

SCIENTIFIC OPINION

Scientific Opinion on the safety of the proposed extension of use of erythritol (E 968) as a food additive¹

EFSA Panel on Food Additives and Nutrient Sources added to Food^{2,3}

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ABSTRACT

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) provides here a scientific opinion on the safety of erythritol (E 968) in light of the proposed extension of use of erythritol to be added at a maximum level of 1.6 % (16 g/L) as a flavour enhancer in non-alcoholic beverages. In 1999, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) evaluated erythritol and assigned an ADI (acceptable daily intake) “not specified”. In 2003, the European Union (EU) Scientific Committee on Food (SCF) concluded that erythritol is safe for use in foods. The EU approval of erythritol does not yet cover its use in beverages because the SCF opinion stated that the laxative threshold may be exceeded, especially by young consumers, through ingestion of erythritol in beverages. Based on the new data comprising a revised exposure estimate taking into account the proposed maximum level of 1.6 % erythritol in non-alcoholic beverages, the history of its use, the absorption characteristics of erythritol and the lack of adverse findings, including laxation, the ANS Panel concluded that the acute bolus consumption of erythritol via non-alcoholic beverages at a maximum level of 1.6 % would not raise concerns for laxation.

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KEY WORDS

food additive, sweetener, erythritol, E 968, laxation, gastrointestinal tolerability

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) provides here a scientific opinion on the safety of erythritol (E 968) in the light of the proposed extension of use of erythritol to be added at a maximum level of 1.6 % (16 g/L) as a flavour enhancer in non-alcoholic beverages. Erythritol (E 968) is a four-carbon polyol that is well tolerated and currently an authorised food additive in the European Union (EU) under Annex II of Regulation (EC) 1333/2008, belonging to groups I and IV (polyols) of food additives. Erythritol (E 968) may be used in several food categories at *quantum satis*. However, group I is used only for non-sweetening purposes, and group IV is used either as a sweetener, only in energy-reduced products or those with no added sugar, or for purposes other than sweetening. In 1999, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) evaluated erythritol and assigned an ADI (acceptable daily intake) “not specified”.

In 2003, the EU Scientific Committee on Food (SCF) concluded that erythritol is safe for use in foods. The EU approval of erythritol does not yet cover its use in beverages, because the SCF opinion stated that the laxative threshold may be exceeded, especially by young consumers and through ingestion of erythritol in beverages.

In order to resolve this issue, the petitioner conducted a double-blind, randomised, controlled gastrointestinal tolerance study in 128 young children aged 4–6 years, utilising a cross-over design versus placebo with three doses of erythritol (5, 15 and 25 g). The study, which lasted 27 months, was specifically designed to assess gastrointestinal tolerance in comparison with an isosweet control sweetened with saccharose and maltodextrin. At the highest dose of 25 g a greater incidence of diarrhoea and/or significant gastrointestinal symptoms was observed following consumption of the erythritol-sweetened beverage than in the controls. The Panel noted that the results of that study demonstrated that ingestion of 15 g of erythritol in a beverage consumed by children aged 4–6 years on a single occasion with a maximum duration of 15 minutes was considered as the NOAEL (no observed adverse effect level) for laxation in these young children, corresponding to 0.71 g/kg bw (body weight).

In 2010, the ANS Panel of EFSA noted that erythritol intake resulting from an incorporation rate of 2.5 % in beverages (i.e. 0.59 g/kg bw at the 97.5th percentile) is below the NOAEL for laxative effects (i.e. 0.71 g/kg bw) and 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 (0.59 g/kg bw) is 1.24 (EFSA ANS Panel, 2010). The Panel concluded that this MoS is too low to ensure that children are adequately protected, taking into account the fact that erythritol is also used in other food categories.

In February 2013, the EFSA ANS Panel adopted a scientific opinion (EFSA ANS Panel, 2013) on a refined dietary exposure assessment of erythritol, taking into account the additional data provided by the petitioner. The Panel concluded that, based on the new data provided on usage levels of erythritol in foods and on the basis of the extension of the authorisation for the use of erythritol in soft drinks at a usage level of 2.5 %, the MoS of 1.54 is too low to protect children (3–9 years of age) adequately.

In May 2014, the Health and Consumers Directorate-General (DG SANCO) received an addendum to an application from the industry requesting authorisation for the use of erythritol as a flavour enhancer in beverages, food category “14.1.4 Flavoured drinks”, at a maximum usage level of 1.6 %, leading to a total intake from all foods and beverages at the 95th percentile of 0.30 g/kg bw.

