subjects and estimate available energy of erythritol in human kinetic data on erythritol were obtained. Five healthy volunteers received 0.3 g/kg bw erythritol (average dose 17.3 g per subject) by oral administration. Blood was taken before and 0.5, 1, 2, 3, 8 and 24 h following administration and urine was sampled in intervals (0.3, 3.8, 8–24, 24–48 h following administration). Erythritol concentrations were measured by flame ionisation detection using gas chromatographic separation after derivatisation with acetic anhydride. The maximum plasma concentration (426.5 ± 113.4 µg/mL) was reached at 30 min after oral administration. The plasma concentration declined with a half-life of 3.4 h. The results indicated quick absorption and fast elimination. The urinary excretion was as the intact erythritol. The cumulative urinary excretion (0–48 h) was 90.3 ± 4.5% of the dose, indicating nearly complete absorption (Noda et al., 1994).

Twenty-four human volunteers (12 males, 12 females; 20 to 46 years old) were randomly allocated to 4 groups which were administered a snack containing 0.4 g erythritol/kg bw (E4 group), 0.8 g erythritol/kg bw (E8 group) or 0.8 g sucrose/kg bw, whereas the fourth group did not receive a snack (negative control group). Venous blood was taken before and hourly until 8 h following ingestion. Urine was sampled in 2 h intervals until 8 h and then from 8 until 22 h following ingestion.

Determination of erythritol was performed by HPLC with a Differential Refractive Index Detector R401 (Millipore Corp., Milford, MA) after separation on a Shodex Ionpack Column KC811 (8 × 300 mm). From the figure given in the publication the peak plasma concentration was about 340 mg/L and 635 mg/L following 0.4 g/kg and 0.8 g/kg, respectively. The urinary excretion is given in the text as 60% whereas the urinary excretion given in figure 5 indicated that 120 g and 270 g, respectively, were excreted in the urine following the indicated doses of 0.4 and 0.8 g/kg bw with 67 kg and 69 kg as the mean body weight of the subjects in the two groups indicating some error in the data. The results of this publication cannot be used for the assessment of the kinetics of erythritol (Bornet et al., 1996b).

Six human volunteers (three males, three females) received 1 g/kg bw erythritol in 250 mg water by oral administration in fasting state. Blood was taken before and at short intervals after ingestion for up to 3 h. Urine was collected in short intervals until 3 h and thereafter until 24 h following ingestion. Determination of erythritol was performed by HPLC with a Differential Refractive Index Detector R401 (Millipore Corp., Milford, MA) after separation on a Shodex Ionpack Column KC811 (8 × 300 mm) using 1,3-butanediol as internal standard. From the figure given in the publication, the peak plasma concentration was about 2200 mg/L following 1 g/kg bw. Urinary excretion amounted to 78 ± 2 (SEM) % of the dose indicating high absorption. Renal clearance of erythritol was calculated from the urinary erythritol excretion between 120 and 180 min and the mean plasma erythritol concentration during this period and amounted to 62.03 mg/min, according to the authors. As the dimension of clearance is volume per time period, the dimension is inaccurate and should be 62.03 mL/min indicating renal reabsorption of erythritol (Bornet et al., 1996a).

The study was performed as a tolerance study in 12 healthy volunteers who in a double-blind. randomised two-way crossover design received erythritol and sucrose by oral administration, each for 1 week. The daily dose was 0.3 g/kg on day 1, 0.6 g/kg bw on day 2 and thereafter 1 g/kg bw, which was divided over the time from 8 AM to 7 PM into five dosing. Urine was sampled in intervals of 3 h between 7 AM and 10 PM and thereafter from 10 PM until 1 AM the next day. Determination of erythritol was performed by HPLC with a Differential Refractive Index Detector R401 (Millipore Corp., Milford, MA) after separation on a Shodex Ionpack Column KC811 (8 × 300 mm) using 1,3-butanediol as internal standard. The authors stated that the urinary excretion was 78% of the dose on the average with a range of 61 to 88% (Tetzloff et al., 1996).

Fourteen children received a dose of 5 g, 57 a dose of 15 g, 55 a dose of 20 g and 56 a dose of 25 g (Biofortis, 2010 in Documentation provided to EFSA No. 6, 12, subsequently published in Jacqz-Aigrain et al., 2015). Urine was collected at home for 24 h after consumption of the test drink. The concentration of erythritol in the urine was analysed by HPLC for erythritol. The amount of erythritol was calculated by multiplying the concentration with the volume off urine excreted within 4 h following ingestion. The percentage of the dose was calculated by dividing the amount excreted during the first 24 h by the dose ingested. The excretion in the urine amounted to 34.8% of the dose for the group with 5 g, 24.8% in the group with 15 g, 18.1% in the group with 20 g and 24.4% in the group with 25 g. No dose-dependency is noted. The low percentage of urinary excretion is remarkable. In studies in adults the urinary excretion is much higher (see above). No information is given in the report on the volume of the urine which was collected. Thus, it is unclear whether the urine could be completely collected in this group of children. The report did not give an explanation.

The aim of the study was to look at the *in vitro* fermentation of erythritol and other sugars by a complex human faecal flora as a model of human colonic fermentation. Total gas, hydrogen and methane gas as well as short chain fatty acids and carbohydrates were measured. With erythritol, gas production was very low (termed 'neglectible' by the authors) as was also hydrogen and methane production. No short chain fatty acids were formed from erythritol and the substance was fully recovered after terminating the incubation. The results of other sugars, for example Actilight, Malbit and Polydextrose, confirmed the ability of the *in vitro* system to metabolise sugars. The study showed that erythritol is not fermented in an *in vitro* human faecal flora model (INRA, 1992 in Documentation provided to EFSA No. 1).

Mice

Four groups of Swiss-outbred (CD-1) mice ($n = 3$) per sex (approximately 4–5 weeks old) were fed diets containing erythritol at levels of 0 (control), 5%, 10% or 20% (equal to 0, 6351, 12,702, 33,939 mg/kg bw per day and 0, 5938, 14333, 33793 mg/kg bw per day in males and females, respectively) for a period of 13 weeks. At week 10 for males and in week 11 for females, mice were placed in metabolic cages for separate collection of urine and faeces over a 48-h period. Erythritol in urine as well as in faeces were determined (by a contractor) but no further details are provided. On average, 95% and 75% of the ingested erythritol was excreted unchanged in the urine in males and females respectively, with 5% in the faeces. The authors assumed that the remaining part was fermented by the intestinal flora (TNO-CIVO Industries, 1992 in Documentation provided to EFSA No. 6, subsequently published in Til et al., 1996).

Rats

Male Wistar rats (8 weeks of age), in fasted state, ($n = 3$) were administered – an oral dose of 1 g/kg bw of [^{14}C] erythritol in distilled water. Rats were then housed individually in metabolic cages, with urine and faeces separately collected for up to 120 h. $^{14}C\text{-}CO_2$ was measured in the expired air. Animals remained fasted for 8 h subsequent to erythritol administration. In further animals ($n = 3$) bile was collected for up to 48 h via bile duct cannulation. 75% of the radioactivity was excreted in the urine until 8 h and 92% until 24 h following administration. Around 4% and 4.8% of the radioactivity was excreted as CO_2 in expired air after 24 and 120 h. Biliary excretion was 0.74% of radioactivity by 48 h. About 1% of radioactivity was

found in the faeces by 120 h. After 120 h, 0.65% of the administered radioactivity remained in the carcass (Nikken Chemicals Co., Ltd, 1990b in Documentation provided to EFSA No. 6, subsequently published in Noda et al., 1996).

Male Wistar rats (8 weeks of age), in fasted state ($n = 3$) were administered an oral dose of 1 g/kg bw of [^{14}C] erythritol in distilled water. Animals were remained fasted for 8 h subsequent to erythritol administration. Blood was sampled up to 24 h after administration and radioactivity was measured in plasma. At termination animals were exsanguinated and organs and tissues removed for analysis. Total body radioactivity was determined in animal carcasses after removal of organs. Three animals were subjected to whole-body autoradiography. The concentration of radioactivity decreased in most tissues and organs in parallel with the decrease in plasma. The whole-body autoradiograms at 24 h indicated that only the Harderian gland, the liver, the cecum and the large intestine showed a low concentration of the radioactivity (Nikken Chemicals Co., Ltd, 1990c in Documentation provided to EFSA No. 6, subsequently published in Noda et al., 1996).

Male Wistar rats (8 weeks of age, $n = 3$ per dose group), were administered an oral dose of 0.125, 0.25, 0.5, 1.0 or 2.0 g/kg bw of [^{14}C] erythritol in distilled water. Animals remained fasted for 8 h subsequent to erythritol administration. Blood samples were collected from the tail vein at 15 min, 30 min, 1, 2, 4, 6, 8, 12, 24, 48 and 72 h after administration. The maximum concentration of radioactivity (Tmax) was observed at 1 h for all dose levels. The blood C_{max} and AUC values showed a dose-proportional increase within the range of 0.125 to 1.0 g/kg bw. At 2.0 g/kg bw non-linear increment of C_{max} and AUC was observed indicating that the extent of absorption is decreasing when increasing the dose. The concentration-time profile showed a biphasic decrease with approximate half-lives of 2 and 20 h. These half-lives were approximately 50% longer in rats dosed with 2.0 g/kg bw (Nikken Chemicals Co., Ltd, 1990d in Documentation provided to EFSA No. 6, subsequently published in Noda et al., 1996).

Four groups of rats (12 weeks of age), three males and three female per group were included in the study. Group A were germfree rats, kept under germfree conditions until start of the experiment (no microbiome), Group B were 'adapted' rats, having received diets with stepwise (weekly) increasing doses of erythritol (5, 10, 20 mg/kg) starting 3 weeks prior to the experiment (microbiome). Group C were 'un-adapted' rats, held under non germ-free conditions (microbiome); Group D were germfree rats, kept under germfree conditions until start of the experiment: Groups A, B and C received non-purified substance which contained erythrose (2.48%) and glucose (0.43%) whereas group D received purified test substance which contained less erythrose (0.12%) and glucose (0.05%). A single dose of 5 µCi 14C-erythrltol per kg bw, diluted with 0.1 g/kg bw of non-radioactive erythritol was administered by gavage to the nonfasted rats. The rats were placed in closed respiratory chambers and expired CO2, urine and faeces were collected for 24 h. Urine was collected at 4, 8 and 24 h following administration and faeces at termination of the experiment. Radioactivity ^{14}C was determined by liquid scintillation with quenching correction by an external standard. The total amount of radioactivity, composed of the radioactivity from urine, faeces, expired air, cage wash and skin wash, excreted within 24 h was 91.5 ± 2.79% of the dose. The 0–24 h urine contained 73.4 ± 8.0% of the radioactivity with no sex difference and no difference between treatments. Urinary excretion was fast with 52.4 ± 10.0% excreted within the first 4 h. In the rat groups A and D, held under germ free conditions (no microbiome), CO_2 excretion was below 1% whereas in group B and C 10.9% and 6.7% of the dose respectively were found in the expired air, indicating that the rat microbiome can metabolise erythritol. Part of $^{14}CO_2$ might be produced by metabolising the impurities erythrose and glucose. No metabolites were found in the biological fluids and the tissue samples (TNO-CIVO Industries, 1990 in Documentation provided to EFSA No. 6).

Male Wistar rats (approximately 220 g bw, five rats per group) were fed a diet containing either 0%, 1%, 5% or 10% erythritol by weight (equal to 0.7, 4.3 and 8.5 g/kg bw per day) for 4 days prior to determinations of erythritol by gas–liquid chromatography (GLC) in collected urine and faeces. Mean and standard error urinary excretion of parent erythritol amounted to 93.9 ± 1. 3, 93.8 ± 0.7 and 83.2 ± 1.1% and faecal excretion amounted to 1. 4 ± 0.0, 1.3 ± 0.1 and 1.2 ± 0.2% of total intake for the 1%, 5% and 10% erythritol groups, respectively. The authors reported that metabolites were not identified (Oku & Noda, 1990b).

Male Wistar rats (200 g bw) were fasted for 18 h prior to oral administration of 0.01, 0.1 or 1 g/kg bw [^{14}C] erythritol. In addition, additional rats were separately administered 0.1 g/kg bw [^{14}C] erythritol by tail vein injection. No comparison to control (unexposed) animals is made. Four rats were used in each treatment group, except that three rats were used in the group that received a dose of 0.01 g/kg. Rats were then placed in individual metabolic cages for separate collection of urine, faeces and expired air. After 24 h, liver, kidney, testis and seminal vesicles were retained. The contents of the stomach, small intestine, caecum and colon were also collected. Radioactivity was determined by scintillation counting. Urine from rats administered [^{14}C] erythritol (0.1 g/kg) orally or intravenously was further analysed by thin layer chromatography (TLC) and HPLC. Urinary excretion within 24 h accounted for 88% of a single 0.1 g/kg bw dose and TLC/HPLC analyses eluted a single radioactive component identified as intact erythritol. The peak time for urinary radioactivity excretion was 8 h after administration. Radioactivity in expired air and faeces was 6% and < 1% of the dose within 24 h. No metabolites were detected in the urine up to 24 h after administration. Similar results were obtained after an intravenous administration of 0.1 g/kg bw [^{14}C]erythritol, with 94% of the dose within 24 h found in the urine and 1% and < 1% of radioactivity expired as [^{14}C]CO_2 and detected in the faeces respectively. An increase in expired [^{14}C]CO_2 was observed with increasing oral doses of [^{14}C] erythritol. More than 16% of the administered radioactivity was excreted as [^{14}C]CO_2 within 24 h at a dose of 1 g/kg body wt. The peaks for expired [^{14}C]CO_2 shifted to a later time after dosing: 6 h for 0.01 g/kg, 8 h for 0.1 g/kg and 12 h for 1 g/kg. Twenty four hours after oral administration of [^{14}C]erythritol, the radioactivity in the liver was found to be 14 and 491 times higher in rats dosed with 0.1 g/kg bw and 1.0 g/kg bw respectively, compared to rats dosed with 0.01 g/kg bw. The radioactivity incorporated into liver, kidney, testis and seminiferous vesicles 24 h after intravenous administration of [^{14}C]erythritol (0.1 g/kg bw) was significantly lower than that of animals that had received the same oral dosage. [^{14}C]

Erythritol (0.1 g/kg body wt) was also administered orally to rats that had been adapted to erythritol through free access to a diet containing 10% w/w erythritol for 2 weeks. [^{14}C]CO_2 excretion in the adapted group was statistically significantly greater than that of the naive controls in the first 6 h. However, the differences were not statistically significant after that time point. [^{14}C]erythritol metabolism was examined in cecal contents isolated from male Wistar rats (200 g body weight) after feeding with either a control diet or one containing 10% w/w erythritol for 2 weeks (11 animals/group). Fermentations were performed under anaerobic conditions at 37°C for 6 h. The majority of [^{14}C]erythritol remained intact (83.9%) with 2% of radioactivity accounted for as [^{14}C]CO_2 and 3% as short chain fatty acids (SCFAs) after 6 h with control caecal contents. Incubation of [^{14}C]erythritol with caecal contents from the 10% erythritol group resulted in near complete disappearance intact erythritol to 0.5% of radioactivity at 6 h, with the majority of the radioactivity incorporated in to [^{14}C]CO_2 (23.7%) and SCFAs (59.7%) (Noda & Oku, 1992).

Data on urinary excretion are reported from satellite groups of a chronic (2-year) oral toxicity and carcinogenicity in rats. Doses of 0%, 2%, 5% and 10% erythritol (equal to 0, 860, 2200, 4600 and 0, 1000, 2600, 5350 mg/kg bw per day in males and females, respectively) were investigated in $n = 20$ male animals per group. Data on the urinary excretion of erythritol and also the exact doses were obtained on day 176, 288, 344, 540 and 708. From day 288 data are available only for the highest dose group. For the study of the erythritol excretion the animals were kept in metabolic cages and urine and faeces were collected. The method by which the concentration of erythritol was analysed is not described in the report which is available. The overall mean of the excretion of unchanged erythritol varied between 60 and 64% of the dose. In the faeces about 2% of the dose were recovered as unchanged substance (TNO-CIVO Industries, 1994 in Documentation provided to EFSA No. 6, 10 subsequently published in Lina et al., 1996).

Dogs

Beagle dogs (6 months of age) were administered an oral dose of 1g/kg bw [^{14}C]erythritol and individual housed in metabolic cages. Animals were further fasted for 8 h after administration. Blood and plasma were sampled at various times up to 120 h after administration. Urine and faeces were separately collected for the periods 0–8, 8–24, 24–48, 48–72 and 72–120 h. A mask for collection of the expired air for determination of radiolabelled CO_2. C_{max} of radioactivity in blood and plasma was 0.5 and 0.6 h, respectively. The concentration-time profile showed a biphasic decrease with half-lives of 0.07 h/0.5 h and 1.67 h/5.43 h, for blood and plasma respectively. Radioactivity was predominantly excreted in the urine, 44.4% during the period up to 8 h and cumulatively 94.0% during the period up to 24 h after administration. 120 h following administration cumulative excretion of radioactivity in faeces and expired air was 0.33% and 1.17%, respectively (Nikken Chemicals Co., Ltd, 1990a in Documentation provided to EFSA No. 1, subsequently published in Noda et al., 1996).

Three Beagle dogs (6 months of age) received 1 g/kg bw [^{14}C]erythritol (14C-NIK-242) (55.55 μCi/g) by oral administration. Urine samples were collected from animals of a previous study (Nikken Chemicals Co., Ltd, 1990a in Documentation provided to EFSA No. 1, subsequently published in Noda et al., 1996). Urine was sampled up to 24 h following intake. Urine samples were separated on a HPLC column (type not given; Gibson 320, Gilson); substance detection was done by an UV-detector at 210 nm or 195 nm. Radioactivity was detected by liquid scintillation counting (Ramona 5-LS, Rytest, Germany). The HPLC tracings of the urine did show a peak with a retention time (RT) corresponding to the RT of [^{14}C]erythritol. No other peak was seen. More than 95% of the radioactivity was excreted in the urine. The authors concluded that erythritol is hardly metabolised in dogs (Nikken Chemicals Co., Ltd, 1994 in Documentation provided to EFSA No. 6).

