Safety of D-ribose as a novel food pursuant to Regulation (EU) 2015/2283

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Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on D-ribose as a novel food (NF) pursuant to Regulation (EU) 2015/2283. The applicant intends to market the NF as ingredient in a variety of foods, food supplements and in certain foods for specific groups. The NF is produced by fermentation using a transketolase-deficient strain of *Bacillus subtilis* and marketed as Bioenergy Ribose™. The information provided on the batch-to-batch variability, specifications, stability, production process and history of the organism used as a source of the NF is sufficient and does not raise safety concerns. The Panel considers that the effects observed in a subchronic toxicity study in rats could be the consequence of nutritional imbalances, but toxicological effects could not be ruled out; from this study, the Panel derived a No observed adverse effect level (NOAEL) of 3.6 g/kg body weight (bw) per day. From the human studies indicating a potential decrease in glucose levels and/or the occurrence of transient symptomatic hypoglycaemia at intakes of 10 g of D-ribose, the Panel defined 70 mg/kg bw per day as the NOAEL with respect to hypoglycaemia that can be considered applicable for adults. For children, the Panel acknowledges the lack of human data directly relevant for this population group. Based on the NOAEL derived from the subchronic toxicity study in rats, an acceptable level of intake of 36 mg/kg bw per day was defined that would also take into account the potentially increased sensitivity of certain population groups to hypoglycaemia. The Panel concludes that the NF is safe for the general population at intake levels up to 36 mg/kg bw per day and considers that the safety of the NF at the intended uses and use levels as proposed by the applicant has not been established.

Keywords: ribose, D-ribose, novel food, ingredient, safety

Requestor: European Commission following an application by Bioenergy Lire Science, Inc.

Question number: EFSA-Q-2017-00461

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Summary

Following a request from the European Commission, the European food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on D-ribose as a novel food (NF) pursuant to Regulation (EU) 2015/2283. The assessment of the safety of this NF, which follows the methodology set out in the EFSA Guidance for the preparation and presentation of an application for authorisation of a NF[1] according to Regulation (EU) 2015/2283 and in the Commission Implementing Regulation (EU) 2017/2469, is based on the data supplied in the application, the initial assessment by the competent authority of the United Kingdom, the concerns and objections of a scientific nature raised by the other Member States and the responses of the applicant, the information submitted by the applicant following EFSA requests for supplementary information and additional data identified by the Panel.

The NF which is the subject of the application is D-ribose produced by fermentation using a transketolase-deficient strain of *Bacillus subtilis* and marketed as Bioenergy Ribose™.

The information provided on the batch-to-batch variability, stability, specifications, production process, and history of the organism used as a source of the NF is sufficient and does not raise safety concerns.

The applicant intends to market the NF as an ingredient in a variety of foods, food supplements and in certain foods for specific groups (total diet replacement for weight control and food for special medical purposes). The maximum proposed use levels range from 0.31 to 5 g/100 g in fortified foods and up to 10 g/day in food supplements.

Based on the proposed uses and maximum use levels and the individual food consumption data from the EFSA Comprehensive Food Consumption Database, the Panel estimated the range of the 95th percentile anticipated intakes of the NF in the European Union (EU) from the consumption of fortified foods only (Table 4). These ranges are: 27–829 mg/kg body weight (bw) per day for infants, 136–553 mg/kg bw per day for toddlers, 102–314 mg/kg bw per day for children, 51–154 mg/kg bw per day for adolescents, 32–106 mg/kg bw per day for adults and 26–93 mg/kg bw per day for the elderly. The expected intake of the NF from food supplements in the target population would be up to 163 mg/kg bw per day for adolescents and 143 mg/kg bw per day for adults.

The Panel acknowledges the limited information available to estimate the intake levels of D-ribose from the background diet and the extent of its daily endogenous production, and is therefore not in the position to estimate the contribution of these sources to the combined intake of the NF.

Considering the possible scenario of combined intake of the NF from fortified foods and from food supplements, the estimated intake for the 95th percentile of the target population would be 214–317 mg/kg bw per day for adolescents and 175–249 mg/kg bw per day for adults and 169–236 mg/kg bw per day for the elderly.

The Panel considers that consumption of the NF is not nutritionally disadvantageous.

The Panel considers that the microbiological information provided does not raise safety concerns.

The Panel notes that the risk of allergenicity is low.

Based on the genotoxicity tests provided, the Panel concludes that there are no concerns regarding genotoxicity of the NF.