The applicant has provided a revised exposure estimate taking into account the proposed maximum usage level of 1.6 % erythritol as a flavour enhancer in beverages, food category “14.1.4 Flavoured drinks”, additional information regarding the history of use of the food additive in beverages, and

additional data on the absorption characteristics and the lack of any adverse findings, including laxation, following exposure to erythritol.

An analysis of the erythritol safety database including the applicant's children's tolerance study supports two factors that impact the safety assessment of erythritol. Firstly, tolerance studies in both adults and children indicated that age has no impact on sensitivity. Studies in adults and children show that the NOAEL for laxation is similar at levels of 0.78 and 0.71 g/kg bw, respectively. The fact that there are no differences in sensitivity suggests that erythritol is handled (absorption and excretion) in an almost identical manner in adults and children following oral administration. Toxicokinetic studies showed that erythritol is rapidly absorbed, with plasma erythritol levels peaking within one to two-hour with the majority of an oral dose (80 to 90 %) being eliminated in the urine within 24-hour. Furthermore, it appeared that the rate of erythritol absorption is more rapid than the rate of plasma clearance. Dose-response studies further indicated that there are no impacts on the levels of absorption at concentrations greater than those requested within the current application. The fact that the majority of an orally administered dose of erythritol is rapidly absorbed indicates that large bolus dosages are more likely to impact on laxation than smaller cumulative doses.

Based on the present application with a maximum proposed level of 1.6 % erythritol as a flavour enhancer in non-alcoholic beverages and on the new available exposure model for acute consumption, a new assessment was performed. In comparison with previous statements, data from the new application combined with an acute consumption scenario in the most relevant population group (children) resulted in a bolus intake (0.6 g/kg bw) lower than the NOAEL for laxation of 0.71 g/kg bw. The Panel noted that using this model at the previous proposed level of 2.5 % would result in a bolus intake (0.94 g/kg bw) greater than the NOAEL for laxation.

The Panel also noted that reducing the use of erythritol in beverages from 2.5 % to a maximum of 1.6 % decreased the total intake from all foods and beverages at the 95th percentile from 0.46 g/kg bw to 0.30 g/kg bw. Considering the same NOAEL, the MoS increased from 1.54 at a usage level of 2.5 % to 2.4 at the proposed usage level of 1.6 % in non-alcoholic beverages.

The Panel concluded that, based on the new data comprising a revised exposure estimate and taking into account the proposed maximum level of 1.6 % erythritol in non-alcoholic beverages, the history of its use, the absorption characteristics of erythritol and the lack of adverse findings, including laxation, the acute bolus consumption of erythritol via non-alcoholic beverages at a maximum level of 1.6 % would not raise concerns for laxation.

TABLE OF CONTENTS

Abstract	1
Summary	2
1. Introduction	5
1.1. Background as provided by the European Commission	5
1.1.1. Reduction of Use Level – Case of Need.....	6
1.1.2. Terms of Reference as provided by the European Commission.....	6
1.2. Interpretation of the Terms of Reference.....	6
1.3. Additional information.....	7
2. Data and Methodologies	7
2.1. Data.....	7
2.1.1. Exposure estimate.....	7
2.1.2. History of use of erythritol in non-alcoholic beverages	8
2.1.3. Erythritol absorption characteristics.....	9
2.1.4. Intestinal tolerance in adults and 4–6 year old children	10
2.2. Methodologies.....	11
3. Assessment	11
4. Conclusion.....	12
Documentation as provided to EFSA.....	13
References	13
Abbreviations	15

1. Introduction

1.1. Background as provided by the European Commission

The use of food additives is regulated under the European Parliament and Council Regulation (EC) No 1333/2008⁴ on food additives. Only food additives that are included in the Union list, in particular in Annex II to that regulation, may be placed on the market and used in foods under the conditions of use specified therein.

Erythritol (E 968) is a four-carbon polyol that is well-tolerated and currently an authorised food additive in the European Union under Annex II of Regulation (EC) 1333/2008, belonging to groups I and IV (Polyols) of food additives. Erythritol (E 968) may be used in several food categories at Quantum Satis, however, at group I only for non-sweetening purposes and at group IV either as a sweetener, in only energy-reduced products or with no added sugar, or for purposes other than sweetening.

In July 2009, the Health and Consumers Directorate-General (DG SANCO) received an application from the industry to approve the use of erythritol in beverage products at a maximum use level of 2.5 % for non-sweetening purposes. Clinical research as reported in the application demonstrated that acute intake of erythritol from such use in beverages is well tolerated, including the potentially highest intake group of young children (4–6 years old).

In June 2010, the European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS) adopted a scientific opinion (EFSA, 2010) in relation to the safety of erythritol in light of that data, including a new paediatric study on the gastrointestinal (GI) tolerability of erythritol in flavoured drinks at a maximum use level of 2.5 % for non-sweetening purposes.