Four groups of four male and four female beagle dogs were fed a daily diet containing 0, 2, 5 or 10% (w/w) erythritol (equal to 0, 761, 1942, 4286 and 0, 816, 2000, 4592 mg/kg bw per day in males and females, respectively) for 53 weeks. The two highest dose groups were gradually introduced to erythritol and were not exposed to their full dose until week 2. Dogs were allowed access to their diet for up to 2 h before being placed in a metabolism cage. Urine and faeces were collected over a single 24 h period pre-trial and at weeks 13, 26, 38 and 52. Urine, faecal and cage wash (last 3 time points only) erythritol levels were determined. The Panel noted that erythritol was excreted in both male and female pre-trial urines (0.4 ± 0.71 and 0.4 ± 0.49 g erythritol/24h, respectively) and faeces samples (1.2 ± 0.59 and 1.2 ± 0.40 g erythritol/24h, respectively) and variably detected in control group urine and faecal samples during the study. The majority of administered erythritol was excreted in urine. The amounts of erythritol excreted over a 24 h period increased in a dose-dependent manner in urine, and to a lesser extent, in faeces. For example, at week 26, urinary excreted erythritols were 0.1 ± 0.18, 6.9 ± 1.03, 7.8 ± 6.22 and 27 ± 10.5 g erythritol/24 h in males and 0.09 ± 0.09, 6.8 ± 0.44, 10 ± 7.19 and 27 ± 14.3 g erythritol/ 24 h in females at the 0, 2, 5 or 10% dose levels respectively. At this time point, faeces excretions amounted to 0 ± 0, 0.97 ± 0.53, 1.6 ± 1.10 and 4.5 ± 0.36 g erythritol/24 h in males and 0 ± 0, 0.71 ± 0.59, 1.3 ± 0.98 and 1.7 ± 1.50 g erythritol/24 h in females at the 0, 2, 5 or 10% dose levels respectively (IRI, 1992 in Documentation provided to EFSA No. 6, subsequently published in Dean et al., 1996).

APPENDIX D

Data extraction forms for genotoxicity studies

Study ID 1016	Young-Shin Chung and Michael Lee. Genotoxicity assessment of erythritol by using short-term assay. Toxicology research vol. 29, No. 4, pp. 249–255 (2013)
Funding	Funding source (public/private): public
Good laboratory practice (GLP) compliance and guideline	Good laboratory practice (GLP): no Guideline studies (if yes, specify): OECD TG 471 (1997), TG 473 (1997), TG 487 (2010) and TG 474 (1997)
Test system	Salmonella/microsome (Ames) test, strains *Salmonella* typhimurium TA98, TA1537, TA100, TA1535 and *Escherichia coli* WP2 *uvrA* (with and without metabolic activation), chromosomal aberrations in chinese hamster fibroblasts (CHL), *in vitro* micronucleus and comet assays in L5178Y mouse lymphoma cells (with and without metabolic activation), *In vivo* micronucleus test in mouse bone marrow
Test material	Identity, batch, purity: commercial sample purchased at a local (Korean) marketplace
Exposure/treatment conditions	Ames test: plate incorporation assay (doses; 156, 312, 625, 1250, 2500 and 5000 µg/plate) Chromosomal aberration test: short (6 h, with and without metabolic activation) and continuous (24 h, without metabolic activation) treatments with 1250, 2500 and 5000 µg/mL *In vitro* micronucleus: short (3 h + 21 h recovery, with and without metabolic activation) and continuous (24 h, without metabolic activation) treatments with 1250, 2500 and 5000 µg/mL; cytochalasin B was not used as cyt B is known to increase spontaneous background of micronuclei in L5178 cells Comet assay: short (3 h, with and without metabolic activation, without recovery) and extended (24 h, without metabolic activation) treatment with 1250, 2500 and 5000 µg/mL *In vivo* micronucleus test: two daily oral administrations of 1250, 2500 and 5000 mg/kg. Mice were sacrificed 24 h after the final administratio
Results	No increase in revertant colonies in the Ames test; no significant and dose related increase in aberrant metaphases or micronuclei In comet assays, a significant (≤2-fold) increase in mean % tail DNA was observed at the top concentration (5000 µg/mL) after short treatment without S9, and at the middle (2500 µg/mL) and high concentration after continuous 24 h treatment *In vivo* micronucleus in mouse bone marrow: inconclusive, i.e. negative as regards the formation of micronucleated PCEs, but with no evidence of bone marrow exposure based on no decrease in the PCE/NCE ratio
Reliability of the study/Relevance of the test system/Relevance of the results	Reliability: The experimental protocols used in the Ames test, in vitro chromosomal aberration and *in vitro* micronucleus tests are basically in agreement with the relevant OECD guidelines, even though the number of scored metaphases in the chromosomal aberration test was lower than currently recommended (200 instead of 300 as in TG 473, 2016). It is also noted that the dose range applied in mammalian assays exceeded the maximum concentration recommended in the updated TG473 and TG487 (2014/2016), but this did not impair the validity of the studies as no overt toxicity was observed at any dose There is no OECD guideline for the in vitro comet assay, which was performed following a published protocol. Overall, the *in vitro* studies are considered reliable without restrictions (Ames test and in vitro micronucleus tests) or with restrictions (*in vitro* chromosomal aberrations and comet assays) The *in vivo* micronucleus tests provided inconclusive results, and therefore it is considered as 'reliability insufficient' Relevance of the test system: High relevance is given to the Ames test, and the *in vitro* chromosomal aberration and micronucleus tests, which are mutational events. Limited relevance is given to the *in vitro* comet assay, as an indicator endpoint Relevance of the result: High relevance is given to the results of the Ames and *in vitro* micronucleus test; limited relevance to the results of the chromosome aberration test and the *in vitro* comet assay; low relevance to the results of the *in vivo* micronucleus test (for the inconclusive result)

APPENDIX E

Data extraction forms for human studies

Studies that are described in this Appendix are only reflecting the information provided in the study reports/papers.

RefID (DistillerSR): numerical identifier generated by the DistillerSR tool.
Type of study: e.g. human controlled trial (HCT), cohort study (Co), case–control study (CaCo), cross-sectional study (CrSe) study type.

Study ID	
RefID (DistillerSR)	**4355**
Reference (authors, year, title, other info)	Teysseire, F., Bordier, V., Budzinska, A., Weltens, N., Rehfeld, J. F., Holst, J. J., Hartmann, B., Beglinger, C., Van Oudenhove, L., Wölnerhanssen, B. K. and Meyer-Gerspach, A. C. (2022). The role of D-allulose and erythritol on the activity of the gut sweet taste receptor and gastrointestinal satiation hormone release in humans: A randomized, controlled trial. *The Journal of Nutrition*, 152(5), 1228–1238. https://doi.org/10.1093/jn/nxac026
Source (published/unpublished)	Published
Study design	
Study type	HCT – Cross-over trial – Randomised – Placebo-controlled
Type of blinding	Double-blind
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	21 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	18 exposed
Sex (male/female)	5 Males and 13 Females
Age (mean or range as reported)	19–39
Geography (country)	Switzerland
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Exclusion criteria included substance and alcohol abuse, acute infections, chronic medical illness or illnesses affecting the GI system
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	On 6 separate test sessions, at least 3 days apart and after a 10-h overnight fast, after taking blood samples ($t = -10$ and -1 min) and breath samples ($t = -10$ min) as well as recording of appetite-related sensations and GI symptoms, participants received one of the following test solutions (at $t = 0$ min) via intragastric administration over 2 min in a randomised order: • 50 g erythritol dissolved in 300 mL tap water • 50 g erythritol and 450 parts per million (ppm) lactisole dissolved in 300 mL tap water • 25 g D-allulose dissolved in 300 mL tap water • 25 g D-allulose and 450 ppm lactisole dissolved in 300 mL tap water • 300 mL tap water (placebo) • 300 mL tap water and 450 ppm lactisole (placebo)
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	After the administration of the test solution, blood samples (at $t = 15$, 30, 45, 60, 90, 120 and 180 min), for analysis of plasma CCK, GLP-1 and PYY, and end-expiratory breath samples (at $t = 15$, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 min), for analysis of gastric emptying rates, were taken Appetite-related sensations (hunger, prospective food consumption, satiety and fullness) were assessed at $t = 15$, 30, 45, 60, 90, 120 and 180 min using visual analog scales (VASs) as previously described Participants were also asked to rate GI symptoms (no symptoms [0 points], mild [1 point] or severe symptoms [2 points]) at $t = 30$, 60, 90, 120, 150, 180 and 240 min after the administration of the test solutions The list included the following symptoms: abdominal pain, nausea, vomiting, diarrhoea, borborygmus, abdominal bloating, eructation and flatulence Vital signs (blood pressure, heart rate) were measured at the beginning and at the end of each study day

Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	D-allulose and erythritol induced a significant release of CCK, GLP-1 and PYY compared with tap water (all PHolm < 0.0001, $dz > 1$). Lactisole did not affect the D-allulose and erythritol-induced release of CCK, GLP-1 and PYY (all PHolm > 0.1) Erythritol significantly delayed gastric emptying, increased fullness, and decreased prospective food consumption compared with tap water (PHolm = 0.0002, $dz = -1.05$; PHolm = 0.0190, $dz = 0.69$; and PHolm = 0.0442, $dz = -0.62$, respectively)
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	A 2-tailed p-value ≤ 0.05 was considered significant and Cohen's dz for paired t-tests was reported as a measure of effect size For all analyses, if the assumption of normally distributed residuals was violated (based on a significant p-value of the Shapiro–Wilk test), natural logarithmic transformations of the dependent variables were used to normalise this distribution. Analysis was performed on transformed data. Logarithmic transformation of the dependent variables adequately normalised the residual distribution. Visit number was included to control for putative order effects in all models. All outcome variables were analysed using (generalised) linear mixed models on changes from baseline (average of pre-infusion time point[s]). 'Test solution' (intragastric D-allulose, D-allulose + lactisole, erythritol, erythritol + lactisole, tap water and tap water + lactisole) and 'time' were included as within-subject independent variables in the models (including their main effects and the interaction). All the models were controlled for baseline values. To follow-up on significant main or interaction effects, planned contrast analyses were performed to test our specific hypotheses, with stepdown Bonferroni (Holm) correction for multiple testing. To test the hypothesis that D-allulose or erythritol induces an increase in GI satiation hormones and retards gastric emptying compared with tap water, were compared post-infusion GI satiation hormone concentrations and gastric emptying (change from baseline) between tap water, on one hand, and D-allulose or erythritol, on the other hand. To test the hypothesis that D-allulose or erythritol increases satiety/fullness and decreases hunger/prospective food consumption compared with tap water, respectively, were compared post-infusion appetite-related sensations between tap water, on one hand, and D-allulose or erythritol, on the other hand. To test the hypothesis that addition of lactisole does (not) decrease GI satiation hormones, retard gastric emptying or change appetite-related sensations in response to D-allulose or erythritol, were compared post-infusion GI satiation hormone concentrations and gastric emptying (change from baseline) to each of the substances with and without added lactisole For the associations, the difference between the test solutions of the significant planned contrasts at each time point was calculated and used as a dependent variable in the model with the same difference at each time point for the GI satiation hormones as an independent variable in addition to time
Further information	
21 participants were recruited for the study. There were three dropouts (one participant had to withdraw due to a knee surgery and two withdrew for personal reasons). Therefore, 18 participants completed the 6 treatments. Complete data from all 18 participants were available for analysis	

Study ID	
RefID (DistillerSR)	**1242**
Reference (authors, year, title, other info)	Kim, Y., Park, S.C., Wolf, B.W., & Hertzler, S.R. (2011). Combination of erythritol and fructose increases gastrointestinal symptoms in healthy adults. *Nutrition Research*, 31, 836–841. https:\\doi.org\10.1016/j.nutres.2011.09.025
Source (published/unpublished)	Published
Study design	
Study type	HCT – randomised, cross-over study
Type of blinding	Double-blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	Participants were enrolled ($n = 62$) until at least 36 completed the study. Subjects were recruited from The Ohio State University community (Columbus, Ohio, USA)
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	37 exposed
Sex (male/female)	13 males and 24 females
Age (mean or range as reported)	23 ± 0.5 years old

Geography (country)	US
Ethnicity	73% White, 5% African American, 19% Asian or Pacific Islander and 3% Hispanic
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Inclusion criteria: 18–75 years old, male or non-pregnant, non-lactating female greater than 6 weeks postpartum, body mass index (BMI) 18–28 kg/m^2 or up to 30 kg/m^2 if waist circumference < 88.9 cm for females or < 101.6 cm for males, no tobacco use, fasting plasma glucose ≤ 5.56 mmol/L, no previous diagnosis of diabetes mellitus or other metabolic or GI diseases, no infection, surgery or corticosteroid treatment within past 3 months or antibiotic therapy within past 3 weeks, and breath hydrogen excretion (> 10 ppm above baseline) after oral lactulose challenge and greater hydrogen than methane excretion.
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	To ensure similar glycogen stores on test days, participants were instructed to consume at least 150 g carbohydrates per day for 3 days before each visit (verified by food records) and to refrain from exercise the day before each visit Also, participants were provided a low-residue, low-fibre (≤ 5 g) standard dinner for consumption between 4 and 7 pm on the day before each visit. The standard dinner consisted of 240 mL Ensure Plus and variable quantities of Ensure Nutrition and Energy Bars (Abbott Nutrition, Abbott Laboratories, Columbus, OH, USA) calculated to provide total energy equal to one third of each participant's estimated daily energy requirement (based on the Harris-Benedict equation multiplied by a light activity factor of 1.3[a]) At each visit, participants consumed one of the three test beverages consisting of 500 mL water plus one of the following: 50 g fructose (control product, 0.56 mol/L), 50 g fructose and 50 g glucose (positive control, 1.11 mol/L), and 50 g fructose and 33.3 g erythritol (experimental product, 1.11 mol/L). Treatment sequence was randomly assigned Participants were instructed to consume the test beverage within 10 min after the first sip and then allowed to drink up to 240 mL water during the 3 h tolerance test Drinks were administered 3–14 days apart
Co-exposure description (if applicable)	Erythritol and fructose (33.3 g and 50 g, respectively)
Endpoint measured, measurement time points and methods	Breath hydrogen samples were collected in sealed evacuated tubes (Exetainer, Labco International Inc., Houston, TX, USA) using an AlveoSampler mouthpiece (Quintron Instrument Company, Milwaukee, Wis., USA) at baseline and hourly during the 3 h tolerance test on site and for an additional 5 h off site. At 4 h postprandial, participants were allowed to consume up to two cans (240 mL per can) of Ensure Plus and then resumed fasting until the 8 h postprandial study product administration breath sample was collected. Samples were analysed for hydrogen, methane and carbon dioxide concentrations by gas chromatography (Quintron Microanalyzer Model SC, Quintron Instrument Company). Participants were identified as having carbohydrate malabsorption if their breath hydrogen concentrations increased more than 10 ppm for 8 h compared with the basal nadir value (i.e. the lowest breath hydrogen value at baseline, 1 or 2 h postprandial). Participants recorded the total number of rectal gas passages using a portable counting device (VWR International, West Chester, PA, USA) during the 3 h tolerance test on site and for an additional 5 h off site. The number of bowel movements for the first 3 h after study product administration was recorded when the participants were on site, and also for an additional 5 h off site. Stool consistency for each bowel movement was rated using a 5-point visual analog scale (VAS). Participants recorded frequency and intensity of nausea, abdominal cramping, distension and flatulence for 0–24 h after study product consumption using a VAS (0 = usual or absent; 10 = more than usual or severe)
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	The breath hydrogen AUC for the fructose and erythritol beverage was 2× the AUC of the fructose beverage and 8.75× the AUC of the fructose and glucose beverage ($p < 0.001$, respectively). Compared with the fructose and glucose beverage and fructose alone, when participants consumed fructose and erythritol combined, the frequency of watery stools increased ($p < 0.05$) and GI tolerance worsened ($p < 0.05$). The data suggested that co-ingestion of equimolar concentrations of fructose and erythritol increased carbohydrate malabsorption A study limitation was the lack of an erythritol-only test beverage, which would have allowed a more complete evaluation of serum erythritol levels and breath hydrogen concentrations. Data for this beverage would help to identify which carbohydrate, either erythritol or fructose, was not well absorbed

Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	After examination for normality, data were analysed using ANOVA with a randomised block design to test for global significant differences; the Tukey–Kramer post hoc test was then used for pairwise comparisons. The NCSS 2000 software package (NCSS computing, Kayesville, Utah, USA) was used for statistical analysis Power analysis on data from a previous study[b] indicated that 36 participants would be required to detect a 47% difference in the incremental AUC for breath hydrogen with 84% power
Further information	

[a]Harris, J. A., & Benedict, F. G. (1919). A biometric study of basal metabolism in man. Carnegie Institute. pp. 227.

[b]Ravich, W. J., Bayless, T. M., & Thomas, M. (1983). Fructose: Incomplete intestinal absorption in humans. *Gastroenterology*, 84, 26–29.