The information on absorption and excretion of D-ribose in rats is limited. The available data indicate that in humans, D-ribose is rapidly and nearly completely absorbed when administered at 200 mg/kg bw per hour for 5 h. In humans, at dose levels above 3 g (about 40 mg/kg bw), absorption was faster than metabolism. Application of D-ribose with meals decreases absorption. In the body, D-ribose is converted mainly to glucose via the pentose phosphate pathway, rather than nucleic acid precursors, which then is further used in the metabolism/biosynthesis. Part of the ribose and its metabolites is excreted via the urine and the percentage increases with increasing dose.

In a subchronic toxicity study, Wistar rats were administered diets containing the NF at levels of 0.0, 3.6, 7.6 and 15.0 g/kg bw per day in the male groups and 0.0, 4.4, 8.5 and 15.7 g/kg bw per day in the female groups. The most prominent findings in this study are effects on body weight, increases in water intake and urine volume (and dilution of the urine), full and empty caecum weight, liver and

[1] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle H, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Vinceti M, Willatts P, Engel K-H, Marchelli R, Pöting A, Poulsen M, Salminen S, Schlatter J, Arcella D, Gelbmann W, de Sesmaisons-Lecarré A, Verhagen H and van Loveren H, 2016. Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal 2016;14(11):4594, 24 pp. https://doi.org/10.2903/j.efsa.2016.4594

other organ weights. Given the high dose levels of D-ribose used in the study, the type of effects observed in this subchronic study and the high purity of the NF, the Panel considers that the observed effects could be the consequence of nutritional imbalances, but toxicological effects could not be ruled out. Therefore, the Panel derived a No observed adverse effect level (NOAEL) of 3.6 g/kg bw per day based on this study.

In a developmental toxicity study, Wistar rats were mated and the females were administered the NF from gestational day 0–21 at levels of 0.0, 4.25, 7.94 and 9.91 g/kg bw per day for the different groups. The Panel notes that besides maternal toxicity (reduced body weight gain), wavy ribs and delayed ossification were detected in the foetuses in the mi D- and high-dose groups. The foetal skeletal alterations are reported to occur frequently in developmental toxicity studies, often secondary to maternal toxicity. The NOAEL for maternal/foetotoxicity in this study is consequently 4.25 mg/kg bw in the diet, while the NOAEL for teratogenicity is 9.91 mg/kg bw per day, the highest dose tested. Therefore, this study supports the NOAEL from the subchronic study, indicating that metabolic imbalances affect both the maternal organism and the developing embryo.

Several human studies were provided which were not designed to assess the safety of D-ribose. The administration of single oral doses of 2–87 g D-ribose consistently report transient decreases of glucose concentrations within 1–3 h. The transient decrease of glucose concentration was not associated with clinical symptoms of hypoglycaemia, except for one case, where a low-weight female experienced short-term symptoms of hypoglycaemia after ingesting 10 g of ribose in the fasted state. While in this and in most of the other studies, blood glucose levels did not fall below 2.8 mmol/L, a temporary significant decline of blood glucose to 2.6 mmol/L was observed in one study following a single oral dose of 10 g D-ribose. The decrease in blood glucose comes along with increases in insulin levels. The glucose-lowering effect occurs also if meals rich in carbohydrate or fat are ingested before uptake of D-ribose.

No studies have been provided that investigated intake of D-ribose in infants, young children and adolescents. Whether young age may be of special concern with regard the glucose-lowering effects of D-ribose is not known. However, the Panel considers that children could be particularly vulnerable to glucose-lowering effects of D-ribose.

The Panel notes that there is a lack of understanding of the mechanisms responsible for the short-term decrease in blood glucose reported in the human studies, only limited data on the dose–response relationship between D-ribose and blood glucose levels, and uncertainty about the risk of symptomatic hypoglycaemia conditions, especially in susceptible persons.

Because the decrease in glucose levels and/or the occurrence of transient symptomatic hypoglycaemia (as reported in one case) is considered adverse, based on the human studies, the lowest observed adverse effect level (LOAEL) would be at intakes of 10 g of D-ribose. Concerning the human data, taking the above issues into account, the Panel concludes that 5 g per day, equivalent to 70 mg/kg bw per day, would be the NOAEL with respect to hypoglycaemia that can be considered applicable for adults. For children, the Panel acknowledges the lack of human data directly relevant for this population group.