The Panel noted that erythritol intake resulting from an incorporation rate of 2.5 % in beverages (i.e. 0.59 g/kg bw at the 97.5th percentile) is below the No Observed Adverse Effect Level (NOAEL) for laxative effects (i.e. 0.71 g/kg bw/day) and 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 (0.59 g/kg bw) is 1.24. The Panel concluded that this MoS is too low to ensure that children are adequately protected taking into account the fact that erythritol is also used in other food categories. The Panel also concluded that there is a safety concern with respect to gastro-intestinal (GI) tolerability for the use of erythritol in beverages at a maximum use level of 2.5 % for non-sweetening purposes.

In March 2012, DG SANCO received an addendum to an application from the industry, including some additional data, with the aim to extend the authorisation of use of erythritol as a flavour enhancer in beverage products at a maximum use level of 2.5 %.

In March 2013, the EFSA ANS Panel adopted a scientific opinion (EFSA, 2013) on a refined dietary exposure assessment of erythritol taking into account the additional data provided. The Panel concluded that based on the new data provided on use levels of erythritol in foods and on the basis of the extension of the authorisation for the use of erythritol to soft drinks at a use level of 2.5 %, the MoS of 1.54 is too low to protect children (3–9 years) adequately.

In May 2014, DG SANCO received an addendum to an application from the industry requesting the authorisation of use of erythritol as a flavour enhancer in beverages, food category “14.1.4 Flavoured drinks”, at a maximum use level of 1.6 %.

⁴ 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. 16–33.

1.1.1. Reduction of Use Level – Case of Need

In order to manage the risk for osmotically-induced laxation by low digestible carbohydrates such as erythritol, according to the ANS Panel of EFSA requires that the exposure at the 95th percentile should not exceed the NOAEL for laxation established in the most sensitive population under the most severe conditions of use. In previous submissions the applicant has followed this approach that justified a maximum level of 2.5 %. The ANS Panel, however, concluded that children (3–9 years of age) are not adequately protected at this use level (EFSA ANS Panel, 2013).

Aiming to address the concerns of EFSA (EFSA ANS Panel, 2013), the applicant has revised the maximum use levels by reducing it from 2.5 % to 1.6 % and considered the implications of such a reduction. The key functionality for using erythritol in beverages is because it is capable – at low levels – to act as a flavour enhancer by improving mouth feel and sweet taste quality (correcting taste deficiencies associated with the use of high intensity sweeteners) such that these low/no calorie drinks taste similar to full-sugar drinks. The benefit for consumers would thus be the availability of better-tasting, energy-reduced drinks or drinks without added sugars, potentially beneficial to consumer's health (because a reduced intake of sugars has been associated with a reduced risk of obesity, diabetes and tooth decay).

1.1.2. Terms of Reference as provided by the European Commission

The European Commission asks the European Food Safety Authority to provide a scientific opinion on the safety of the proposed extension of use of erythritol (E 968) as a food additive (flavour enhancer) in the food category “14.1.4 Flavoured drinks” in accordance with Regulation (EC) No 1331/2008⁵ establishing a common authorisation procedure for food additives, food enzymes and food flavourings.

The food additive (E 968, flavour enhancer) is to be added at maximum level of 1.6 % (16 g/L) in the products of food category “14.1.4 Flavoured drinks” of Annex II to Regulation (EC) No 1333/2008 on food additives.

1.2. Interpretation of the Terms of Reference

The Panel considered that the Terms of reference can be answered by evaluation of the laxation potential of erythritol in adults and children using the following information:

- Exposure estimate
- History of use of erythritol in non-alcoholic beverages
- Erythritol absorption characteristics
- Intestinal tolerance of erythritol in adults and children

⁵ Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and flavourings. OJ L 354, 31.12.2008, p. 1–6.

1.3. Additional information

The Joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) reviewed the acceptability of erythritol for human consumption in 1999 and assigned an ADI (acceptable daily intake) “not specified” (WHO, 2000). In 2003, the Scientific Committee on Food (SCF) issued an opinion on erythritol following a request by several applicants for the use of erythritol in non-alcoholic beverages up to an inclusion rate of 3.5 %. The conclusion reached by the SCF was that erythritol is safe for use as a food additive. In line with earlier opinions on other polyols, the SCF did not consider it appropriate to set a numerical ADI for erythritol.

The SCF further concluded that in adults the bolus NOAEL for laxation when consumed in a beverage is 0.5 g/kg bw. When consumption is spread over the day from various foods and beverages, the NOAEL for laxation is 1 g/kg bw (SCF, 2003).