Study ID	
RefID (DistillerSR)	**4298**
Reference (authors, year, title, other info)	Biofortis, 2010. Study of Gastrointestinal Tolerability of Erythritol (Polyol) in Children. Report Ref. CER_TDEOH05.
Source (published/unpublished)	Unpublished
Study design	
Study type	HCT – multi-centre, randomised, placebo-controlled, cross-over (with placebo only) study
Type of blinding	Double-blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	185 participants (172 participants per protocol population)
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	184 exposed
Sex (male/female)	95 males and 77 females (per protocol population)
Age (mean or range as reported)	4–6 years old
Geography (country)	France
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Inclusion criteria: healthy children, 4–6 years old on day 1 of study (i.e. day of consumption of first beverage), BMI ≥ 13 kg/m^2, accustomed to having breakfast, having a regular stool frequency ≤ 2 per day, able to drink 250 mL within 15 min, toilet-trained/able to use a potty (day and night), informed consent of both parents/guardians, affiliated to the French social security Non-inclusion criteria: participation in any clinical trial that included blood sampling and/or administration of substances up to 90 days before day 1 of the study, participation in any non-invasive clinical trial up to 30 days before day 1 of this study (including blood sampling and/or, intravenous, inhalatory administration of substances), having a history of medical or surgical events that may significantly affect study outcome (e.g. gastric and digestive diseases), any current metabolic or endocrine diseases (including diabetes mellitus), use of medication (including antibiotics, laxatives and steroids), having regular GI complaints (e.g. stomach upsets, diarrhoea, constipation, flatulence, abdominal colic) Temporary exclusion (non-inclusion) criteria: no consumption of breakfast before consumption of the test product, failure to consume at least one solid food during breakfast, vaccination within 7 days before day 1 of study or during study, regular stomach aches within 7 days before day 1 of the study, period of more than two faeces per day within 7 days before day 1 of study, light solid products consumption (e.g. confectionery, chocolate, chewing gum, biscuits) within 24 h of test product consumption
Other information	

Intervention/exposure	
Test material	Erythritol (Cargill)
Description of the intervention and estimated dietary exposure	Children were required to consume breakfast approximately 2 h before attending the test centre, where they were provided the test drink for consumption within 15 min. Test drinks contained 5 g ($n = 14$), 15 g ($n = 57$), 20 g ($n = 58$) or 25 g ($n = 55$) erythritol in 250 mL of non-carbonated fruit-flavoured drink (Cargill). Placebo groups consumed 250 mL of non-carbonated fruit-flavoured drink, sweetened with saccharose and maltodextrin (Cargill) to a sweetening power equivalent to the corresponding erythritol beverages Children were not allowed to eat anything (and only drink water) for at least 1 h after consuming the test drink. For approx. 2 h after consumption, children remained at the test centre under observation of the investigator (collecting the eventual urine). At home, until 48 h after consumption, the legal guardians were asked to keep a defecation-frequency diary for their child, collect urine for 24 h following consumption of the test substance, and complete a questionnaire on GI symptoms at 6 h and 24 h after consumption of the test substance The second test day was a repeat of the first test day except subject history was not taken. Children were asked to eat the same breakfast as before There was a washout period of ≥ 5 days between test days
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Primary outcome variable: GI tolerability as measured by the incidence of diarrhoea and/or significant GI symptoms following consumption of test item Secondary outcome variables: stool frequency and consistency, GI symptoms, total symptom intensity score, urinary erythritol excretion For each group, erythritol treatment effects were compared to the effects of treatment with placebo for: (i) diarrhoea (= single watery stool (i.e. Bristol Stool Scale (BSS) = 7) and/or > three faeces in 24 h), (ii) stools frequency and BSS ratings (for BSS, if no stool was passed for a subject, subject was not included in the analysis), (iii) GI symptoms (occurrence, frequency and intensity during 0–6 h and 6–24 h after consumption). A composite score of symptoms' intensity was computed for abdominal pain, nausea, borborygmi, bloating and gas. For each individual symptom's intensity and frequency scores and for the composite score, the maximum was taken into account, for analysis on overall period (0–24 h) and (iv) erythritol concentration in urine To measure group effect of erythritol: Y = product + sub-group + product × sub-group. A sensitivity analysis was performed on primary criteria where all missing data on GI symptoms or BSS were replaced by 'strong intensity' and 'BSS = 7' regardless of the product consumed. Additionally, all GI adverse events (AEs) reported in the case-report form and for which no data on GI symptoms were available in the questionnaire were considered as clinically relevant diarrhoea/GI symptoms
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Following consumption of 20 g erythritol, there was a significant difference between the groups for the incidence of diarrhoea and/or significant GI symptoms with the erythritol group having significantly more events than the placebo group ($p = 0.0286$), that was also significant for the 25 g dose ($p < 0.0001$) but not for the 5 g and 15 g doses. Therefore, 15 g erythritol in a single drinking occasion was the maximum tolerated dose in children
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	In the first instance, the number of children required was calculated based on the following: first-order risk $\alpha = 10\%$, statistical power = 80%, PE-PP ≥ 30%, (PE = % of subjects having the AE in question under erythritol, and PP = % of subjects having the AE under placebo). On this basis, the number of children required to be randomised in a given sub-study was 13. In order to get a higher power, the number of 14 children per group was chosen Then, sample size was recalculated based on a first-order risk $\alpha = 10\%$, the two-sided confidence interval of the difference (PE-PP) = 90% (where PE is the percentage of subjects having an AE under erythritol, and PP the percentage of subjects having an AE under placebo) and the higher boundary of the confidence interval of (PE-PP) ≤ 39%. On the basis of the above hypotheses, the number of children required to be randomised in a given sub-study was 56 Analyses were performed using SAS 9.1.3 Service Pack 4. Statistical analyses accounting for the cross-over design of the study were of risk type 1 error (α), set at 0.10 for the assessment of the threshold level dose and at 0.05 for all other statistical tests Primary analysis: qualitative variables were analysed using one-tailed Mainland Gart's test, which takes into account that the product groups were not independent and that products were not given in the same order. This analysis was performed after each sub-study in order to go to next step (risk type 1 error set at 0.1). To ensure that erythritol was not inferior to placebo when no statistically significant difference was found, a confidence interval at 90% was computed applying the May and Johnson method Secondary analysis: one-tailed Mainland Gart's test was also used for binary variable. For nominal or ordinal variable bilateral Kappa test was used. Qualitative variables were described as frequencies and percentages of the number of individuals examined. Quantitative variables were analysed using repeated measures ANOVA with product group, sequence and product group by sequence interaction as effects. Models were reduced in a stepwise manner until only significant ($p \leq 0.05$) terms or product group remained. Quantitative variables, including those related to demographic data, were summarised in tables displaying sample sizes, means, SDs, medians, minimum and maximum values
Further information	
Data from this unpublished study report were subsequently published in Jacqz-Aigrain et al. (2015)	

Study ID	
RefID (DistillerSR)	**759**
Reference (authors, year, title, other info)	Storey, D., Lee, A., Bornet F., & Brouns, F. (2007). Gastrointestinal tolerance of Erythritol and Xylitol ingested in a liquid. *European Journal of Clinical Nutrition*, 61, 349–354. https://doi.org/10.1038/sj.ejcn.1602532
Source (published/unpublished)	Published
Study design	
Study type	HCT – randomised, placebo-controlled, cross-over study
Type of blinding	Double-blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	70 participants. Subjects were randomly recruited from the student population of the University of Salford
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	65 exposed
Sex (male/female)	34 males and 36 females
Age (mean or range as reported)	18–24 years old
Geography (country)	UK
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Potential recruits were included according to the procedures as described by Lee and Storey[a]
Other information	Five male subjects failed to complete the study: 3 dropped out due to illnesses unrelated to the study and 2 due to adverse GI effects following consumption of xylitol-containing test products For one subject, reporting was incomplete for all GI symptoms except for data on stools, therefore data were based on 64 subjects
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	20 g, 35 g and 50 g erythritol in test drinks consumed in subjects' homes on test days whilst maintaining their normal diets Test materials were provided as 400 mL orange-flavoured non-carbonated drinks (2 × 200 mL glass bottles; Cerestar R&D, Vilvoorde, Belgium). For all test drinks, sweetness intensity was corrected to 11.25 sucrose equivalent value using aspartame. Consumption of test drinks was separated by 1-week washout periods. Dietary restrictions included no prior consumption of polyol-containing products. Subjects consumed the drinks either mid-morning following consumption of a normal breakfast or mid-afternoon following consumption of a normal lunch. Drinks were consumed within 15 min and subjects requested not to consume food or drinks (except up to 300 mL water) for the following 2 h. Subjects were debriefed within 24 h to determine adherence to dietary restrictions and consumption and to assess GI responses
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Subjects were given printed sheets on which to report the prevalence and magnitude of flatulence, borborygmi, bloating, colic, nausea, bowel movements and the passage of faeces of an abnormally watery consistency for the 24 h period following consumption. A hedonic scale was used: 0 = normal function, 1 = slightly more symptom than usual, 2 = noticeably more symptom than usual and 3 = considerably more symptom than usual. Symptom scores were derived by summing each subject's GI responses. Subjects recorded the number of bowel movements to pass faeces of normal, hard or watery consistency, where watery faeces were defined as those of an abnormally watery consistency (e.g. loss of firm shape owing to high-water content)
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Consumption of 20 and 35 g erythritol in a liquid by healthy volunteers was well tolerated and without symptoms. At 50 g erythritol, there were significant increases only in the number of subjects reporting borborygmi ($p < 0.05$) and mild nausea ($p < 0.01$) Xylitol produced significantly more watery faeces than erythritol when comparing all intake levels: 50 g xylitol versus 35 g erythritol ($p < 0.001$), 50 g xylitol versus 20 g erythritol ($p < 0.001$) and 35 g xylitol versus 20 g erythritol ($p < 0.05$)

Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Symptoms were classified as categorical, and considered to be non-parametric. GI responses were compared by 2 × 2 contingency table analysis (chi-squared) according to the methods of McNemar.[b] The binomial test was used when the expected frequency in each cell of the contingency table was less than 5. The chi-squared test was used to test for differences in the occurrence of multiple symptoms following consumption. The frequency of bowel movements to pass normal, watery and hard faeces were analysed by one-way ANOVA, followed by Dunnet's post hoc test to detect differences in case of an overall significant treatment effect
Further information	
Test drinks containing sucrose (45 g) and xylitol (20, 35 and 50 g) were also tested	

[a]Lee, A., & Storey, D. M. (1999). Comparative gastrointestinal tolerance of sucrose, lactitol, or D-tagatose in chocolate. *Regulation of Toxicology Pharmacology*, 29, S78–S82.
[b]McNemar, Q. (1947). Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika,* 12, 153–157.

Study ID	
RefID (DistillerSR)	**3789**
Reference (authors, year, title, other info)	Tetzloff, W., Dauchy, F., Medimagh, S., Carr, D. and Bär, A. (1996). Tolerance to subchronic, high-dose ingestion of erythritol in human volunteers. *Regulatory Toxicology and Pharmacology*, 24(2), 286–295. https://doi.org/10.1006/rtph.1996.0110
Source (published/unpublished)	Published
Study design	
Study type	HCT - Two-way crossover study
Type of blinding	Double-blinded
Duration of the study and length of follow-up	7 days erythritol and 7 days sucrose
Subjects	
Number of participants in the study	12 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	12 exposed
Sex (male/female)	Males
Age (mean or range as reported)	Range: 22–46
Geography (country)	Not reported
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Not reported
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	The 14-day protocol comprised two treatment periods with administration of erythritol and sucrose for 7 days each. Six randomly selected subjects received erythritol in the first and sucrose in the second week; for the other six subjects the sequence of the treatments was reversed. The subjects were not informed about their dosing sequence Each treatment period started on a Saturday morning and ended on a Friday evening. In order to adapt the subjects to the treatments, the test compounds were provided at a dose of 0.3 g/kg bw on Saturdays and 0.6 g/kg bw on Sundays (adaptation period). Exposure to the full dose of 1 g/kg bw began on Monday morning and ended on Friday evening (test period) The total daily dose of 1 g/kg bw of erythritol or sucrose was consumed in five portions. At breakfast (8A M), about 20% of the total daily dose was consumed, at coffee break (10:30 AM) about 10%, at lunch (12:30 AM) about 30%, during afternoons (12:30 AM–7 PM) about 20%, and at dinner (7 PM) about 20%. In practice, fixed amounts of the test compounds were given with test foods at each meal except for dinner at which time the test compounds were dosed individually so as to reach the nominal dose level of 1 g/kg bw per day for each subject. The test substances were given with yogurt (breakfast, dinner), cookies (breakfast, morning coffee), soft drink (lunch) and chocolate (afternoon) Subjects were asked to abstain from alcohol intake during the adaptation period. During the test periods, no alcoholic beverages were consumed. Beverages, such as mineral water and fruit juice, were allowed ad libitum but the consumption of coffee or tea was limited to four cups per day
Co-exposure description (if applicable)	Not applicable

Endpoint measured, measurement time points and methods	During the 2-day adaptation periods, each participant recorded their food and beverage consumption on daily report sheets. During the 5-day test periods, food and beverage intake was recorded On each day of the two test periods, body weight and pressure, and sitting blood pressure were measured. Each subject was interviewed about their subjective perception of general well-being, satisfaction with the offered test foods, feelings of hunger and thirst, desire for sweet or salty foods, and subjective perception of regularity, consistency and quantity of stool, frequency and quantity of urine, gastrointestinal intolerance and other side effects For determination of the urinary electrolytes, enzymes, proteins, urea and creatinine, the urines were thawed at room temperature, vortexed and centrifuged (3000 rpm, 20 min, 47C). The supernatants were then analysed for sodium, potassium, chloride, calcium, phosphate, citrate, gamma-glutamyl transferase (GGT), *N*-acetyl glucosaminidase (NAG), b2-microglobulin (b2M), urea and creatinine. Although GGT was analysed, the data are not reported For determination of erythritol, the urine samples were thawed, vortexed and filtered through a 0.45-µm filter; 1,3-butanediol was added as an internal standard. HPLC was performed on a Shodex Ionpack colum KC 811 (0.8×300 mm) at 75°C using 1.8 mM H2SO4 as an eluant (sample volume, 5 µL; flow rate, 1 mL/min) Erythritol and 1,3-butanediol were detected in the effluent by measurement of the refractive index (Waters RI-Detector R401)
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	During the two test periods (i.e. Days 3–7 of each treatment period), the mean body weights varied only slightly. A treatment-related difference was not observed. All blood pressure values were within the normal physiological range. Statistical analysis of the data did not reveal treatment-related effect During the erythritol test period, erythritol was detected in the urine of all subjects on all days. The value on any of the 48 subject-days was 38.4 g/day corresponding to 54.3% of the nominal ingested dose. On average of all subject-days, the erythritol excretion was 62.4 g/day, corresponding to about 78.0% of the nominal ingested dose. Since erythritol absorption is estimated at about 80%–90% from other studies, this value documents good compliance with the test regimes of the present subjects Urine production was increased during the erythritol period by about 7% (difference not statistically significant, $p = 0.08$) Urinary osmolality and the hourly urinary output of osmotically active solutes were significantly increased during the erythritol test period. The observed increase of 576 mOsm/24 h corresponds well to the expected increase calculated from the erythritol range The urinary output of creatinine, urea, Na+, K+, Cl-, Pi and citrate was not influenced by erythritol treatment. Only calcium was significantly increased during the erythritol treatment ($p < 0.04$). However, in absolute terms, this increase was small (4%). The urinary NAG-, beta2M- and albumin outputs were significantly increased during the erythritol test period. However, these increases, which were significant also after normalisation for creatinine excretion, were numerically small and all values remained well within the physiological range The participants reported that the frequency of their faeces did not differ between the treatments however the appearance was judged slightly more often as being '*softer than usual*' during the erythritol treatment than during the sucrose treatment (14/60 vs. 8/60 observations). On the other hand, the quantity of stool was more often rated as 'less than usual' during the erythritol treatment than the sucrose treatment period (13/60 vs. 5/60) Gastrointestinal side effects such as flatulence, bloated feeling and sensation of fullness were reported by six subjects on a total of 10 occasions during the erythritol test period and 13 occasions during the sucrose test period
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	The data on body weight, systolic and diastolic blood pressure, and fluid intake were analysed by repeated measures analysis of variance (ANOVA) (Wiener, 1977). For each of these parameters, 120 observations (i.e. 2 treatments × 5 observation days × 12 subjects) were available for statistical analysis. From the data on urinary electrolyte, enzyme, protein, urea and creatinine concentrations (i.e. mmol/L, U/L, µg/L), the respective hourly outputs (i.e. mmol/h, U/h, µg/h) as well as excretions relative to that of creatinine (i.e. mmol/mmol creatinine, U/mmol creatinine) were calculated. From the data on hourly outputs and excretions relative to that of creatinine, as well as from the data on pH, osmolality and conductivity, 24 h means were then calculated for each subject and each treatment day. For calculating these means it was taken into account that the overnight sample represented a period three times longer (9 h) than the samples collected during the daytime (3 h each). The urine flow was expressed in ml/hr for each sampling interval, and time-weighed 24 h means were calculated as well. For calculating the 24 h means of the different parameters, the urine produced between 10 PM of Day 3 (i.e. urine collected at 7 AM of Day 4) and 10 PM of Day 4 (i.e. urine collected at 10 PM of Day 4) was considered to represent the first full 24 h cycle. In this way, four complete 24 h cycles were available for evaluation for each of the two treatment periods For the statistical assessment of treatment-related differences of urinary parameters, a repeated measures ANOVA was applied to the 24 h mean values (2 treatments × 12 subjects × 4 24 h periods = 96 observations for each parameter). Since one of the assumptions of ANOVA is that the residuals from the model are approximately normally distributed, the normality (Shapiro–Wilk test), skewness and kurtosis of the data were examined. Where the conditions for ANOVA were not fulfilled, inverse scores of ranks were calculated and the repeated measures ANOVA was applied to these transformed values For descriptive analysis, the hourly outputs of urine, NAG, beta2M and erythritol and the excretion of osmotically active solutes (mOsm/litre; mOsm/h) were depicted graphically for each test period (i.e. excretion profiles from 7 AM of Day 3 to 10 PM of Day 7)
Further information	