For the animal study, the Panel considered an uncertainty factor of 100 as sufficient given the nature of the NF and the magnitude of the effects observed. Based on the NOAEL of 3,600 mg/kg bw per day derived from the subchronic toxicity study in rats, an acceptable level of intake would be up to 36 mg/kg bw per day. This is half the NOAEL value identified in the human studies for adults with respect to hypoglycaemia. The Panel concludes that 36 mg/kg bw per day would also take into account the potentially increased sensitivity of certain population groups to hypoglycaemia, including children.

The Panel therefore concludes that the NF, D-ribose, is safe for the general population at intake levels up to 36 mg/kg bw per day.

The Panel considers that the safety of the NF at the intended uses and use levels as proposed by the applicant has not been established.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

On 17 March 2008, the company Bioenergy Lire Science, Inc. submitted a request in accordance with Article 4 of the Novel Food Regulation (EC) No 258/97 to place on the market D-ribose to the competent authority of the United Kingdom. However, a request for additional information to resolve uncertainties arising from a study on reproductive toxicity was made. In November 2013 the company submitted a revised dossier.

On 23 February 2016, the competent authority of the United Kingdom forwarded to the Commission its initial assessment report, which came to the conclusion that D-ribose meets the criteria for acceptance of a NF defined in Article 3(1) of Regulation (EC) No 258/970.

On 17 May 2016, the Commission forwarded the initial assessment report to the other Member States. Several Member States (MS) submitted comments or raised objections.

The concerns of a scientific nature raised by the MS can be summarised as follows:

- No data have been presented by the applicant to show that any significant amount of free D-ribose would be consumed as part of the normal diet. The fact that D-ribose serves as an endogenous intermediate in metabolic routes in living cells does not imply that it would be suitable as food.
- The information regarding the metabolic fate of ingested D-ribose relies on old publications without elaborating if this description is considered to be well-established and sufficiently up-to-date.
- The possibility for combined intake from both fortified foods and food supplements, although considered unlikely by the applicant, should be considered as a realistic scenario that could have a significant effect on total intake for high level users.
- The occurrence of gastrointestinal problems, short-term hypoglycaemia and hyperuricemia in some of the studies presented and the lack of long-term studies analysing the effect of high doses of D-ribose, does not allow determining the safety and tolerance of a long-term intake of D-ribose.
- In both a subchronic toxicity study and a developmental toxicity study in rats, effects were observed in the mid-dose and high-dose groups (wavy ribs and delayed ossification). The initial assessment performed by the UK authority concludes that these effects are not expected to be relevant for humans at the proposed intake levels. Nevertheless, the observed effects may not yet be understood sufficiently to allow drawing a firm conclusion.
- A margin of exposure of 21 for toddlers is not considered to be sufficient, as they are a particularly sensitive group of individuals.

On 19 May 2017 and in accordance with Article 29(1)(a) of Regulation (EU) 178/2002,[2] the Commission asked the European Food Safety Authority to provide a scientific opinion by carrying out the additional assessment for D-ribose as a NF in the context of Regulation (EU) No 258/97 and to consider the elements of a scientific nature in the comments raised by the other MS.

According to Article 35 (1) of Regulation (EU) 2015/2283,[3] any request for placing a novel food on the market within the Union submitted to a Member State in accordance with Article 4 of Regulation (EU) 258/1997 and for which the final decision has not been taken before 1 January 2018 shall be treated as an application under this Regulation. This is the case for the present application.

In accordance with Article 10 (3) of Regulation (EU) 2015/2283, EFSA shall give its opinion as to whether the update of the Union List referred to in Article 10 (1) is liable to have an effect on human health.

[2] Regulation (EU) 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. 1–24.

[3] Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 2013/0435 (COD). OJ L 327, 11.12.2015, p. 1–22.

2. Data and methodologies

2.1. Data

The safety assessment of this novel food (NF) is based on data supplied in the application and information submitted by the applicant following European Union Food Safety Authority (EFSA) requests for supplementary information.

During the assessment, the Panel identified additional data which were not included in the application.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469.[4]

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application[1]. As indicated in this guidance, it is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data, including both data in favour and not in favour to supporting the safety of the proposed NF.

This NF application includes a request for protection of proprietary data in accordance with Article 26 of Regulation (EU) 2015/2283. Data claimed to be proprietary by the applicant include: Oral embryotoxicity/teratogenicity study with D-ribose in rats [TNO report V2657], subchronic (13-week) oral toxicity study with D-ribose in rats [TNO report V99.1155].