In 2010, the European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) concluded that in children aged 4–6 years the bolus no observed adverse effect level (NOAEL) for laxation when consumed in a drink is 0.71 g/kg bw. The maximum erythritol daily intake (97.5th percentile beverage consumption level) in children four to six years of age is estimated to be 11.6 g/person (0.59 g/kg bw based on a proposed level of 2.5 % in soft drinks) (EFSA ANS Panel, 2010). The ANS Panel concluded that the margin of safety (MoS) between the NOAEL of 0.71 g/kg bw and 0.59 g/kg bw of 1.24 was too low to ensure that children are adequately protected.

In 2013, the Panel considered a refined exposure assessment of children aged 4–6 years, again based on a level of 2.5 % in soft drinks. The total daily intake of up to 0.46 g/kg bw from drinks and all other foods at their maximum usage levels resulted in an increased MoS of 1.54, which was considered by the Panel to be too low to protect children adequately.

2. Data and Methodologies

2.1. Data

The applicant has provided a revised exposure estimate taking into account the proposed maximum usage level of 1.6 % erythritol (instead of the previous usage level of 2.5 %) as a flavour enhancer in beverages, food category “14.1.4 Flavoured drinks”, additional information regarding the history of use of the food additive in beverages, additional data on the absorption characteristics of erythritol and the lack of any adverse findings, including laxation, following exposure to erythritol and a scientific explanation why such effects have not been become evident in the European Union (EU).

2.1.1. Exposure estimate

In the previous application provided by the petitioner (2012), the approach for estimating erythritol exposure from all current and proposed food uses in children in the UK was calculated using the following conservative elements:

- The maximum usage level of erythritol was used in the food categories identified as being potential sources of erythritol.
- It was assumed that all foods of which the food industry was aware that could contain significant amounts of erythritol were considered in the assessment.
- Regular foods were included in the category, as it was not possible to reliably include only low-calorie foods from the United Kingdom’s National Diet and Nutrition Survey (UK NDNS, 2008-11) food codes (e.g. confectionery, biscuits/cookies; apart from table top sweeteners, sugar-free chewing gum and low-calorie beverages, where these could specifically be identified).

- UK consumers are usually identified as being one of the highest consumers of soft drinks (including low-calorie ‘diet’ beverages) in the EU.
- Intake data from only consumers were used (i.e. children who were identified as being a consumer of a meal including an erythritol-containing drink).
- Intake data from young children aged 4–6 years were included in the UK NDNS assessment. If slightly older children were included (i.e. three to nine years), this would probably have reduced the per kilogram body weight intakes, thereby producing a higher MoS.

Taking this conservative intake approach, the petitioner used single meal-time consumption data for children aged 4–6 years taken from the UK NDNS survey to model the acute bolus exposure scenario. By varying the maximum usage levels of erythritol in non-alcoholic beverages from 1.5 % to 2.5 %, it was established that total intakes from all foods and beverages at the 95th percentile changed from 0.28 g/kg bw to 0.46 g/kg bw. Considering a bolus NOAEL for laxation of 0.71 g/kg bw the resulting MoS ranged from approximately 2.5 at a usage level of 1.5 % in non-alcoholic beverages to 1.54 at a usage level of 2.5% in non-alcoholic beverages.

In 2013, the Panel did not have a suitable exposure model for acute consumption of non-alcoholic beverages, therefore the Panel made an estimate of total (daily) exposure from all sources which was slightly greater than the NOAEL for laxation following bolus consumption of drinks. The estimated MoS of 0.93 for children aged 3–9 years (EFSA ANS Panel, 2013) was based on the bolus NOAEL divided by the total (daily) erythritol intakes from all foods at the 95th percentile in children (0.76 g/kg bw/day).

The EFSA Comprehensive Database now allows a more appropriate estimate of potential acute or single occasion consumption of soft drinks. Based on this scenario, the high level (97.5th percentile) acute consumption of soft drinks on a single occasion in the main relevant population group of children 3–9 years old would result in an exposure of 0.6 g/kg bw of erythritol, which is lower than the NOAEL following bolus consumption.

2.1.2. History of use of erythritol in non-alcoholic beverages

The applicant has submitted the following information in support of the history of use of erythritol in beverages.

Erythritol has a history of safe use in products, including beverages, being consumed since 1990 after being authorised for use in foods in many countries including Japan, the USA, Canada, Brazil, Argentina, Paraguay, Uruguay, China, India, Israel, Mexico, the Philippines, Singapore, Australia, New Zealand, Japan, Korea, Taiwan and Thailand.

Erythritol is currently approved and marketed in more than 60 countries around the world and is authorised for use in foods including beverages at levels typically around 3.5 %, equivalent to 35 g/L. These beverage categories include mainstream products such as coffee and tea, liquid dietary supplements, near-water beverages and vitamin water.