Study ID	
RefID (DistillerSR)	**3788**
Reference (authors, year, title, other info)	Oku & Okazaki, 1996. Laxative threshold of sugar alcohol erythritol in human subjects. *Nutrition Research*, 16(4), 577–589. https://doi.org/10.1016/0271-5317(96)00036-X
Source (published/unpublished)	Published
Study design	
Study type	HCT
Type of blinding	Not reported
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	38 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	38 exposed
Sex (male/female)	14 Males workers and 24 Females students
Age (mean or range as reported)	M: 45.3 ± 2.6 F: 21.7 ± 4.4
Geography (country)	Japan
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Not reported
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	One, two or three cups of jelly containing erythritol (25 g in a cup) were given to a half of the male and female subjects, and 1, 1.5 or 2.5 cups of jelly were fed to the other half of the subjects to produce a detailed distribute of values of g of erythritol/kg of bw. The jelly (about 85 g) containing 25 g of erythritol, sorbitol or sucrose was administered in order from the smallest to the largest amount and stopped at the dose level that caused diarrhoea or at the maximum dose level used in the study. Sorbitol which readily induces diarrhoea was used as a positive control, and sucrose which does not produce diarrhoea was used as a negative control On the day prior to administration, the ingestion of foods and beverages containing other sugar substitutes which might affect diarrhoea were avoided On the day of administration, the jelly containing the test substance was given with water, if needed, 2–3 h after lunch or breakfast and subjects were permitted to take any foods except for wine and other fermented foods containing erythritol or sorbitol which they were asked to avoid for about 2 h after test substance intake Only a half (sorbitol 12.5 g) or 1 (sorbitol 25 g) cup of jelly containing sorbitol was given to all subjects. The dose level was lower than that of erythritol because it readily causes diarrhoea. The dose level of jelly containing sucrose was the same as the level of erythritol that caused diarrhoea The order of ingestion of test substances was erythritol, sorbitol and sucrose. When the ingestion of test substance did not cause diarrhoea, the next ingestion of test substance was carried out on the following day or the day after next day. When the ingestion of test substance caused diarrhoea, the next ingestion of test substance was carried out after abdominal symptoms associated with the ingestion of the test substance disappeared Who ingested the jelly containing erythritol were also administered a palatable solution containing the same amount of erythritol to compare the effect of two different forms and no significant difference was observed. The diarrhoeal symptoms were self-reported
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	A questionnaire on diarrhoea included classification of stool shape, i.e. very hard (ball shape like rabbit stool), hard, normal (banana shape), soft (pastelet), very soft (muddy) and watery. For the macroscopic classification of the stool, pictures of stool shape meeting the criteria for classification were handed to each subject to standardise their judgement of faecal condition. The detection of muddy or watery stool was defined as diarrhoea. A question on abdominal symptoms asked about upper and lower abdominal pain, vomiting, nausea, thirst, flatus, gurgle, borborygmus and tenesmus
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable

Results	
Findings reported by the study author/s	When female subjects ($n = 24$ h) ingested 25 g of erythritol (0.34–0.64 g/kg bw), no one experienced watery or muddy faeces. With the ingestion of 37.5 or 50 g of erythritol (0.63–1.16 g/kg bw), 12.5% of subjects had watery or muddy faeces and about 50% of subjects had normal faeces. The ingestion of 62.5 or 75 g of erythritol (1.04–1.74 g/kg bw) caused watery or muddy faeces in 14 out of 21 subjects (66.7%). One subject experienced constipation. On the other hand, no male subjects ($n = 14$) experienced watery or muddy faeces with the ingestion of 25 g of erythritol (0.33–0.44 g/kg bw). With the ingestion of 37.5 g or 50 g of erythritol (0.53–0.88 g/kg bw), 21.4% of subjects had watery or muddy faeces, and more than 50% of subjects had normal faeces. With the ingestion of 62.5 or 75 g of erythritol (O-83-1.32 g/kg bw), 4 out of 11 subjects (36.4%) experienced watery or muddy faeces. Only one of 24 female subjects showed muddy faeces with the ingestion of 12.5 g of sorbitol (0.17–0.32 g/kg bw) and 13 out of 23 subjects (56.5%) had watery or muddy faeces with the ingestion of 25 g of sorbitol (0.42–0.58 g/kg bw). For male subjects ($n = 14$), the ingestion of 12.5 g of sorbitol (O-17-0.22 g/kg bw), 6 out of 14 subjects (42.8%) experienced watery or muddy faeces and the ingestion of 25 g of sorbitol (O-33-0.44 g/kg bw) caused muddy faeces in one out of eight male subjects (12.5%) The laxative threshold of erythritol was estimated as 0.80 g/kg bw for females and 0.66 g/kg bw for males, respectively. The effective dose (ED) 50 was 1.58 g/kg bw for the female group and 1.07 g/kg bw for the male group The results suggest that female subjects are more resistant than male subjects to diarrhoea caused by a high ingestion of erythritol and that the diarrhoeal effect of sorbitol is stronger than that of erythritol.
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	The minimum dose level per kg body weight (g/kg) which first caused diarrhoea, was calculated for each subject, and the values obtained were plotted from lowest to highest. Thus, the cumulative incidence of dose–response diarrhoea was obtained. From the minimum dose level which induced diarrhoea and the cumulative incidence of diarrhoea, a regression equation was made, and the maximum permissible dose level which did not cause diarrhoea was calculated. The side-effect symptoms of erythritol, sorbitol and sucrose were compared using the Wilcoxon signed-rank test
Further information	

Study ID	
RefID (DistillerSR)	**4301**
Reference (authors, year, title, other info)	Nikken Chemicals Co. Ltd., Japan. (1992a). Study on the Maximum No-Effect Level of Erythritol Using Transient Diarrhoeal Action as Index.
Source (published/unpublished)	Unpublished
Study design	
Study type	HCT – Dose escalation cross over trial – Not randomised
Type of blinding	Not blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	12
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	12
Sex (male/female)	Eight males and four females
Age (mean or range as reported)	M: 39.0 ± 11.5 F: 25.3 ± 15.1
Geography (country)	Not reported
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Healthy adults without liver or kidney disorders
Other information	Three out of twelve subjects dropped out from the sugar group because of the pain due to the extreme sweetness of large amounts of sugar, and 3 of 12 subjects dropped out from the sorbitol group because of sorbitol
Intervention/exposure	
Test material	Erythritol

Description of the intervention and estimated dietary exposure	The study substances were dissolved as sweetener in coffee, tea or warm water (150–180 mL). Ingested amount: Erythritol 30, 40 and 50 g Sorbitol 10g Sugar 60 g On the day before ingestion, the subjects avoided foods and drinks likely to cause diarrhoea, as listed in the questionnaire, and ingested the study substances on a day when they felt in good physical condition. Ingestion was completed within 10 min. The study substances were ingested in the order of sugar, erythritol and sorbitol and if diarrhoeal symptoms were noted, the next study substance was ingested after an interval of 3–4 days, when the abdominal condition had stabilised. The erythritol dose increased stepwise every 1–2 days and when diarrhoeal symptoms were noted, ingestion of the next higher dose was discontinued. The subjects were observed without any restrictions on ingested foods and liquids, based on their normal eating habits
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	A survey by questionnaire was conducted before ingestion of the test substance on items such as age, body weight, normal gastrointestinal condition, evacuation pattern, favourite foods, evacuation and foods eaten on the day before ingestion. The time of ingestion was more than 2 h after meals on a day when the subjects felt in good physical condition, and abdominal condition (abdominal pain, feeling of enlarged abdomen and gas), presence and time of occurrence of diarrhoeal symptoms, frequency of diarrhoeal stools and condition of stool (round, banana- shaped, semi- soft, muddy, watery stools) were investigated
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	The median ED50 of erythritol inducing diarrhoea was estimated to be 0.83 g/kg bw for the males and at 1.30 g/kg bw for the females. The NOEL estimated was at 0.55 g/kg for the males and at 0.76 g/kg for the females, with the females showing higher tolerance than the males In cases of abnormal physical condition (abdominal anomalies, diarrhoea symptoms) due to ingestion of the maximum dose of erythritol (50 g) the anomalies occurred within 3 h after ingestion, and diarrhoeal symptoms (muddy to watery stools) were noted one to three times. There were no further complaints after these abdominal and diarrhoeal symptoms had normalised within 24 h, and they are thus attributed to transient action Other than abdominal symptoms due to erythritol ingestion, strange sensation in the throat (feeling of irritation, thirst) was noted in 1 of 12 subjects receiving 30 g, in 2 subjects receiving 40 g and in 1 subject receiving 50 g. This is attributed to osmotic pressure induced by the high-concentration liquid, resulting from the low molecular weight of erythritol. The symptom was promptly eliminated by drinking water. Temporary headache after ingestion was observed in one subject each of the 30 and 50 g dose groups, but it was attributed to mental factors and subsequently disappeared
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Not reported
Further information	
No diarrhoea at all was noted in nine subjects of the sugar ingestion group, but diarrhoea was observed in three out of nine subjects in the 10 g sorbitol ingestion group (incidence: 33%)	

Study ID	
RefID (DistillerSR)	**4302**
Reference (authors, year, title, other info)	Mitsubishi Kasei Corporation, Food Business Department, 1992. Study concerning transient diarrhoea induced by Erythritol.
Source (published/unpublished)	Unpublished
Study design	
Study type	HCT – Dose escalation cross over trial – Not randomised
Type of blinding	Not described
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	Six participants

Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	Six exposed
Sex (male/female)	Males
Age (mean or range as reported)	26–46 years old
Geography (country)	Not reported
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Not reported
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	A prescribed amount of the test substance was mixed in about 180 mL of water or weak coffee to prepare solution for ingestion. The method of ingestion was as follows: The test substance was mixed in water or weak coffee and taken within 10 min from the initiation of ingestion Ingestion of the test substance was performed in the order of sucrose, erythritol and sorbitol Amount ingested: Erythritol: 30 g, 40 g, 50 g, 60 g Sorbitol: 10 g Sucrose: 60 g When diarrhoea was observed, ingestion of the next test substance was performed after 3–4 days of, recovery period to assure stable abdominal condition The dose of erythritol was increased step by step to reach 60 g. If diarrhoea was observed at any dose of erythritol higher doses were not given to the subject. For 24 h after the ingestion, there was no special limitation on the meals and water consumption of the subjects
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Before the ingestion of the test substance, age, body weight, ordinary condition of the gastrointestinal system, condition of evacuation, luxury materials, condition of evacuation on the day before ingestion and contents of meal were asked in questionnaire. Questionnaire was also made on the abdominal condition until 24 h after the ingestion, diarrhoea or not, onset time of and times of diarrhoea if occurred and appearance of the stool
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Diarrhoea was not induced in any subject by the ingestion of 30 g of erythritol. By the ingestion of 60 g of erythritol, all subjects were considered to show diarrhoea. NOEL of erythritol making diarrhoea was estimated to be 0.51 g/kg bw (30 g/person). The abnormal physical signs induced by the bulk ingestion of erythritol were as follows: about 3 h or earlier after the ingestion, abdominal pain and/or growling occurred. Then, one to three times of diarrhetic symptoms (muddy to watery stool) occurred. These abdominal and/or diarrhetic symptoms recovered to normal within 24 h. Other than the abdominal symptoms, thirst and headache were observed after the ingestion of erythritol
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Not reported
Further information	
All the subjects complained of the pain of high sweetness due to the bulk consumption of erythritol and sucrose. However, there was no dropout case	

Study ID	
RefID (DistillerSR)	**4300**
Reference (authors, year, title, other info)	Nikken Chemicals Co. Ltd., Japan. (1992b). The effect of continuous injection of erythritol with laxative action serving as index.
Source (published/unpublished)	Unpublished
Study design	
Study type	HCT
Type of blinding	Not blinded

Duration of the study and length of follow-up	Twice a day for 5 days continuously
Subjects	
Number of participants in the study	10 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	10 exposed
Sex (male/female)	Eight Males and two Females
Age (mean or range as reported)	M: 46 (average) F: 55.5 (average)
Geography (country)	Not reported
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Not reported
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	Erythritol, dissolved in 1 cup (150–180 mL) of cold water (5–10°C), was orally ingested in single 20g doses twice a day (40 g/day), 2–3 h after meals (breakfast, lunch) and was subsequently continuously ingested in the same manner for a total of 5 days. On the day before the start of ingestion, the subjects avoided foods and drinks likely to cause diarrhoea, as listed in the questionnaire, and started ingesting the test substance on a day where they felt in good physical condition The subjects ingested the prepared erythritol solution over a period of 10 min at least 2 h after meals. Subsequent ingestion was discontinued in the subject who experienced diarrhoea during the trial During the study, the subjects were observed without any restrictions on food and liquids, under conditions of normal food and normal daily activities
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	The subjects were asked by questionnaire before ingestion of the test substance about their age, body weight, normal gastrointestinal condition, evacuation pattern, favourite foods, and evacuation and foods eaten on the day before ingestion and after ingestion about their abdominal condition (abdominal pain, feeling of enlarged abdomen, gas, etc.), the presence, time of occurrence and frequency of diarrhoeal symptoms, and evacuation
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	At an erythritol intake of 40 g/day, no laxative action such as diarrhoea was noted in nine subjects. No cumulative effect due to continuous erythritol ingestion was observed Three of the 10 subjects noted single reoccurrence of a feeling of enlarged abdomen on days 2 and 3 of ingestion, but since there was no subsequent worsening and no recurrence of this feeling of enlargement abdomen after subsequent erythritol ingestion, the symptoms are not attributed to erythritol but to effects on the physical condition due to other factors. No other symptoms were observed Meanwhile, laxative action was noted in 1 case on day 2 of ingestion, but since this subject had a disposition toward frequent diarrhoea, reported laxative action even when ingesting 10 g of sorbitol (the maximal ineffective dose), and felt a strange sensation after ingestion, he is considered a mentally susceptible type, who is hypersensitive to sugar alcohol
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Not described
Further information	

Study ID	
RefID (DistillerSR)	**3859**
Reference (authors, year, title, other info)	Meyer-Gerspach, A.C., Wingrove, J.O., Beglinger, C., Rehfeld, J.F., Le Roux, C.W., Peterli, R., Dupont, P., O'Daly, O., Van Oudenhove, L. and Wölnerhanssen, B.K. (2021). Erythritol and xylitol differentially impact brain networks involved in appetite regulation in healthy volunteers. *Nutritional Neuroscience*, 25(11), 2344–2358. https://doi.org/10.1080/1028415x.2021.1965787
Source (published/unpublished)	Published

Study design	
Study type	HCT – Cross-over trial – Randomised – Placebo-controlled
Type of blinding	Double-blind
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	23 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	20 exposed
Sex (male/female)	10 Males and 10 Females
Age (mean or range as reported)	21–45
Geography (country)	Switzerland
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Exclusion criteria were smoking, substance abuse, regular intake of medications, medical or psychiatric illness, any MRI contraindication (e.g. claustrophobia, non-removable metal devices) and any abnormalities detected upon laboratory screening
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	On the evening before each study day, subjects consumed a restricted simple carbohydrate standard dinner before 08:00 pm and fasted from 12:00 am (midnight) until the study visit, which started at 08:00 am on four separate occasions, at least 3 days apart. On arrival, a polyvinyl feeding tube was inserted into the stomach. The rationale for intragastric administration of the test substances was to bypass oro-sensory cues to provide information on the isolated post-oral effects At $t = 0$ min, subjects received an ig load of one of the following test solutions, freshly prepared each morning, over 2 min: (i) 75 g glucose in 300 mL tap water (Haenseler AG, Herisau, Switzerland), (ii) 50 g xylitol in 300 mL tap water (Mithana GmbH, Zimmerwald, Switzerland), (iii) 75 g erythritol in 300 mL tap water (Mithana GmbH, Zimmerwald, Switzerland), (iv) 300 mL tap water (placebo)
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	An intravenous catheter was inserted into an antecubital vein for blood sample collection at specific time intervals ($t = -15, -5, +15$ and $+60$ min) for determination of plasma CCK, PYY, insulin and glucose concentrations At 6 and 21 min after administration, resting blood oxygenation level-dependent (rBOLD) (for 5 min) followed by resting cerebral blood flow (rCBF) (for 4 min) data were acquired, respectively Appetite-related sensations (hunger, prospective food consumption, satiety and fullness) were assessed by visual analog scales (VAS) after each blood sample collection During the study day, the volunteers were asked to report gastrointestinal symptoms such as nausea, bloating and diarrhoea
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	– Xylitol, but not erythritol, increased rCBF in the hypothalamus, whereas glucose had the opposite effect. – Graph analysis of resting functional connectivity revealed a complex pattern of similarities and differences in brain network properties following xylitol, erythritol and glucose. – Erythritol and xylitol induced a rise in CCK and PYY. – Erythritol had no and xylitol only minimal effects on glucose and insulin. – The administration of 50g of xylitol led to bloating and diarrhoea in 40% of all subjects (8 out of 20), and 75 g of erythritol had the same side effects in 16.6% of all subjects (3 out of 20; xylitol vs. erythritol $p = 0.16$). Despite diarrhoea (which usually stopped after one to two bowel movements), no study session had to be terminated prematurely.

Statistical analysis

Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	A two-tailed p-value < 0.05 was considered significant To analyse the time course of the subjective and endocrine responses to the different infusions, marginal linear mixed model analyses were performed - one for each dependent variable. The optimal variance–covariance structure was chosen based on the observed variance–covariance matrix and the best fit indicated by the lowest value of Akaike's Information Criterion (AIC). If the assumption of normally distributed residuals was violated (based on a significant p-value of the Shapiro–Wilk test), box-cox transformations on the dependent variables were used to normalise the residual distribution. Observed untransformed values will be shown on graphs to facilitate interpretation and comparison with previous results The treatment-by-time interaction effect (testing the difference between the four treatments between the three time points) are the effects of interest. To follow-up on the latter effect and test specific hypotheses on the difference in the change from pre-infusion baseline at each of the two post-infusion time points between the four treatments, planned contrast analyses were performed using paired Student's t-tests, with step-down Bonferroni (Holm) correction for multiple testing. Specifically, were compared the change from pre-infusion baseline at each of the two post-infusion timepoints between treatments. Further, was tested whether this change from pre-infusion baseline at each of the two post-infusion time points was significantly different from zero in each treatment separately by planned contrast analyses using one-sample Student's t-tests, with step-down Bonferroni (Holm) correction for multiple testing. Similar models and contrasts were used to analyse the brain data. Finally, to explore putative relationships between the differences in hormone response and brain response to the different sweet substances, were used Spearman's rank non-parametric correlations

Further information

23 volunteers were recruited, but 2 did not meet the eligibility criteria, and one did not tolerate the nasogastric tube. This person's data was excluded from analysis and replaced by a new participant, giving a final total of 20 participants

Study ID

RefID (DistillerSR)	**3850**
Reference (authors, year, title, other info)	Wölnerhanssen, B. K., Drewe, J., Verbeure, W., le Roux, C. W., Dellatorre-Teixeira, L., Rehfeld, J. F., Holst, J. J., Hartmann, B., Tack, J., Peterli, R., Beglinger, C., & Meyer-Gerspach, A. C. (2021). Gastric emptying of solutions containing the natural sweetener erythritol and effects on gut hormone secretion in humans: A pilot dose-ranging study. *Diabetes Obesity Metabolism*, 23(6), 1311–1321. https://doi.org/10.1111/dom.14342
Source (published/unpublished)	Published

Study design

Study type	HCT – Cross-over trial – Randomised – Placebo-controlled
Type of blinding	Double-blinded
Duration of the study and length of follow-up	1 day per test material

Subjects

Number of participants in the study	12 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	12 exposed
Sex (male/female)	Seven Males and five Females
Age (mean or range as reported)	18–40
Geography (country)	Switzerland
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	The exclusion criteria included substance and alcohol abuse, regular intake of medications (except for oral contraceptives), acute infections, chronic medical illness or illnesses affecting the GI system, a history of food allergies, dietary restrictions or pre-existing consumption of erythritol on a regular basis
Other information	

Intervention/exposure

Test material	Erythritol

Description of the intervention and estimated dietary exposure	On four separate occasions, at least 3 days apart and after a 10-h overnight fast, after taking fasting blood ($t = -10$ and -1 min) and breath samples ($t = -10$ min), as well as assessing appetite-related perceptions and GI symptoms, participants received one of the following test solutions (at $t = 0$ min) directly into the stomach by use of a nasogastric feeding tube over 2 min: 10, 25 or 50 g erythritol +50 mg of 13C-sodium acetate dissolved in 300 mL tap water or 300 mL tap water +50 mg of 13C-sodium acetate (placebo). The active treatments were given in a completely randomised order
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Following administration of the test solution blood samples (after 15, 30, 45, 60, 90, 120 and 180 min for analysis of plasma CCK, aGLP-1, PYY, GIP, motilin, glucose, insulin and glucagon), and breath samples (after 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 min for analysis of gastric emptying) were taken. Appetite-related sensations were assessed immediately after each blood collection; participants were asked to rate GI symptoms at 30, 60, 90, 120, 150, 180 and 240 min after administration of the test solutions. Extra blood samples were taken during the visit, with the highest erythritol load (50 g) for analysis of serum total cholesterol, high- and low-density lipoprotein (HDL and LDL, respectively), triglyceride and uric acid concentrations. Blood samples were collected on ice into tubes and analysed using enzyme- or radioimmunoassay. Gastric emptying was determined using a ^{13}C-sodium acetate breath test: test solutions were labelled with 50 mg of ^{13}C-sodium acetate, an isotope that is absorbed readily in the proximal small intestine then transported to the liver where it is metabolised to $^{13}CO_2$, which is then exhaled rapidly and can therefore be used as an indirect marker of gastric emptying. Validated visual analog scales were used to rate the appetite-related sensations (hunger, prospective food consumption, satiety and fullness)
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	A dose-dependent stimulation of CCK, aGLP-1 and PYY, and slowing of GE: there was an overall statistically significant difference for 10 and 50g of erythritol versus placebo comparing the iAUCs for 0–60 min and for the iAUCs for 0–180 min Emptying of erythritol-containing solutions from the stomach was slower compared with placebo No effect on blood glucose, insulin, motilin, glucagon or glucose-dependent insulinotropic polypeptide No effect on blood lipids and uric acid No abdominal pain, nausea or vomiting
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Descriptive statistics were used for demographic variables such as age, weight, height and BMI. For hormone and glucose profiles, gastric emptying and appetite-related sensations, incremental values were used to calculate the incremental area under the curve (iAUC) by the trapezoidal rule. Isolated missing values (because of technical problems or being below the detection limit) were replaced by the treatment group median to enable calculation of the iAUC. The maximum and minimum deviations from baseline – iCmax and iCmin, respectively – were determined using baseline-corrected data. For iAUC calculations, in addition to the total time interval of 180 min, an interval of 60 min is reported because in some variables (CCK and GLP-1) the main effect was observed during this time period. Linear mixed effects modelling was applied to describe differences between the different treatments (placebo, 10, 25 and 50 g). In the case of significant overall treatment effects, pairwise post hoc within-subject comparisons were performed using a Šidak multicomparison test. In addition, for the variables of interest (e.g. iAUCs of 0–60 min for CCK, aGLP-1 and PYY), the minimum detectable differences were estimated on the basis of the observed data in the current study by a simulation with power analysis and sample size 2020 software (NCSS, LLC, Kaysville, UT, USA) using 1000 iterations per run. The order of treatments was evaluated as a covariate. To explore putative relationships between different gut hormone responses (e.g. CCK, PYY and aGLP-1) and gastric emptying of the different treatments, the integrated responses (iAUC 0–60 min) were correlated on an individual basis by linear matrix correlation. The goodness of this correlation was expressed by Pearson's correlation coefficient, R. All statistical analysis was performed using SPSS statistics for windows version 25.0 (IBM, Armonk, NY, USA)
Further information	
All the subjects tolerated the study well, and there were no adverse events during the period of the study. Five subjects did not receive placebo treatment and, therefore, complete data for seven (placebo) to 12 participants (all erythritol doses) were available for analysis	

Study ID	
RefID (DistillerSR)	**3759**
Reference (authors, year, title, other info)	Wölnerhanssen, B. K., Cajacob, L., Keller, N., Doody, A., Rehfeld, J. F., Drewe, J., Peterli, R., Beglinger, C., & Meyer-Gerspach, A. C. (2016). Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects. *American Journal of Physiology-Endocrinology and Metabolism*, 310, E1053–E1061. https://doi.org/10.1152/ajpendo.00037.2016
Source (published/unpublished)	Published

Study design	
Study type	HCT – single-centre, randomised, placebo-controlled, cross-over study
Type of blinding	Double-blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	20 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	20 exposed
Sex (male/female)	Five males and five females in the lean group; Five males and five females in the obese group
Age (mean or range as reported)	24.6 ± 0.2 years old in the lean group; 27.2 ± 2.8 years old in the obese group
Geography (country)	Switzerland
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Lean or obese
Inclusion and exclusion criteria in the study	Inclusion criteria: in general good health, 18–50 years old and BMI < 18 and > 25 kg/m^2 in the lean group and > 30 kg/m^2 in the obese group Exclusion criteria: smoking, substance abuse, regular intake of medications, psychiatric or medical illness, and any abnormalities detected by physical examination or laboratory screening. None of the subjects had a history of GI disorders, food allergies or dietary restrictions
Other information	
Intervention/exposure	
Test material	Erythritol (Mithana, Switzerland)
Description of the intervention and estimated dietary exposure	On the day prior to each study day, subjects consumed a restricted, simple-carbohydrate standard dinner before 20:00 h and then fasted from midnight. On the study day, subjects were admitted to the test centre and an antecubital catheter was inserted into a forearm vein for blood collection. Subjects swallowed a polyvinyl feeding tube (external diameter 8 French) that was placed through an anaesthetised nostril. Study days were identical in design, except for the different test solutions administered: 75 g erythritol dissolved in 300 mL of tap water or 75 g glucose dissolved in 300 mL of tap water (positive control) or 300 mL of tap water alone (negative control). The washout period was not stated
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Plasma glucose, insulin, active GLP-1, CCK, gastric emptying and subjective feelings of satiation Intragastric infusions were freshly prepared each morning of the study day and were at room temperature when administered. After recording two fasting blood samples (t = –10 and –1 min) and a fasting breath sample (t = –1 min), subjects received the test solution via the feeding tube within 2 min (t = 0–2 min). Blood samples were then taken at regular intervals (15, 30, 45, 60, 90, 120 and 180 min) on ice into tubes containing EDTA (6 µmol/L), a protease inhibitor cocktail (Complete®, EDTA-free, 1 tablet/50 mL of blood; Roche, Mannheim, Germany) and a dipeptidylpeptidase IV inhibitor (10 µL/mL; Millipore, St. Charles, MO, USA). Tubes were centrifuged at 3000 rpm for 10 min at 4°C, and plasma samples were stored at –70°C until analysis of plasma glucose, insulin, active GLP-1 and CCK was performed Plasma glucose concentration was measured by a glucose oxidase method (Rothen Medizinische Laboratorien, Basel, Switzerland). Plasma insulin was measured using a commercial electrochemiluminescence immunoassay (Cobas/Roche Diagnostics, Mannheim, Germany). Plasma active GLP-1 was measured with a commercial ELISA kit (Millipore, St. Charles, MO, USA). Plasma CCK concentrations were measured with a sensitive radioimmunoassay using a highly specific antiserum (No. 92128) Test solutions were labelled with 50 mg ^{13}C-sodium acetate for determination of gastric emptying. End-expiratory breath samples were taken at fixed time intervals (15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 min) after instillation of the test solution. The subject's vital signs (blood pressure and heart rate) were measured before and after each study intervention. Appetite perceptions (feelings of hunger, satiety, fullness and prospective food consumption) were assessed by VAS The ^{13}C exhalation was determined by nondispersive infrared spectroscopy using an isotope ratio mass spectrophotometer (IRIS; Wagner Analysen Technik, Bremen, Germany) and expressed as the relative difference from the universal reference standard (carbon from Pee Dee Belemnite limestone). ^{13}C enrichment was defined as the difference between preprandial ^{13}C exhalation and postprandial ^{13}C exhalation at defined time points, over basal. Δ values were converted into atom percent excess and then into percent of administered dose of ^{13}C excreted per h (CO_2 production of the subjects was used, assumed to be 300 mmol/h multiplied by the body surface area as calculated by the weight height formula of Haycock et al. (1978)[a]

Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Erythritol administration led to a marked increase in CCK and GLP-1, whereas insulin and plasma glucose were not affected. Erythritol also induced a significant retardation in gastric emptying compared to placebo. Subjective feelings of appetite were not significantly different after erythritol intake compared with placebo Limitations of the study included: high acute doses, greater than those likely to be encountered in a real-life scenario, that did not permit the investigation of potential adaptive processes
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Hormone and glucose profiles were analysed by AUC from baseline values. The Shapiro–Wilk test was used to test parameters for normality. General linear model repeated measures ANOVA was applied to describe differences between lean subjects and obese participants in the different treatment groups, where obesity status was used as between-subject factor in this analysis. Pairwise post hoc within-subject comparisons were done with the Šidak multi-comparison test and between-subject comparisons by univariate ANOVA. All statistical analysis was done using the statistical software package SPSS for Windows, version 23.0 (SPSS, Chicago, IL., USA). Prevalence of diarrhoea associated with intake was compared by use of Fisher's exact test The sample size was reported to have been chosen based on practical considerations rather than statistical estimation, though the authors considered that a sample size of 8–12 subjects would likely allow the detection of large differences in parameters (50%) between the treatment groups
Further information	
Subjects were also administered a test solution containing 50 g xylitol dissolved in tap water (300 mL) Subjects were instructed to abstain from alcohol, caffeine, black and green tea, coke, chocolate and strenuous exercise for 24 h before each treatment and, also to abstain from sprouts, broccoli and grapefruit for the study duration	

[a] Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. (1978). Geometric Method for Measuring Body Surface Area: A Height-weight Formula validated in Infants, Children, and Adults. *Journal of Pediatry*, 93, 62–66.

Study ID	
RefID (DistillerSR)	**3810**
Reference (authors, year, title, other info)	Bornet, F., Blayo, A., Dauchy, F., & Slama, G. (1996a). Plasma and Urine kinetics of erythritol after oral ingestion by healthy humans. *Regulatory Toxicology and Pharmacology*, 24(2 Pt 2), 280–285. https://doi.org/10.1006/rtph.1996.0109
Source (published/unpublished)	Published
Study design	
Study type	HCT
Type of blinding	Not blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	Six participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	Six exposed
Sex (male/female)	Three males and three females
Age (mean or range as reported)	24–43 years old (mean: 32.67 ± 6.8)
Geography (country)	Not reported
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	No subjects were included in the study who had fasting blood sugar levels above 5.5 mmol/L, were pregnant, had diabetes mellitus or were HIV positive
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	Following an overnight fast, all subjects ingested a single oral dose of 1 g erythritol/kg bw dissolved in 250 mL of water. The total dose administered to each subject ranged from 56 to 78 g, depending on the body weight of the individual
Co-exposure description (if applicable)	Not applicable

Endpoint measured, measurement time points and methods	Fifteen minutes prior to erythritol administration and every 30 min during the period from 0 to 3 h post ingestion, blood samples were collected for analysis of plasma glucose and insulin levels Blood samples also were collected for analysis of plasma erythritol levels every 5 min during the period from 0 to 15 min post ingestion, every 15 min during the period from 15 min to 1 h post ingestion, and every 30 min during the period from 1 to 3 h post ingestion. A blood sample also was taken prior to erythritol ingestion for the determination of plasma creatinine levels At 30 min and 1, 2 and 3 h post ingestion, urine was collected, its volume was measured, and erythritol and creatinine concentrations were determined. Over the next 21 h, total urine output was measured Follow-up medical examinations were performed 24 h after erythritol administration Urine samples were stored at –20°C for 5 weeks prior to erythritol determinations. Similarly, plasma samples were stored at –20°C for 4 to 5 weeks prior to erythritol and insulin determinations. Plasma glucose determinations were conducted immediately after collection GI symptoms were self-reported
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Four out of six subjects (three females and one male) described gastrointestinal symptoms at the 24-h follow-up examination: two reported diarrhoea, while the others reported abdominal cramping, discomfort and flatulence The data indicate that neither plasma glucose nor plasma insulin was affected by the ingestion of erythritol Blood erythritol levels: increased during the first 30 to 40 min, reaching a maximum value of approximately 2.2. mg/mL after 90 min. Then declined gradually to approximately 1.5–1.7 mg/mL at the end of the 3-h sampling period Urine erythritol levels: An average of 30% of the ingested amount of erythritol was excreted unchanged in the urine during the first 3 h. Total urinary excretion of ingested erythritol increased to 78% after 24 h The mean erythritol clearance for the six subjects was 62.0 ± 2.8 mL/min. During the same period, creatinine clearance was 120.2 ± 12.3 mL/min
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Not reported
Further information	

Study ID	
RefID (DistillerSR)	**3793**
Reference (authors, year, title, other info)	Bornet, F., Blayo, A., Dauchy, F., & Slama, G. (1996b). Gastrointestinal response and plasma and urine determination in human subjects given erythritol. *Regulatory Toxicology and Pharmacology*, 24(2 Pt. 2), 296–302. 10.1006/rtph.1996.0111
Source (published/unpublished)	Published
Study design	
Study type	HCT
Type of blinding	Not reported
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	24 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	24 exposed
Sex (male/female)	12 Males and 12 Females
Age (mean or range as reported)	Range: 20–46 Negative control group (4M/2F): 28.0 ± 8.3 Sucrose group (1M/5F): 33.5 ± 8.2 E4 group (3M/3F): 26.7 ± 7.4 E8 group (4M/2F): 27.3 ± 9.2
Geography (country)	Not reported
Ethnicity	Not reported
Confounders and other variables as reported	Not reported

Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Subjects were excluded from the study if they were pregnant, had digestive or hepatic abnormalities, or had cardiac or renal abnormalities
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	The subjects were randomly divided into four groups of six individuals. Three of the groups were administered a snack containing 0.4 g erythritol/kg bw per day (E4 group), 0.8 g erythritol/kg bw per day (E8 group) or 0.8 g sucrose/kg bw per day (sucrose control group). The fourth group no snack (negative control group)
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Plasma glucose levels (expressed in mmol/litre) were measured by a glucose oxidase method (Beckman analyser II). Plasma insulin levels (expressed in mU/litre) were determined using a radioimmunological assay with dextran–charcoal separation (intraassay variability = 6%). Plasma creatinine levels (expressed in μmmol/litre) were measured using a kinetic colorimetric assay (Synchron CX3, Beckman). Plasma sodium, potassium and chloride levels were measured using a Hitachi 717 automated chemistry analyser. Plasma bicarbonates were determined using an enzymatic technique (Biomerieux kit). Albumin was measured using a colorimetric technique with bromocresol green. Urea was measured using an enzymatic technique (Urease, Biomerieux kit). Osmolarity was determined by measuring the freezing point depression Urinary levels of NAG and GGT were measured using a Boehringer kit and a Roche kit, respectively. The plasma erythritol concentration was determined using an HPLC method with 1,3-butanediol as an internal standard (IS). 1,3-Butanediol has similar chromatographic properties to erythritol and was added to plasma samples before the deproteinisation step. A 1/100 dilute solution of IS was originally prepared and the area under the HPLC curve measured under the conditions of the assay Plasma samples were centrifuged and analysed in triplicate. One millilitre of the 1/100 dilution of IS was mixed with 3 mL of centrifuged plasma sample before the deproteinisation step. Deproteinisation was performed by mixing, in a centrifuge tube, 3 mL of icecold perchloric acid (0.6 mol/litre) with the IS/plasma sample mixture. After centrifugation, 1 mL of potassium carbonate solution (0.75 mol/litre) was mixed with 3 mL of supernatant and centrifuged after 3 min in an ice bath. The supernatant was immediately frozen at –20°C for HPLC analysis at a later time. After thawing, the samples were centrifugated and the supernatant was decanted and put into HPLC vials. Erythritol was measured by means of HPLC using a Waters HPLC Solvent Delivery System M45 with a Waters HPLC Differential Refractive Index Detector R401 (Millipore Corp., Milford, MA). A Shodex Ionpack Column KC811 with an internal diameter of 8 mm and a length of 300 mm was used. The injected sample volume was 5 µL. The column operating temperature was 75°C and the flow rate was 1 mL/min. HPLC-grade water containing 0.0018 H2SO4 was used as the eluent Sample preparation and HPLC processing were designed to avoid manipulation errors, such as adding the IS before the deproteinisation step. Based on the original amount of IS added, the recovery of the IS in the final sample was calculated. Also, the percentage recovery was applied to the analytically determined erythritol levels to compensate for manipulation errors A dilution factor of 2.60 was used to account for dilution of samples which occurred during plasma separation and protein precipitation. Results were expressed as erythritol concentration (g/litre) After thawing, urine samples were rehomogenised and filtered through a 0.45 µm filter. Samples of 0.5 mL were mixed with 0.25 mL of the IS before being placed in HPLC vials. The HPLC method was the same as described for the plasma erythritol determinations Urine erythritol concentration was expressed as g/litre and erythritol output as g/min Satiety was evaluated before each meal using an arbitrary scale upon which the subjects recorded their sensation of hunger, ranging from no hunger (0) to extreme hunger (100) The presence of digestive complaints was evaluated on the day following the test using a questionnaire similar to that used by Briet et al. (1995). Items on the questionnaire included abdominal pain, nausea, rumblings, bloating, flatulence, decrease in defecation, increase in defecation, soft faeces and hard faeces. Each item was graded by the subject on a scale of 0 (no effect) to 3 (severe effect)
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable

Results	
Findings reported by the study author/s	Ingestion of erythritol did not affect voluntary intake of water. The mean cumulative water consumptions for the negative control, sucrose, E4 and E8 groups were 1.20 ± 0.37, 1.13 ± 0.15, 1.21 ± 0.33 and 1.11 ± 0.32 litres, respectively There was no difference in the perception of hunger among the subjects receiving snacks containing erythritol and those receiving the snack containing sucrose The only significant difference ($p < 0.005$) in hunger perception was among groups receiving a snack and those which did not receive a snack (negative control group). Although gastrointestinal effects were reported more frequently in subjects in the E4 and E8 groups than in the subjects in the negative control or sucrose groups, these differences were not statistically significant Plasma glucose levels remained normal in all the test groups throughout the study period. Plasma insulin levels remained stable in the two erythritol groups but were significantly increased in the sucrose control group at 1 and 2 h following ingestion of the chocolate snack. Plasma erythritol levels were proportional to the amount of erythritol consumed. As expected, the plasma erythritol levels were higher in the E8 group ($P < 0.06$) than in the E4 group from 2 h following ingestion to the end of the study. No significant variations in plasma osmolarity were observed among any of the test groups throughout the study period. Plasma calcium concentration also did not vary significantly among the test groups Urine volume was not significantly different among the groups with the exception of the sucrose control group which showed a statistically significant increase during the period from 8 to 22 h following snack ingestion when compared to that of the negative controls or E8 groups Urine erythritol levels in the E8 group was approximately twice that of the E4 group ($p < 0.0001$). Over the entire study period (22 h following the ingestion), 61 and 62% of the ingested amount of erythritol were excreted in the urine in the E4 and E8 groups
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Analytical results were analysed by a variance analysis and the differences between test groups were analysed by nonpaired test using ANOVA (Macintosh Stat view). For the analysis of urinary electrolytes and NAG, if any treatment group-related effects were found to be statistically significant, pairwise comparisons of interest among the treatment groups were performed using the least significant difference. The NAG data were first log-transformed. The results from the questionnaire were analysed by the non-parametric Kruskall–Wallis test

Further information

Study ID	
RefID (DistillerSR)	**4299**
Reference (authors, year, title, other info)	Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Department of Metabolic Endocrinology and Department of Nutrition (1993). The effect of continuous administration of the sweetener erythritol on diabetes patients
Source (published/unpublished)	Unpublished
Study design	
Study type	HCT – Not randomised
Type of blinding	Not reported
Duration of the study and length of follow-up	2 weeks
Subjects	
Number of participants in the study	11 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	11 exposed
Sex (male/female)	Three Males and eight Females
Age (mean or range as reported)	M: 65 ± 6 F: 50 ± 14 Mean age: 54 ± 14
Geography (country)	Japan
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Outpatients with non-insulin-dependent type 2 diabetes mellitus
Inclusion and exclusion criteria in the study	Not reported
Other information	

Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	The Erythritol dosage was set at 20 g/day, and after 1 week of outpatient treatment the subjects used erythritol in drinks and foods daily for 14 days. Blood samples were taken before and after administration during hospital visits. The subjects listed the contents of their food for 3 days before the administration and for 3 days before completing administration on case record forms. The ingested energy and the nutritional amount were computed on the basis of these case record forms
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Body weight, fasting blood sugar (FBS) and HbA1c were measured as indices of diabetes control, and BUN, creatinine, beta2-microglobulin and urinary proteins as indices of renal function
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Interviews at the outpatient examination following the 2-week erythritol ingestion on the physical condition during the ingestion period revealed no cases of diarrhoea and no specific subjective symptoms In the 3- day food surveys before and at completion of administration, no significant postdosing changes were noted in ingested energy, proteins, fats and carbohydrates as well as other nutrients Body weight tended to drop from a pre-dosing mean of 60.8 ± 11.6 kg to a postdosing mean of 58.1 ± 9.5 kg, but the difference was not significant. FBS tended to decrease from a pre-dosing mean of 181 ± 60 mg/dL to a postdosing mean of 165 ± 57 mg/dL. The decrease was especially pronounced in patients with high pre-dosing levels. HbA1c showed a significant drop from a pre-dosing mean of 8.5 ± 1.5% to a postdosing mean of 7.5 ± 1.6% ($p < 0.05$). Two- week administration of erythritol thus had no negative effect on body weight or blood glucose control BUN, an index of renal function, showed no large postdosing changes, either in patient whose pre-dosing levels were higher than the normal levels of 21 mg/dL or in patients with normal levels, and the pre-dosing mean of 15.3 ± 5.0 mg/dL hardly differed from the postdosing mean of 14.0 ± 7.3 mg/dL. None of the patients showed an abrupt postdosing rise in blood creatinine levels, with the postdosing mean of 0.8 ± 0.2 mg/dL virtually unchanged from the pre-dosing mean of 0.9 ± 0.2 mg/dL Patient with higher pre-dosing levels than the normal 1.9 mg/L for Beta2-MG, another index of renal function, tended to show a postdosing drop, but there were no cases of a significant rise Likewise, there were no postdosing changes in urinary proteins. The indices of renal function in diabetes patients thus showed no large changes even after 2-week administration of 20 g of erythritol
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Not reported
Further information	

Study ID	
RefID (DistillerSR)	**5111**
Reference (authors, year, title, other info)	Teysseire, F., Bordier, V., Budzinska, A., Van Oudenhove, L., Weltens, N., Beglinger, C., Wölnerhanssen, B. K., & Meyer-Gerspach, A. C. (2023). Metabolic effects and safety aspects of acute D-allulose and erythritol administration in healthy subjects. *Nutrients*, 15(2), 1228–1238. https://doi.org/10.1093/jn/nxac026
Source (published/unpublished)	Published
Study design	
Study type	HCT – Cross-over trial – Randomised – Placebo-controlled
Type of blinding	Double-blinded
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	21 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	18 exposed
Sex (male/female)	5 Males and 13 Females

Age (mean or range as reported)	19–35
Geography (country)	Switzerland
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Subjects were eligible for the study when meeting all of the subsequent inclusion criteria: age between 18 and 55 years, BMI of 19.0–24.9 kg/m^2 and normal eating habits (no diets, no dietary changes). Exclusion criteria were medical or drug abuse including alcohol dependence, acute or chronic infection or illness, illnesses affecting the GI tract, pre-existing consumption of D-allulose and/or erythritol more than once a week, pregnancy and involvement in another study with an investigational drug within 30 days preceding and/or during the study
Other information	
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	Each subject took part in three separate study visits as follows: 25 g D-allulose, 50 g erythritol or 300 mL tap water (placebo). The solutions were dissolved in 300 mL tap water. The order of the study visits was randomised and counterbalanced among subjects. The study visits took place at least 3 days apart and after a 10 h overnight fast. All study visits started at 08:30 in the morning and, upon arrival, a cannula was inserted into a forearm vein for blood collection. Next, a nasogastric feeding tube (external diameter of 8 French) was inserted into the stomach
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	After taking blood samples in a fasting state ($t = -10$ and -1 min), subjects received one of the solutions (at $t = 0$ min) via the nasogastric feeding tube over 2 min. More blood samples were taken at $t = 15$, 30, 45, 60, 90, 120 and 180 min for the analysis of glucose, insulin and ghrelin, and at $t = 30$, 60 and 120 min, for analysis of blood lipids, uric acid and hsCRP. Blood pressure and heart rate were measured at the beginning and at the end of each study visit
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	Glucose and insulin concentrations were lower after D-allulose compared to tap water ($p = 0.001$, $dz = 0.91$ and $p = 0.005$, $dz = 0.58$, respectively); however, Bayesian models show no difference for insulin in response to D-allulose compared to tap water, and there was no effect after erythritol. An exploratory analysis showed that ghrelin concentrations were reduced after erythritol compared to tap water ($p = 0.026$, $dz = 0.59$), with no effect after D-allulose; in addition, both sweeteners had no effect on blood lipids, uric acid and hsCRP
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	For the metabolic effects (glucose, insulin and ghrelin) and safety aspects (blood lipids, uric acid and hsCRP) parameters, no sample size calculations were performed. However, in a sensitivity power calculation, the sample size of 18 participants yields 80% power to detect a medium effect size (Cohen's $d = 0.65$) for the comparison of D-allulose and erythritol with tap water using a one-tailed paired t-test with Holm multiple testing correction ($\alpha = 0.0375$). The one-tailed test is justified by the directional nature of our hypothesis regarding the effects on ghrelin. Data is presented as the mean ± SEM unless otherwise stated. A two-tailed p-value < 0.05 was considered significant and Cohen's dz for paired t-tests was presented for effect sizes. Kolmogorov–Smirnov testing and quantile plots were used to assess normality; for instance, if necessary, natural logarithmic transformations of the data were used to normalise distributions. The visit number was included to control for putative order effects in all models. The metabolic and safety outcome variables were analysed using linear mixed models on changes from baseline (average of pre-infusion time point(s) for the metabolic parameters) and absolute values for the safety aspect parameters. 'Solution' and 'time' were included as within-subject independent variables in the models (including their main effects and the interaction). The metabolic outcome models controlled for baseline values. To follow-up on significant main or interaction effects, planned contrast analyses were performed to test the specific hypotheses, with stepdown Bonferroni (Holm) correction for multiple testing To test the hypotheses that glucose and insulin concentrations, in response to D-allulose and erythritol, will be similar to tap water and that ghrelin will be reduced in response to D-allulose and erythritol compared to tap water, respectively, were compared the post-infusion glucose, insulin and ghrelin concentration changes from the baseline between tap water and D-allulose or erythritol. Was not formulate any a priori hypotheses about the safety outcomes. Given the hypothesis about glucose and insulin concentrations being similar for the two solutions compared to tap water, was complemented the frequentist statistical analysis with Bayesian analyses
Further information	
21 subjects were randomised. There were three drop-outs (one subject withdrew due to knee surgery and two withdrew for personal reasons). A total of 18 subjects completed the three study visits. Complete data sets from all 18 subjects were available for analysis	

Study ID	
RefID (DistillerSR)	**3756**
Reference (authors, year, title, other info)	Overduin, J., Collet, T.-H., Medic, N., Henning, E., Keogh, J. M., Forsyth, F., Stephenson, C., Kanning, M. W., Ruijschop, R. M. A. J., Farooqi, I. S. and van der Klaauw, A. A. (2016). Failure of sucrose replacement with the non-nutritive sweetener Erythritol to alter GLP-1 or PYY release or test meal size in lean or obese people. *Appetite*, 107, 596–603. https://doi.org/10.1016/j.appet.2016.09.009
Source (published/unpublished)	Published
Study design	
Study type	HCT - single centre, randomised, cross-over study
Type of blinding	Single-blinded (though one test meal had a larger volume)
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	20 participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	20 exposed
Sex (male/female)	10 males and 10 females
Age (mean or range as reported)	Lean group: 33.4 (26.3–47.0) years old Obese group: 34.6 (24.9–46.7) years old
Geography (country)	UK
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	10 lean (BMI < 25 kg/m^2) and 10 obese (BMI > 30 kg/m^2)
Inclusion and exclusion criteria in the study	Exclusion criteria: administering any medication, presence of any medical illnesses including diabetes, lactose intolerance or any food allergies
Other information	
Intervention/exposure	
Test material	Erythritol (Zerose™ Erythritol, Cargill, Vilvoorde, Belgium)
Description of the intervention and estimated dietary exposure	On three occasions separated by ≥ 1 week, subjects fasted from 22:00 h the night before each study day and were then admitted to the test centre the following morning to consume one of the following: (a) the sucrose control meal, (b) an isovolumic (reduced calorie) serving of the erythritol meal, (c) an isocaloric (larger volume) serving of the erythritol meal to match for calories to the control meal The breakfast test meals were semi-solid custard (NIZO Food Research B.V. (Ede, The Netherlands) allowing the manipulation of sucrose/erythritol content and the required volume for each volunteer. The calorie content of the sucrose control meal was standardised for each participant to match 20% of the individually calculated energy requirements, based on Schofield[a] equations for basal metabolic rate, multiplied by a physical activity index of 1.25 The sucrose control meal contained 10 g of sucrose per 100 g of meal (10% w/w) and the erythritol meal contained 8% (w/w) erythritol and 2% (w/w) sucrose and had a 25% lower energy density than the sucrose meal. Care was taken to match the sweetness of the erythritol and sucrose control meals: as erythritol provides approximately 0.7× the sweetness of sucrose, 0.004 g sucralose per 100 g of the erythritol food was added
Co-exposure description (if applicable)	Erythritol and sucrose (8% and 2% w/w, respectively)
Endpoint measured, measurement time points and methods	Gut hormone (GLP-1 and PYY) levels, hunger and satiety scores, ad libitum food intake, sucrose preference and intake after the manipulations For GLP-1 and PYY: an intravenous cannula was inserted, and volunteers rested for 30 min. Blood was drawn and VAS scores completed to assess hunger and fullness half-hourly from 07:30 h until 12:00 h. The first two measurements were averaged as the baseline before breakfast. Test breakfasts were given at 08:00 h and consumed within 20 min. VAS were measured on a 10 cm line for liking of the meal and sweet and savoury sensations to assess potential within-meal and between-meal sensory differences after a mouthful and after completion of the test breakfast. The sucrose control and erythritol test meals were rated as equally palatable and as equally sweet An ad libitum buffet lunch was served at 12:30 h, consisting of 3 common food items (chicken korma, sweet and sour chicken, orange cake). There were two versions of each item designed to provide low sucrose and high sucrose content; meals were covertly weighed before and after consumption: all were presented to participants at the same time and they were instructed to select items at will and eat until comfortably full (in individual rooms). Consumption of each food item was then covertly weighed Blood was collected in EDTA tubes containing 100 mL aprotinin (for PYY and total GLP-1), lithium heparin tubes (for insulin) and fluoride oxalate tubes (for glucose). Plasma samples were centrifuged immediately at 4°C and stored at −80°C until assays were performed. Plasma glucose was assayed on the same day using the glucose oxidase method. Insulin was quantified using a commercially available immunoassay (AutoDELFIA Insulin Kit; PerkinElmer, Wellesley, MA, USA). Plasma PYY and total GLP-1 were measured by an established in-house radioimmunoassay[b,c]

Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	There was a greater difference in postprandial glucose and insulin levels after the sucrose meals, rather than the erythritol meals. There were no differences in GLP-1 or PYY levels or subsequent energy intake and sucrose preference between sucrose control and isovolumic erythritol meals. In lean (but not obese) participants, hunger decreased to a greater extent after the isocaloric erythritol meal compared to the control meal ($p = 0.003$) due to the larger volume of the erythritol meal. Comparable hunger and satiety scores, GLP-1 and PYY levels, and subsequent sucrose preference and intake were recorded when sucrose was replaced with erythritol Limitations of the study included: potential changes in the rate of gastric emptying were not assessed, the study assessed the AUC of GLP-1 and PYY levels and therefore transient changes in blood levels may have been missed, the study had limited power to assess small changes in VAS scores, and the effects of an erythritol-pure meal were not tested
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Data were analysed using Stata software package (v. 12.1, StataCorp, College Station, TX, USA). The AUC was calculated for the VAS, glucose, insulin and the gut hormones between the three breakfasts. Peak values between the three breakfasts were also compared for glucose and insulin: lean and obese participants were first analysed separately by ANOVA with repeated measures to test for within-subjects changes and between breakfast differences. Multivariate ANOVA with repeated measures was then performed to investigate group differences between lean and obese volunteers with test meal as within-subjects factor and group as between subjects' factor. The within-subjects p-value was adjusted using the Greenhouse–Geisser correction factor (ε) for lack of sphericity. Pairwise comparisons of the study phases were performed by two-sided Student's t-test when appropriate. $p = 0.05$ was considered significant after Bonferroni correction for multiple comparisons Sample size was based on effect differences from previous studies. Post hoc power analysis of repeated measures ANOVA in a crossover study with this sample size showed power ranged 74% – 99.8% for hormone AUC comparisons (except for PYY AUC in obese participants: 33%)
Further information	

[a]Schofield, W. N. (1985). Predicting basal metabolic rate, new standards and review of previous work. *Human Nutrition Clinical Nutrition,* 39(Suppl. 1), 5–41.