Euromonitor has published consumption levels of erythritol from 2007 to 2012 inclusive. The results show that, on a worldwide basis, the consumption levels of erythritol in 2012 accounted for approximately 25 500 metric tonnes.

The applicant stated that it is not aware of any reports of digestive tolerance issues in adults or in children at usage levels greater than twice those requested within the present European application.

2.1.3. Erythritol absorption characteristics

The applicant has submitted additional data to illustrate the absorption characteristic of erythritol.

In a study conducted in healthy humans (six healthy volunteers) by Bornet et al. (1996a), it was found that, following a large bolus oral dose of 1 g/kg in 250 mL of beverage, the majority (approximately 80 %) was rapidly absorbed and eliminated unchanged in the urine within a 24-hour period, leaving a potential maximum of 10 to 20 % that would be unabsorbed and excreted in the faeces. The mean peak plasma concentration was reported to occur around 90 minutes, with a C_{\max} of 2.2 g/L.

Another study (Ishikawa et al., 1996) looking at the effects of oral administration of erythritol in patients with diabetes found that, following administration of a bolus dose of 20 g in solution, serum levels of erythritol peaked within one hour of administration ($C_{\max} = 649.4 \pm 37.4 \mu\text{g/mL} \equiv 0.65 \text{ g/L}$), then showed a log linear decrease over time. Total urinary excretion within the 24-hour after ingestion was estimated to be approximately 80 %.

The rapidity with which the majority of an oral dose of erythritol is absorbed was further supported in a gastrointestinal response study following single oral administrations of erythritol at dose levels of 0.4 and 0.8 g/kg bw in a milk chocolate snack in groups of six healthy volunteers (Bornet et al., 1996b). Again, the plasma erythritol data indicated that the peak plasma concentration occurred within one to two-hour of administration and that the majority was eliminated from the plasma within an eight-hour time period, supporting rapid absorption. Approximately 60 % of the erythritol was found in the urine within 22-hour. In fact, the rate of absorption was determined using specifically the plasma erythritol time–concentration data from the diabetic study, as well as the 0.8 g/kg dose group from the milk chocolate snack study.

Using a method of residuals (Roberts and Renwick, 2009), whereby the plasma concentration–time curve is extrapolated to time zero, permits the difference between the actual data obtained and the extrapolated line to be determined. This difference is due to the absorption of erythritol into the circulation. Plotting the difference between these points (although limited in number) indicates that erythritol undergoes first-order absorption and that the rate of absorption (k_a) is greater than that of elimination (k_{el}). In addition, from knowing that 40 % of an oral dose of erythritol administered within a beverage is eliminated in the urine within the first three-hour and 60 to 70 % within eight-hour of administration, the petitioner concluded that the majority of the dose (an estimated minimum of 60 to 70 %) is absorbed from the gastrointestinal tract within the first three-hour time frame. The Panel agreed with this conclusion.

The peak plasma concentrations at the 0.4 and 0.8 g/kg dose levels were likewise estimated to be around 0.35 and 0.6 g/L, respectively, indicating a linear dose–response relationship, which was further supported by the urinary excretion data, which showed that twice the amount of erythritol was excreted at the higher dose within the same time period.

The bolus dose administration from a beverage resulted in a greater peak plasma concentration, on a gram dosage basis, than that which occurred following incorporation in a chocolate bar, further supporting the fact that bolus dose administration of erythritol in beverages is absorbed more rapidly than administration from other food matrices.

In addition, the plasma erythritol concentration–time curves and the urinary excretion data in both of these studies support the fact that the absorption and clearance characteristics are linear over a dose range of 0.4 to 0.8 g/kg bw when administered in chocolate. The petitioner concluded that the rapid and near-complete absorption of lower amounts of erythritol following administration within other food matrices during the day indicates that this would result in low levels remaining in the gut that would not significantly affect the laxation potential from a large single bolus dose.

The Panel agreed with this conclusion.

2.1.4. Intestinal tolerance in adults and 4–6 year old children

A significant number of adult human tolerance studies conducted with erythritol have found that the NOAEL for laxation following bolus dose administration within a beverage ranges between 0.51 and 0.8 g/kg bw, with the lowest NOAEL determined in a study in which erythritol was administered on an empty stomach in six subjects, some of whom had previously experienced digestive disorders. However, a study conducted in 65 healthy adults (Storey et al., 2007) indicated that the NOAEL for laxation equated to a dose of 50 g, which was equivalent to a bolus dose of 0.78 g/kg bw. This NOAEL was found to be similar to those found in other erythritol tolerance studies (Bornet et al., 1996b; Oku and Okazaki, 1996).