[b]Adrian, T. E., Ferri, G. L., Bacarese-Hamilton, A. J., Fuessl, H. S., Polak, J. M., & Bloom, S. R. (1985). Human Distribution and Release of a Putative New Gut Hormone, Peptide YY. *Gastroenterology*, 89(5), 1070–1077.

[c]Kreymann, B., Williams, G., Ghatei, M. A., & Bloom, S. R. (1987). Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet,* 2(8571), 1300–1304.

Study ID	
RefID (DistillerSR)	**3808**
Reference (authors, year, title, other info)	Noda, K., Nakayama, K., & Oku, T. (1994). Serum glucose and insulin levels and erythritol balance after oral administration of erythritol in healthy subjects. *European Journal of Clinical Nutrition*, 48(4), 286–292.
Source (published/unpublished)	Published
Study design	
Study type	HCT – Cross-over trial – Not randomised
Type of blinding	Not reported
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	Five participants
Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	Five exposed
Sex (male/female)	Males
Age (mean or range as reported)	45–58
Geography (country)	Japan
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	Healthy
Inclusion and exclusion criteria in the study	Not reported
Other information	

Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	Five healthy male subjects received 20% aqueous solution of erythritol in oral dosages of 0.3 g/kg body weight (the average dosage was about 17.3 g/person). One week after the administration of erythritol, they received 20% solution of glucose of the same dosage. Following 12 h fasting, all subjects received each saccharide at 9.30 AM and took lunch at 12.30 PM. They were permitted to take any foods after then except for wine and other fermented foods containing erythritol
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	Urine samples were collected for 48 h after each administration for determination of erythritol, osmotic pressure, sodium, potassium and chloride. Blood was collected at 0.5, 1, 2, 3, 8 and 24 h for determination of serum insulin, glucose, erythritol, total cholesterol (TC), triacylglycerol (TG), free fatty acids (FFA), sodium, potassium and chloride
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	In glucose administration both serum glucose and insulin levels increased rapidly within 30 min and returned to basal values 3 h after dosage. Serum levels of glucose and insulin were not affected for 3 h after erythritol administration. Peak glucose levels were significantly lower after erythritol administration (104 ± 5 mg/dL) than after glucose (142 ± 10 mg/dL). Similarly, insulin release was significantly lower after erythritol administration (7.6 ± 0.9 μU/mL) than after glucose (25.0 ± 3.6 μU/mL). Serum levels of TC and TG were also determined, and no significant difference was found between erythritol and glucose group for 24 h after administration. FFA levels were different between the two groups but they were kept at normal levels. Serum levels of Na, K and Cl were not significantly different between both groups The urine volume for 3 h after erythritol administration at a dose of 0.3 g/kg was not significantly higher than that after glucose administration at the same dosage in humans Osmotic pressure of the urine for 3 h after erythritol administration was slightly higher than that after glucose administration but not significantly so. The urinary excretion of sodium, potassium and chloride for 48 h after the administration showed no significant difference between erythritol and glucose. The plasma concentration of erythritol reached the maximum concentration (426.5 ± 113.4 μg/mL) at 30 min after oral administration and declined to 13.5 ± 3.2 μg/mL at 24 h with a half-life of 3.4 h, indicating that erythritol was absorbed quickly and excreted readily in humans The cumulative urinary excretion as the intact form of erythritol within 48 h after oral administration (0.3 g/kg) was 90.3 ± 4.5%. The urinary excretion rate of erythritol was 11.6%/h for the period of 0–3 h and decreased to 0.2%/h for the period of 24–48 h
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Data were expressed as the mean value and the standard error and were statistically evaluated by Student's *t*-test or Duncan's multiple range test using a significance level of $p < 0.05$. The peak serum concentration of erythritol and the corresponding sampling time were obtained from the observed data. Other pharmacokinetic parameters were calculated by the non-linear least squares programme Automated Pharmacokinetic Analysis System (Yamaoka & Tanigawara, 1983) with one compartment model on averaged serum levels of erythritol
Further information	

Study ID	
RefID (DistillerSR)	**4297**
Reference (authors, year, title, other info)	Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Department of Metabolic Endocrinology and Department of Nutrition. (1992). The effect of erythritol on glucose tolerance in diabetes patients.
Source (published/unpublished)	Unpublished
Study design	
Study type	HCT – Not randomised
Type of blinding	Not reported
Duration of the study and length of follow-up	1 day per test material
Subjects	
Number of participants in the study	Five participants

Number of exposed/non-exposed subjects or number of cases/controls (if applicable)	Five exposed
Sex (male/female)	Gender unspecified
Age (mean or range as reported)	Range: 52.4 ± 19.2
Geography (country)	Japan
Ethnicity	Not reported
Confounders and other variables as reported	Not reported
Special health condition of participants	All patients had non-insulin-dependent type 2 diabetes mellitus and were hospitalised
Inclusion and exclusion criteria in the study	Not reported
Other information	All subjects relied only on dietary therapy as treatment and none showed clear hepatic dysfunctions
Intervention/exposure	
Test material	Erythritol
Description of the intervention and estimated dietary exposure	20 g of erythritol powder was dissolved in 100 mL of water and used as test solution The oral load test was conducted during stable diabetes control of the diabetes patients. The erythritol solution was taken orally at 9 AM, and 10 mL blood samples were taken before and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 h after load. The measuring items included blood glucose, immunoreactive insulin (IRI), non-esterified fatty acids (NEFA), 3-hydroxybutyric acid (3-OHBA) and erythritol. Urine was collected 24 h before and 0–24, 24–48 and 48–72 h after load, and erythritol concentration in urine was measured. The subjects were allowed to eat food 3 h after load Erythritol concentration (in blood and urine) was measured by gas chromatography
Co-exposure description (if applicable)	Not applicable
Endpoint measured, measurement time points and methods	The effect on glucose tolerance, the changes in erythritol blood level and the urinary recovery rate
Were sub-groups analyses predefined? (yes/no, including justification)	Not applicable
Results	
Findings reported by the study author/s	No significant changes in blood glucose and IRI were noted till 3 h after load NEFA was significantly increased to 0.7 ± 0.3 mEq/L 2 h after load, compared to 0.6 ± 0.2 mEq/L before load, but dropped significantly to 0.2 ± 0.1 mEq/L after ingestion of food (6 h after load). 3-OHBA also tended to increase till 3 h after load, but dropped after ingestion of food (6 h after load) to 10.4 ± 9.0 μ M/L, showing a significant decrease from the pre-load level of 79.0 ± 52.3 μ M/L Blood erythritol level reached a peak of 649,4 ± 37.4 μ g/mL 1 h after load, followed by a rapid decrease and virtually all erythritol was eliminated after 24 h The urinary excretion rate was 80%–90% after 24 h and 72 h, respectively
Statistical analysis	
Statistical methods (including power analyses, multiple comparison, potential sources of bias, adjustment for confounders, test for interactions)	Statistical analysis was conducted with StatView II for Macintosh, and the Mann–Whitney U-test was used as test of significant difference
Further information	
Data from this unpublished study report were subsequently published in Ishikawa et al. (1996).	

APPENDIX F

Additional human studies and case-reports

In accordance with the protocol (EFSA, 2020a), human studies performed with mixtures of sweeteners and case-reports were reviewed using a narrative approach. In addition, the study by Hootman et al., 2017 was considered relevant to be included in the opinion with a narrative approach only because no information on exposure to erythritol was provided at the individual participant level.

In the study by Hootman et al., 2017, a prospective non-interventional study, factors were investigated in 172 participants which may influence the development of adiposity gain in young females and males were investigated in 172 participants. The study period was 9 months with data available at the beginning and at the end of the academic year. Anthropometric data were collected and plasma metabolome data were obtained in an open frame approach. Five metabolites differed between the stable adiposity gain group and the incident central adiposity gain group, the phenotype of the two groups being defined by the authors. The five metabolites were further analysed using a targeted GC–MS approach with absolute quantification of erythritol, fructose, lactic acid and three branched chain amino acids using pooled blood samples. The concentration of erythritol was 14.7-fold greater (95% confidence interval [CI]: 13.27, 16.25) in incident central adiposity gain pooled samples compared with pooled samples of participants with stable adiposity (60.8 [SE = 3.1] vs. 4.1 [SE = 0.0] μmol/L; $p < 0.0001$). In further experiments using ^{13}C-glucose (stable isotope), it was shown that in human volunteers erythritol is synthesised *in vivo* from glucose in the PPP, an alternate pathway of glucose catabolism, as shown in specialised experiments. The experiment was also performed in an *in vitro* assay with human blood. In an additional experiment, the plasma concentration of erythritol was investigated in three volunteers following ingestion of 50 g erythritol. Concentrations of erythritol were measured at nine time points up to 3 h with peak plasma concentrations at 90 min. Erythronate, a secondary metabolite, was measured, whereas the primary metabolite erythrose could not be detected. The study shows that endogenously formed erythritol may be related to weight gain.

Human studies on mixtures of sweeteners

Four interventional studies in humans that assessed mixtures of sweeteners including erythritol (sample size; ranging from 25 to 40 subjects) were retrieved from the literature (Fukuda et al., 2010; Gan et al., 2022; Mohsenpour et al., 2019; Shin et al., 2016). Two studies were randomised, three studies implemented a cross-over design, and one study was a pre-post study. Regarding the populations under study, none of the four studies assessed European populations (Japan, $n = 1$; Iran, $n = 1$; Korea, $n = 1$; China, $n = 1$) and they included either patients with type 2 diabetes ($n = 2$) or subjects with glucose intolerance ($n = 1$) or healthy individuals ($n = 2$). Different mixtures were assessed in each study (per 100 g; 27.4 g lactose, 12.9 g fructose, 5.6 g sucrose, 54.1 g of erythritol; 1.6 g rebaudioside A, 98.6 g erythritol; 0.58 g aspartame, 0.25 g acesulfame K, 98.98 g erythritol; 65 or 66 g maltitol, 8 g erythritol) and the study duration varied (1 h, $n = 1$; 1 day, $n = 1$; 5 days (non-consecutive), $n = 1$; 2 weeks, $n = 1$). In the comparative studies, glucose ($n = 2$) and/or sucrose ($n = 3$) were used as controls. The endpoints under study included blood glucose ($n = 4$), insulin ($n = 2$), C-peptide ($n = 1$), quality of life ($n = 1$) and adverse GI reactions ($n = 1$). In the pre-post study, no statistically significant results were reported. Both randomised studies reported statistically significant decrease for blood glucose and one of them reported a statistically significant decrease for insulin.

Mohsenpour et al., 2019, within a single dose double-blind randomised cross-over trial framework, assessed the effect of three 300 mL beverages containing 50 g glucose, 50 g sucrose or 50 g lacritose (a mixture of lactose, fructose, sucrose and erythritol) respectively on postprandial serum glucose up to 2 h post-intervention and on GI adverse effects 1 day post-intervention ($n = 40$, Iran). Study participants were adults with either type 2 diabetes ($n = 21$) or healthy subjects ($n = 20$). Inclusion criteria for T2 diabetic patients were age 20–60 years, FPG < 200 mg/dL, oral T2 diabetes treatment and stable treatment for dyslipidaemia, hypertension or T2 diabetes for at least 1 month. Healthy subjects were 20–60 of age and disease-free (self-report). The lacritose composition (per 100 g) was: 27.4 g of lactose, 12.9 g of fructose, 5.57 g of sucrose and 54.13 g of erythritol, with a glycaemic index of 19.72 and an energy load of 1.98 kcal/g. The analyses performed were adjusted for BMI, gender, age. The mean serum glucose was statistically significantly lower in all time points after ingestion of the lacritose for participants with type 2 diabetes compared to glucose and sucrose. The blood glucose levels were statistically significantly lower in the 30 and 60 min for healthy subjects. Adverse GI reactions were not significantly different between the test beverages.

Shin et al. (2016) in a non-randomised, open label, before-after study evaluated glycaemic effects of rebaudioside A and erythritol in people with glucose intolerance (Korea, $n = 25$). Participants were instructed not to take any other sweeteners and were administered packs containing 16 mg of rebaudioside A and 986 mg of erythritol; they were further instructed to consume two packs dissolved in water, twice a day (after breakfast and dinner) for 2 weeks. The participants were evaluated for plasma fructosamine, fasting glucose, C-peptide, insulin and 2-h glucose before and after the consumption of the sweeteners mixture. No statistically significant differences were reported.

Fukuda et al. (2010) performed a randomised placebo-controlled double-blind crossover trial in Japan including treatment-naïve T2 diabetic patients ($n = 38$). The intervention arm consisted of a commercial high-intensity sweetener (three times sweeter than glucose) containing aspartame (0.58%) blended with acesulfame K (0.25%) and erythritol (98.98%); in two crossover sets, participants were offered meals consisting of white rice, and two side dishes flavoured with the sweetener or sugar; or with sweets flavoured with the sweetener or sugar. The use of the sweetener statistically significantly reduced postprandial levels of blood glucose and insulin when compared to sugar without changes in palatability, sweetness or quality of life (QOL).

Gan et al., 2022 conducted a prospective cross-over study on healthy adults ($n = 17$). Three types of gummy candies were used in the study, a total sugar substitute gummy (T-SG), a partial sugar substitute gummy (P-SG) and a sucrose-based gummy used as comparison (CG). The sugar substitute gummies contained, expressed as carbohydrates percentage, 65% maltitol, 8% erythritol and 2% concentrated apple juice or 66% maltitol and 8% erythritol, for the P-SG and T-SG, respectively. The CG contained, expressed as carbohydrate percentage, 41% glucose syrup, 31% sucrose and 2% concentrated apple juice. All participants underwent glucose tolerance tests after consumption of glucose or the three sample gummies (CG, P-SG, T-SG). The tests were performed for 5 non-consecutive days with ≥ 72 h intervals. The results showed that the P-SG and T-SG groups elicited a better glucose tolerance and were classified as low-glycaemic index foods.

Limited conclusions can be drawn from these studies due to the mixture approach used, that hinders the potential to identify erythritol-specific effects.

Case-reports

Through the literature search, the following new case-reports were retrieved and described below in detail. Evaluations are provided according to the protocol EFSA 2020a and revised version, (according to WHO-UMC (Uppsala monitoring centre) system for standardised case causality assessment).

Katsue et al. (2014) reported a case of adverse reaction in a 32-year-old woman in Japan after 10 min drinking an energy drink containing 500 mg of erythritol, 20 mg of sucralose and 30 mg of acesulfame potassium. The patient reported having hives and throat discomfort. A prick tests for the latter three components were performed and the results were negative. Oral challenge test with each of these three components were performed and gave no reaction, except for acesulfame potassium. A wheal and erythema developed 20 min after the ingestion of 30 mg of acesulfame potassium. Hence, this case is assessed as unrelated to erythritol.

Harada et al. (2016) reported a case in Japan of immediate-type allergy in a 18-year-old woman with a history of atopic dermatitis in childhood, developing anaphylaxis after eating desserts on three occasions. An oral challenge test in the patient was performed in the hospital. Thirteen minutes after taking 1.1 g of erythritol the following symptoms were observed: wheals, eyelid oedema, oral discomfort and cough. A skin prick test with erythritol showed no reactions. The *in vitro* basophil histamine release test (HRT) from the patient and from two healthy adult volunteers showed no release of histamine by erythritol at concentrations from 0.1 to 10 mg/mL. However, the *in vitro* basophil activation test (BAT) with erythritol, showed a small increase in surface expression of CD203c in a dose-dependent manner in cells from the patient. This case is certainly causally related to erythritol exposure.

Sugiura et al. (2013) describes the case of an 8-year-old girl with a medical history of allergic rhinitis who developed 5 recurrent anaphylactic episodes caused by dietary exposure to erythritol. The diagnosis was confirmed by an oral food challenge test, a skin prick test and a basophil activation test. Although exact details on the time sequence are not reported, this case is causally related to erythritol exposure with certainty.

Shirao et al. (2013) described an 11-years old boy hospitalised with anaphylaxis. From the age of 7, the child had experienced episodes of urticaria and wheezing. Despite elimination of known food allergens, repeated episodes occurred. Food challenge with a sweetener containing mainly erythritol but also other sweeteners (acesulfame K and sucralose) compared to granulated sugar as control resulted in cutaneous pruritus followed by wheezing, dyspnoea and generalised urticaria immediately after ingestion. Skin prick test using two '*commercially available erythritol-containing sweeteners*' induced wheals. A scratch test of pure erythritol solution gave a positive reaction in a dose-dependent manner. Although this case-report suggest a rare episode of allergic reaction to erythritol, a major limitation is the use of mixture of sweeteners (despite erythritol being the dominant component) for food challenge and commercially available erythritol sweetener for skin prick test, with no information on purity. The scratch test using pure erythritol in distilled water does however provide more direct evidence for a causal link and the case can be assessed as probably related to erythritol.

Kim et al. (2022) described the case of a 36-years old woman presented to the emergency department (Korea) with dyspnea and angioedema after drinking a peach-based diet beverage containing erythritol. After 10 days, she drank another peach- based diet beverage and experienced urticaria. No serum-specific immunoglobulin E findings were observed. A skin prick test (SPT) was performed using a peach, the two ingested diet beverages, another peach-containing beverage never consumed by the patient and subsequently with 2, 20 and 200 mg/mL erythritol solution. The SPT results for the peach and the peach-containing product were negative, but positive for the two diet beverages containing erythritol as well as for the SPT with erythritol. The patient was diagnosed with anaphylaxis to erythritol. This is a case in which the acute allergic reaction can causally be related to exposure toward erythritol with certainty.

Mori et al. (2022) reported on a 6-years old boy who developed allergic reactions following ingestion of food containing erythritol. He showed a positive skin prick test result and a negative basophil activation test result. An oral food challenge elicited eyelid oedema, lip swelling and cough with wheezing 20 min after ingesting 1 g of erythritol. This case is certainly causally related to erythritol exposure.