The tolerability of erythritol determined in adults as a result of bolus administration was likewise established by the petitioner in young children aged 4–6 years following a single drinking occasion (unpublished data). It was a double-blind, randomised, controlled gastrointestinal tolerance study applying a cross-over design. In this study, three doses of erythritol (5, 15 and 25 g) were administered in comparison with an isosweet control (saccharose and maltodextrin) in a total of 128 children. Diarrhoea and significant gastrointestinal symptoms were carefully evaluated.

For the 5- and 15-g erythritol test groups, there was no difference in the incidence of diarrhoea or significant gastrointestinal symptoms between the erythritol-sweetened test beverages and the saccharose and maltodextrin-sweetened (control) product, the incidence of gastrointestinal symptoms in the placebo group ranging from 4 to 14 %. Specifically at the 15-g dose, an 18 % incidence of gastrointestinal effects versus 11 % in the placebo group ($p = 0.2482$) was noted. At the 25-g dose, the incidence of diarrhoea and/or significant gastrointestinal symptoms was observed to be greater following consumption of the erythritol-sweetened beverage (32 %) than the isosweet control (3.5 %) ($p = 0.0002$). The average number of stools during the study period was not different between erythritol and control for the 5- and 15-g groups, while a small but a statistically significant increase in daily stool frequency was noted in the 25-g dose group: 2.3 versus 1.9 stools per day for erythritol-sweetened beverage and control, respectively ($p = 0.0188$). A similar observation was made for mean stool consistency measured by the Bristol Scale score. The incidences of nausea, vomiting, borborygmi, excess flatus and abdominal pain were not different in the erythritol and control groups; however, abdominal bloating was higher in the 25-g dose erythritol group than in the control group (7 % versus 0 %; $p = 0.046$).

In this rising dose study design, the petitioner established that a 15-g dose when administered orally within a 15-minute time frame was the NOAEL for laxation, which equates to a bolus dose of 0.71 g/kg bw. As such, the tolerability data reported for both adults and children are almost identical, producing NOAELs of ~0.78 g/kg bw and 0.71 g/kg bw, respectively, following bolus dose administration.

A higher dose of 25g (1.23 g/kg bw) resulted in a slight but statistically significant effect on laxation, including an increase in daily stool frequency for an erythritol-sweetened beverage in comparison with control. Abdominal bloating was higher in the 25-g dose erythritol group than in the control group (7 % vs. 0 %; $p = 0.046$).

Based on these observations, the petitioner concluded that there is no difference in terms of erythritol tolerability between children and adults and, thus, the data provide evidence that children are not more sensitive than adults in terms of laxation on a body weight basis, indicating that children handle erythritol in a similar way to adults following bolus administration.

The Panel agreed with this conclusion.

The present application requests an upper usage level of 1.6 % in beverages in the EU. Using the same scenario as outlined above, an assessment of the likely erythritol exposure in children aged 4–6 years was evaluated by the petitioner using information from the UK NDNS. Looking specifically at the

daily fluid intake for 4–6 year-old children, it was determined that the mean and 90th percentile beverage consumption equates to 855 mL and 1 254 mL, respectively.

An erythritol incorporation level of 1.6 % in a standard European serving size of 250 or 330 mL beverage would result in an intake of 4.0 and 5.3 g, respectively. As laxation in children 4–6 four years of age will be in the region of 20 to 25 g, the petitioner determined that a child in this age group would need to consume a beverage volume of at least 1.25 L in a single serving, which approximates the daily fluid intake at the 90th percentile.

2.2. Methodologies

The current “Guidance for submission for food additive evaluations” (EFSA ANS Panel, 2012) has been followed by the ANS Panel for the evaluation of the proposed extension of the authorisation of the already authorised food additive erythritol (E 968).

In 2013 the Panel did not have a suitable exposure model for acute consumption of non-alcoholic beverages, therefore it made an estimate of total potential exposure from all sources (EFSA ANS Panel, 2013). As the EFSA Comprehensive Database now allows a more appropriate estimate of consumption of soft drinks on a single occasion, a revised and more relevant assessment is therefore feasible. This relevance derives from the MoS for laxation being based on data from a study in children in which erythritol was administered within a 15-minute time frame.

3. Assessment

In its scientific opinion of 2003, the SCF expressed concerns that the laxative threshold for erythritol may be exceeded, especially by young consumers, through ingestion of erythritol in beverages (SCF, 2003). The UK Committee on Toxicity (COT) expressed similar concerns in 2004, concluding that it was not acceptable for erythritol to be used in beverages at a 3.5 % usage level because convincing evidence was not yet available to demonstrate digestive tolerance for acute bolus (single drinking occasion) exposure in young children, in particular those aged 4–6 years (COT, 2004).

In order to resolve this issue, the petitioner conducted a double-blind, randomised, controlled gastrointestinal tolerance study in 128 young children aged 4 to 6 years, utilising a cross-over design with three doses of erythritol (5-, 15- and 25-g). The study, which lasted 27 months, was specifically designed to assess gastrointestinal tolerance in comparison with an isosweet control sweetened with saccharose. At the highest dose of 25-g, a greater incidence of diarrhoea and/or significant gastrointestinal symptoms was observed following consumption of the erythritol-sweetened beverage versus the control.

The Panel noted that the results of that study demonstrated that ingestion of erythritol in a beverage consumed by children aged 4–6 years on a single drinking occasion of a maximum duration of 15 minutes indicates a NOAEL for laxation in these young children of 15 g, corresponding to 0.71 g/kg bw.

In 2010, the EFSA ANS Panel noted that erythritol intake resulting from an incorporation rate of 2.5 % in beverages (i.e. 0.59 g/kg bw at the 97.5th percentile) is below the NOAEL for laxative effects and that the MoS between this NOAEL and the estimated daily intake of erythritol is 1.24. The Panel concluded that this MoS is too low to ensure that children are adequately protected, taking into account the fact that erythritol is also used in other food categories.

In February 2013, the EFSA ANS Panel adopted a scientific opinion (EFSA ANS Panel, 2013) on a refined dietary exposure assessment of erythritol, taking into account the additional data provided by the petitioner. The Panel noted that the MoS was < 1 in high-level child consumers and concluded that, based on the new data provided on usage levels of erythritol in foods and on the basis of the

extension of the authorisation for the use of erythritol to soft drinks at a usage level of 2.5 %, the MoS of 1.54 is too low to protect children (3–9 years of age) adequately.

In May 2014, DG SANCO received an addendum to an application from the industry requesting the authorisation of use of erythritol as a flavour enhancer in beverages, food category “14.1.4 Flavoured drinks”, at a maximum usage level of 1.6 %, leading to a total intake from all foods and beverages at the 95th percentile of 0.30 g/kg bw.

The applicant has provided a revised exposure estimate taking into account the proposed maximum usage level of 1.6 % erythritol as a flavour enhancer in beverages, food category “14.1.4 Flavoured drinks”, additional information regarding the history of use of the food additive in beverages, additional data on the absorption characteristics, and the lack of any adverse findings, including laxation, following exposure to erythritol and a scientific explanation of why such effects have not been become evident in the EU.

An analysis of the erythritol safety database including the applicant’s tolerance study in children supports two important factors that impact the safety assessment of erythritol. Firstly, tolerance studies in both adults and children have indicated that age has no impact on sensitivity. Studies in adults and children show that the NOAEL for laxation is similar at levels of 0.78 and 0.71 g/kg bw, respectively. The fact that there are no differences in sensitivity suggests that erythritol is handled (absorption and excretion) in an almost identical manner in adults and children following oral administration. Toxicokinetic studies have shown that erythritol is rapidly absorbed, with plasma erythritol levels peaking within one to two-hour and the majority of an oral dose (80 to 90 %) being eliminated in the urine within 24-hour. Furthermore, it appears that the rate of erythritol absorption is more rapid than the rate of plasma clearance. Dose–response studies have further indicated that there are no impacts on the levels of absorption at concentrations greater than those requested within the current application. The fact that the majority of an orally administered dose of erythritol is rapidly absorbed indicates that large bolus dosages are more likely to impact laxation than smaller cumulative doses.

Lack of an effect of erythritol on laxation is evident following a long history of use in many parts of the world including the USA. Erythritol has been permitted for sale in the USA for more than 15 years and US data indicate that beverage incorporation levels up to 3.5 % do not produce adverse effects in children or adults. In children, this is not surprising given that the volume of a beverage required to generate laxation in a single serving equates to a fluid volume that is approximately 75 % of the mean daily fluid intake for a child of this age group. Therefore, the petitioner considered that it is unlikely that adverse effects will occur following the introduction to the market of beverages in the EU containing an upper level of 1.6 %, as requested in the present application.

4. Conclusion

Based on the present application for a maximum proposed level of 1.6 % erythritol as a flavour enhancer in non-alcoholic beverages and on the new available exposure model for acute consumption, the Panel performed a new assessment. In comparison with previous statements, data from the new application combined with an acute consumption scenario in the most relevant population group (children) resulted in a bolus intake of 0.6 g/kg bw, which is lower than the NOAEL for laxation of 0.71 g/kg bw.