Based on the currently available evidence coming from extremely small number of case-reports, the Panel concluded that acute allergic reactions related to erythritol consumption was observed in rare cases, which were all reported from the Asian region.

APPENDIX G

Other studies

Studies in animal disease models

Chukwuma et al. (2018) examined the acute effect of a bolus oral dose of 1 g/kg bw erythritol on intestinal glucose absorption, gastric emptying and postprandial blood glucose increase in normal male rats and in streptozotocin-induced diabetic male rats. Erythritol statistically significantly reduced glucose absorption in the 1st quarter of the small intestine of normal and diabetic animals and statistically significantly delayed gastric emptying in normal animals. There was a statistically significant accelerated gastric emptying in diabetic animals, an effect significantly reduced by erythritol treatment. Erythritol did not significantly influence blood glucose increase in normal animals, while in diabetic animals, erythritol statistically significantly inhibited blood glucose increase compared to the diabetic control group. The same study also examined the acute effect of a bolus oral dose of erythritol on glucose tolerance, insulin secretion, liver and muscle gluconeogenic and glycolytic enzyme activities and mRNA and protein expression of muscle Glut-4 and insulin receptor substrate-1 (IRS-1) in normal male rats and in streptozotocin-induced diabetic male rats. Erythritol did not significantly affect the activities of muscle hexokinase, liver glucokinase and liver glucose-6 phosphatase in normal control animals. Erythritol treatment induced muscle hexokinase and liver glucokinase activities in diabetic animals, but these changes were not statistically significant. In contrast, erythritol treatment significantly reduced hepatic glucose-6 phosphatase activity in diabetic animals. Treatment with erythritol increased liver and muscle glycogen content in diabetic animals (which were lower than normal control animal levels), but these increases were not statistically significant. Erythritol had no apparent effects on liver and muscle glycogen contents of normal animals. Erythritol treatment did not statistically significantly alter muscle Glut-4 and IRS-1 mRNA transcript and protein levels in normal control animals. Muscle Glut-4 protein levels were unaltered whereas muscle IRS-1 protein as well as muscle Glut-4 and IRS-1 mRNA transcript levels were markedly decreased in diabetic animals. These changes in diabetic animals were statistically significantly reversed by erythritol treatment.

Another study by Chukwuma et al. (2018) was conducted to investigate the effect of erythritol on glucose absorption and glucose uptake in isolated male rat jejunum or psoas muscle. Erythritol did not influence glucose absorption in isolated rat jejunum but caused a statistically significant concentration-dependent increase in glucose uptake by isolated psoas muscle at all concentrations. Addition of insulin (200 mU/mL) enhanced glucose uptake alone and resulted in an enhanced 50% increase in glucose uptake by erythritol.

Wen et al. (2018) examined the effect of erythritol in specific-pathogen-free (SPF) grade control and diabetic swiss albino male mice. It is not indicated for how long animals were treated with erythritol. Diabetes was induced by a single intravenous injection of aqueous alloxan monohydrate. Erythritol treatment did not statistically significantly affect the changes in blood glucose concentrations compared to normal control animals that occur due to the co-administration of starch and the glucose AUC, although reduced by erythritol, was not statistically significantly reduced. In contrast, erythritol treatment statistically significantly reduced both the increase in blood glucose due to the co-administration of starch and the glucose AUC in diabetic animals. The authors proposed that erythritol most likely exerts its anti-postprandial hyperglycaemic activities by inhibiting α-glucosidase in a competitive manner based on enzyme inhibition data (tissue not declared) and molecular modelling.

Msomi et al. (2023) used a rat diabetes model (young adult male Sprague Dawley rats fed 10% fructose solution followed by i.p. streptozotocin); confirmed-diabetic rats were administered 0%, 5%, 10% or 20% erythritol in drinking water for 8 weeks. Food and water intake were measured daily; body weight and blood glucose levels weekly; an oral glucose tolerance test was carried out in week 8. Endpoints were end-of-study serum insulin, TC, HDL and triglycerides, aspartate and alanine aminotransferases (AST and ALT), creatine kinase-myocardial band (CK-MB), creatinine, urea and uric acid, oxidative stress markers of serum and pancreatic tissue (malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT)), and pancreas weight and histopathology. Erythritol reduced food and water intake and body weight gain in the diabetic rats. Mean blood glucose and serum CK-MB were reduced dose-relatedly; ALT, AST and creatinine were decreased in all treated groups without dose-dependence; urea and uric acid were unaffected. Serum MDA was decreased and GSH, SOD and CAT were increased by erythritol. Serum insulin and insulin secretion in terms of HOMA-IR and HOMA-β were increased by erythritol, but relative pancreas weights were unaffected. The authors reported that the control diabetic rats had significantly smaller pancreatic islets compared to the non-diabetic controls, and that normal morphology was '*significantly restored*" in the erythritol-treated diabetic rats; no quantitative data were reported. The authors tested xylitol in addition to erythritol and concluded that xylitol has better antioxidant and antidiabetic effects compared to erythritol.

Thirty-six male C57BL/6J mice were equally randomly-divided into four dietary groups and fed a normal diet (ND), a high-fat diet (HFD, 20% fat, 1% cholesterol, w/w) and a HFD with 5% erythritol (ERY) for 16 weeks (Han, et al., 2020a). A pair-feeding was used to ensure that all groups kept on the high-fat diet received the same calorie intake. The mice on HFD without or with 5% erythritol added had increased body weight relative to the ND group. Compared to HFD control, the HFD-ERY group had a statistically significantly reduced body weight and increased relative muscle weight. The body weight gain, relative spleen and liver weights, total relative weights of white adipose tissue, visceral, interscapular brown adipose tissue, epididymal, perirenal, retroperitoneum or sub-cutaneous fat were not statistically significantly different between the HFD and HFD-ERY groups. In contrast, the total relative weights of mesenteric and interscapular white adipose tissue were statistically significantly decreased in the HFD-ERY group. Compared to HFD, inclusion of 5% erythritol in the diet statistically significantly reduced food and energy intake but had no effect on food efficiency ratio or adipocyte

enzyme activity-related lipid metabolism. There were no statistically significant differences between the HFD and HFD-ERY groups in plasma levels of free fatty acids, triglycerides, total cholesterol, apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), non-HDL-cholesterol (TC – HDL-cholesterol), ratio of HDL-cholesterol to total cholesterol), atherogenic index (total cholesterol–[HDL-cholesterol/HDL-cholesterol]), hepatic triglycerides, cholesterol and fatty acid levels, fatty acid synthase, beta oxidation and HMG CoA reductase activities but the hepatic acyl-CoA:cholesterol acyltransferase activity was statistically significantly reduced in HDF-ERY group. The authors reported fibrosis in liver sections stained for collagens in both the HFD and HDF-ERY groups. However, the Panel noted that different regions of the liver lobule were presented on the photos and the staining demonstrated normal vascular structures in the samples.

Thirty-six C57BL/6J mice were divided into four groups and fed with a ND, a HFD (20% fat, 1% cholesterol, w/w), a HFD with 5% erythritol or a HFD with 5% allulose for 16 weeks (Han et al., 2020). A pair-feeding approach was used to ensure that all groups kept on the high-fat diet received the same calorie intake. Compared to the HFD group, inclusion of 5% erythritol in the HFD diet statistically significantly decrease food and energy intakes. There were no statistically significant differences in abdominal, visceral and epididymal fat weights, total white adipose tissue weight, plasma levels of free fatty acids, triglycerides, TC, Apo B, leptin, resistin adiponectin and leptin:adiponectin ratio (L:A ratio) between the HFD and HFD-ERY groups. A statistically significant decrease was observed in plasma levels of Apo A1 in HDF-ERY group compared to the HFD group, however no statistically significant difference was observed in Apo A1/Apo B ratio. The fasting blood glucose concentration was statistically significant decreased in the HDF-ERY group compared to the HFD group. The intraperitoneal glucose tolerance test and AUC showed significantly improved glucose tolerance in the HDF-ERY group compared to HFD group. Other parameters i.e. insulin and glucagon levels, homeostatic index of insulin resistance (HOMA-IR = (fasting glucose (mmol/L) × fasting insulin (μL·U/mL))/22.5), glucokinase (GK), hepatic phosphoenolpyruvate carboxy-kinase (PEPCK), glucose-6-phosphate, hepatic glycogen, gastric-inhibitory polypeptide (GIP), glucagon-like peptide 1 (GLP-1), were not statistically significantly different between the HDF and the HFD-ERY groups. Examination of hepatic levels of lipids revealed no statistically significant differences in hepatic triglycerides, cholesterol and fatty acid levels between the HFD and HDF-ERY groups. There were no statistically significant differences in fatty acid synthase, beta oxidation and HMG CoA reductase levels between the two groups except for a statistically significant reduction in hepatic acyl-CoA:cholesterol acyltransferase and a in plasma glutamic-pyruvic transaminase (GPT) but not in glutamic-oxaloacetic transaminase (GOT) levels in the HFD-ERY group. There were no statistically significant changes in the relative liver weight between the HFD-ERY and HFD groups. The histological examination of the liver (focusing on lipid droplet formation) indicated no difference between the HFD-ERY and HFD groups. In the HFD-ERY group, no statistically significant changes were reported concerning concentration of inflammatory cytokines and tumour necrosis factor (TNF)-α compared to the HFD group.

Kawano et al. (2021) investigated the effects of erythritol (0 or 5% in drinking water) on metabolic disorders induced feeding male C57BL/6J mice a high-fat (60%) diet for 12 weeks (number of animals not reported, except for information in the legends to figures that the parameters were examined from 6 animals per group). Endpoints measured were body weight, glucose tolerance, energy expenditure, fat deposition in the liver, adipocyte size, inflammation markers in the small intestine, concentrations of short chain fatty acids in serum, faeces and white adipose tissue, and innate immunity markers (lymphoid cell interleukin (IL) C3 counts in the lamina propria of the small intestine and ILC2 counts in white adipose tissue, IL-22 expression in the small intestine). In the HFD-erythritol group, the body weight was statistically significantly lower than in the HFD control group, while the cumulative feed and water intakes did not statistically significantly differ between the two groups. In the iPGTT and ITT, the AUCs of blood glucose in the HFD-erythritol group were significantly lower than those in the HFD control group. Activities of serum AST and ALT, blood levels of triglycerides, TC, LDL cholesterol and NEFA were statistically significantly lower and HDL cholesterol was statistically significantly increased in the HFD-erythritol group. There were no statistically significant differences in the liver and epididymal fat weights between the two groups. Histological examination of the liver samples revealed less hepatic fat and fibrosis in the HFD-erythritol compared to the HFD control group. The average cell area and lipid droplet area per cell in epididymal white adipose tissue (eWAT) were significantly lower in the HFD-erythritol group than those in the HFD control group. Histological examination of small intestine showed that the HFD-erythritol group had an increased villus height and width, and a lower crypt depth compared to the HFD control group. Levels of SCFAs, in serum, faeces and in eWAT, were statistically significantly increased in the HFD-erythritol group. A lower ratio of M1 pro-inflammatory macrophages in CD45 positive cells and higher ratio of M2 anti-inflammatory macrophages in CD45 positive cells were recorded in the HFD-erythritol group compared to those in the HFD control group. The innate immunity markers i.e. ILC2 counts in the eWAT and ILC3 counts and IL-22 expression in the lamina propria of the small intestine were statistically significantly higher in the HFD-erythritol group than in the HFD control group.

In Ortiz and Field (2021), two groups of young (8 weeks old at the start of the study) and two groups of old (20 weeks old at the start of the study) male C57BL/6J mice ($n = 16$/group/age) received either a low fat diet i.e. a standard diet (in which 16% of the calories were derived from fat) or a 'Western-type-high-fat diet' (HFD) in which 45% of the calories were derived from fat) for 2 weeks. Thereafter, half the number of mice in each age group continued on the same LFD ($n = 8$) or HFD ($n = 8$) for next 6 weeks and served as controls. The other half of the mice in each age group received either a LFD or a HFD, in which 4% of corn starch was replaced by 4% of erythritol, for next 6 weeks. Young and old male mice on LFD or HFD added erythritol had a statistically significantly increased plasma erythritol concentration compared to the endogenous concentration in the respective controls and this was about up to 60 times higher than in the control group. Replacement of 4% corn starch with erythritol in the LFD or the HFD for 6 weeks had no effect on body weight in young and in old male mice kept on the LFD when compared with respective controls. According to the study authors, in old mice fed HFD with

4% erythritol there was a slight but not statistically significant increase in body weight during and at the end of the dietary exposure to erythritol. The authors reported a significant interaction of erythritol supplementation and time on body weight when comparing the group on HFD with 4% erythritol to a control group on HFD with corn starch. The glucose tolerance, the total body fat and the weight of inguinal white tissue were not different in young and old mice receiving 4% erythritol in either LFD or HFD compared to the respective control groups. No statistically significant changes were observed regarding the weight of the epididymal white adipose tissue in LFD and HFD groups receiving 4% erythritol compared to that in the respective controls. Measurements of endogenous erythritol in four tissues from young mice fed LFD or HFD for 2 weeks revealed the higher concentrations in the kidneys and the liver than in the muscle (quadriceps) or the epididymal white adipose tissue. Consumption of erythritol up to 8 weeks did not affect brown adipose tissue uncoupling protein 1 expression.

In Ortiz and Field (2023), male wild-type 8-weeks old C57BL/6J mice were fed LFD or HFD with plain drinking water or 30% sucrose water for 8 weeks ($n = 8$/group). Plasma and urinary erythritol were measured in nonfasted samples at 2, 5 and 8 weeks, and after a 5-h fast at 7 weeks (control levels typically 2 and 0.1uM, respectively). Consumption of 30% sucrose water versus plain water significantly elevated plasma (around four fold in animals fed a LFD; around two fold in animals fed a HFD) and urinary (around three fold in animals fed a LFD; around two fold in animals fed a HFD) erythritol concentrations in both LFD- and HFD-fed mice, and significantly elevated erythritol in kidney and quadriceps muscle, but not in liver, at 8 weeks. In fasted animals, there was no difference in plasma or urinary erythritol concentration compared to controls.

Witkowski et al. (2023) reported a study in an in vivo mouse thrombosis model. Carotid artery thrombosis formation was measured in young adult BL/6J using a carotid artery injury (FeCl3) model with fluorescently tagged platelets and intravital microscopy with video software; occlusion time was monitored by direct visualisation of when platelets cease to pass downstream of the growing thrombus. Time to cessation of flow was reduced by intraperitoneal erythritol 25 mg/kg bw. The Panel noted that this method was poorly documented; also, the time from administration of erythritol to induction and measurement of thrombus formation was not specified.

The Panel considered that data from studies using animal disease models discussed above were of limited relevance to the risk assessment of erythritol. However, they have been described for completeness.

In vitro mechanistic study by Witkowski et al. *(*2023*)*

The *in vitro* mechanistic studies performed in the publication by Witkowski et al. (2023) are described below in detail.

Witkowski et al. (2023) reported *in vitro* studies using human platelet-rich plasma (PRP), washed platelets or whole blood from adult volunteers with no chronic illness ($n = 55$). In washed platelets, intracellular calcium release induced by a submaximal concentration of thrombin (0.02 U/mL) (quantified by Fura 2-AM fluorescence luminometry) was significantly increased by incubation for 30 min at 22°C with erythritol 45 μM. In washed platelet suspensions (2 × 10E8/mL) with 0.109 M sodium citrate anticoagulant, platelet activation markers P-selectin (CD62P) and PAC-1 (quantified by fluorophore-conjugated antibody flow cytometry) were concentration-dependently increased after pre-incubation for 30 min at 22°C with erythritol 4.5, 18, 45, 90 and 270 μM (not statistically significant for P-selectin at 4.5 μM). Stimulus-dependent platelet aggregation of PRP (2 × 10E8/mL with 0.109 M sodium citrate anticoagulant) in response to submaximal concentrations of two platelet agonists (2–5 μM adenosine diphosphate (ADP) and 5–10 uM thrombin receptor-activated peptide (TRAP6)) was significantly increased by pre-incubation for 30 min at 22°C with erythritol 45, 90 or 270 μM. Platelet aggregation was not significantly increased by 4.5 and 18 μM. *In vitro*, whole blood platelet activation and adherence to immobilised type I collagen, quantified in microfluidic shear flow experiments by computer-assisted imaging of CD42b stained thrombi, was increased after pre-treatment for 30 min at 22°C with erythritol 45 μM. These *in vitro* studies showed that erythritol can activate platelets at minimal concentrations from 4.5 to 18 uM.

The Panel described the *in vitro* data from the Witkoswki et al. (2023) for completeness, although considered of limited relevance to the risk assessment of erythritol.

ANNEX A

Exposure data and estimates

Dietary surveys used for the estimation of chronic dietary exposure to erythritol (E 968).

Summary of reported use levels (mg/kg or mg/L as appropriate) of erythritol (E 968).

Summary of occurrence data submitted by Member States on erythritol (E 968) (μg/kg).

Concentration data used in the exposure assessment scenarios (mg/kg or mL/kg as appropriate) for erythritol (E 968).

Number and percentage of food products labelled with food additive erythritol (E 968) out of the total number of food products present in the Mintel GNPD per food subcategory between 2015 and 2020.

Summary of estimated exposure to erythritol (E 968) for the refined maximum level exposure scenario and the refined brand-loyal exposure scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day).

Main food categories contributing to the exposure of erythritol (E 968) (number of surveys by contribution class) in the brand-loyal scenario.

Main food categories contributing to the exposure of erythritol (E 968) (number of surveys by contribution class) in the refined MPL scenario.

Summary of estimated exposure to erythritol (E 968) for each food in the relevant consumer only maximum level and brand-loyal scenarios (including standard and refined MPL scenarios and scenarios with no facets filtering) per population group and survey: mean and 95th percentile (mg/kg bw per day).

ANNEX B

List of excluded studies

ANNEX C

Weight of Evidence (WoE) tables for human studies