The Panel also noted that reducing the use of erythritol in beverages from 2.5 % to a maximum of 1.6 % decreased the total intake from all foods and beverages at the 95th percentile from 0.46 g/kg bw to 0.30 g/kg bw. Applying the same NOAEL and exposure scenario used in the previous opinions, the MoS increased from 1.54 at a usage level of 2.5 % to 2.4 at the proposed usage level of 1.6 % in non-alcoholic beverages.

The Panel concluded that, based on the new data comprising a revised exposure estimate and taking into account the proposed maximum level of 1.6 % erythritol in non-alcoholic beverages, the history of use, the absorption characteristics of erythritol and the lack of adverse findings, including laxation, the acute bolus consumption of erythritol via non-alcoholic beverages at a maximum level of 1.6 % would not raise concerns for laxation.

DOCUMENTATION AS PROVIDED TO EFSA

1. Addendum to Previous Request to the European Commission for an Amendment of Annex II to Regulation (EC) 1333/2008 for the Inclusion of Erythritol (E 968) in Flavoured Beverages. May 2014. Submitted by Cargill R&D Centre Europe.
2. Clinical study report on paediatric trial of erythritol gastrointestinal tolerability, Cargill 2009.

REFERENCES

- Bornet FR, Blayo A, Dauchy F and Slama G, 1996a. Plasma and urine kinetics of erythritol after oral ingestion by healthy humans. *Regulatory Toxicology and Pharmacology*, 24, S280–285. doi:10.1006/rtph.1996.0109
- Bornet FR, Blayo A, Dauchy F and Slama G, 1996b. Gastrointestinal response and plasma and urine determinations in human subjects given erythritol. *Regulatory Toxicology and Pharmacology*, 24, S296–302. doi:10.1006/rtph.1996.0111
- COT (Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment), 2004. Erythritol. In: *Annual Report 2004*. COT, London, 10.
- EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 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* 2010;8(7):1650, 17 pp. doi:10.2903/j.efsa.2012.1650
- EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2012. Guidance for submission for food additive evaluations. *EFSA Journal* 2012;10(7):2760, 60 pp. doi:10.2903/j.efsa.2012.2760
- EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2013. Statement on a refined dietary exposure assessment of erythritol (E 968) taking into account additional data provided. *EFSA Journal* 2013;11(3):3121, 11 pp. doi:10.2903/j.efsa.2013.3121
- Ishikawa M, Miyashita M, Kawashima Y, Nakamura T, Saitou N and Modderman J, 1996. Effects of oral administration of erythritol on patients with diabetes. *Regulatory Toxicology and Pharmacology*, 24, S303–308. doi: 10.1006/rtph.1996.0112.
- Munro IC, Berndt WO, Borzelleca JF, Flamm G, Lynch BS, Kennepohl E and Modderman J, 1998. Erythritol: an interpretive summary of biochemical, metabolic, toxicological and clinical data. *Food and Chemical Toxicology*, 36, 1139–1174.
- Oku T and Okazaki M, 1996. Laxative threshold of sugar alcohol erythritol in human subjects. *Nutrition Research*, 16, 577–589. doi:10.1016/0271-5317(96)00036-X.

- Roberts A and Renwick, A, 2009. Toxicokinetics. In: General and applied toxicology, Vol. 1, 3rd edition. Eds Ballantyne B, Marrs TC and Syversen T. John Wiley & Sons Limited, Chichester, UK, 147–180.
- SCF (Scientific Committee on Food), 2003. Opinion of the Scientific Committee on Food on Erythritol. Available online: http://ec.europa.eu/food/fs/sc/scf/out175_en.pdf.
- Storey D, Lee A, Bornet F and Brouns F, 2007. Gastrointestinal tolerance of erythritol and xylitol ingested in a liquid. *European Journal of Clinical Nutrition*, 61, 349–354.
- UK NDNS (National Diet and Nutrition Survey), 2008. National Diet and Nutrition Survey, 2008-2011. National Centre for Social Research, Medical Research Council, Resource Centre for Human Nutrition Research and University College London. doi:10.5255/UKDA-SN-6533-2
- WHO (World Health Organization), 2000. Erythritol: Report TRS 896-JECFA 53/18-Tox monograph: FAS-44-JECFA 53/15. Available online: http://www.inchem.org/documents/jecfa/jecval/jec_698.htm.

ABBREVIATIONS

ADI	acceptable daily intake
ANS Panel	Panel on Food Additives and Nutrient Sources added to Food
bw	body weight
COT	Committee on Toxicity (Food Standards Agency, UK)
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MoS	margin of safety
NOAEL	no observed adverse effect level
SCF	Scientific Committee on Food
UK NDNS	United Kingdom National Diet and Nutrition Survey
WHO	World Health Organization