2.2. Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications and the principles described in the relevant existing guidance documents from the EFSA Scientific Committee. The legal provisions for the assessment are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of the Commission Implementing Regulation (EU) 2017/2469.

This assessment concerns only risk that might be associated with consumption of the NF under the proposed conditions of use, and it is not an assessment of the efficacy of D-ribose with regard to any claimed benefit.

3. Assessment

3.1. Introduction

This application refers to D-ribose as a NF as defined in article 3 of the NF Regulation 2015/2283. The applicant intends to market the NF as an ingredient in a variety of foods, food supplements and in certain foods for specific groups (total diet replacement for weight control and food for special medical purposes).

3.2. Identity of the NF

The NF which is the subject of the application is D-ribose (marketed as Bioenergy Ribose™). Bioenergy Ribose™ is produced by fermentation using a transketolase-deficient strain of *Bacillus subtilis*. The production strain is unable to utilise D-ribose, which accumulates in the fermentation medium.

Chemically, D-ribose (CAS No: 50-69-1; molecular formula: $C_5H_{10}O_5$) is an aldopentose monosaccharide, with a molecular mass of 150.13 Da. In aqueous solution, D-ribose exists in equilibrium between five possible chemical structures: one linear form and two-five-ring (α- and β-ribofuranose) and two-six-ring forms (α- and β-ribopyranose). Figure 1 represents one of the structures.

[4] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 64–71.

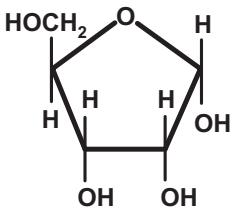

Figure 1: Chemical structure of D-ribose in its α- D-ribofuranose form

3.3. Production process

Bioenergy Ribose™ is manufactured in accordance with Good manufacturing practice (GMP) in a Hazard analysis and critical control points (HACCP)-registered and ISO 9001:2000-certified facility. Bioenergy employs *B. subtilis* ATCC No. 21951 (originally designated as *Bacillus pumilus*), which is a non-genetically modified organism. *B. subtilis* is widely distributed in the environment and is naturally present in many foods that have been consumed by humans for decades without evidence of adverse effects (Hui et al., 2004; Logan et al., 2007). In the initial step of the production process, *B. subtilis* is cultivated in a nutrient rich medium, followed by fermentation. During fermentation, D-glucose is converted to D-ribose, which accumulates in the culture broth. In the following production step, the culture broth is filtered to remove bacteria and bacterial fragments, solid particles and large molecules and is then purified and decolourised. Inorganic ions are then removed by ion exchange, and further filtration removes salts and small molecules. These filtration and purification steps are followed by concentration through evaporation. D-ribose is then crystallised with ethanol out of the concentrated solution and crystals recovered by centrifugation, dried and packaged.

The absence of residual biomass in the final product was confirmed by the results of a Bradford assay (limit of detection 0.1 μg/mL) on six randomly selected production lots. No protein was detected in the samples using the method described therefore excluding the presence of residual protein. Upon request of the UK Advisory Committee on Novel Foods and Processes (ACNFP), the applicant provided the results of a Kjeldahl assay (limit of detection 0.16%) that did not detect proteins in samples of five production lots of D-ribose.

The amounts of residual ethanol from the crystallisation step were analysed in five production lots. The analysis reported residual ethanol values ranging from 82 to 170 μg/g.

Finally, the applicant provided a list of control points and general considerations excluding the presence of potential impurities resulting from the production process.

The Panel considers that the production process is sufficiently described and does not raise safety concerns.

3.4. Compositional data

The applicant provided product analysis of five independent production lots (Table 1). The applicant indicated that the analyses of Bioenergy Ribose™ are performed according to the methods specified for ribose in the United States Pharmacopeia (USP40-NF35, 2017).

Table 1: Batch-to-batch analyses of the novel food

Parameter	Lot number				
	M01666501/ 20130205	**M0276501/ 20130206**	**M0336501/ 20130306**	**M0376501/ 20130512**	**M04066501/ 20130515**
Appearance (dry with powdery texture, white to slightly yellow in colour)	Conforms	Conforms	Conforms	Conforms	Conforms
Specific rotation, $[\alpha]_D^{25}$	−20.1	−20.1	−20.1	−20.2	−20.1
Purity, %	99.4	99.3	99.3	98.6	99.2
Loss on drying (moisture), %	0.15	0.17	0.23	0.36	0.22
Ash, %	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1

Parameter	Lot number				
	M01666501/ 20130205	M0276501/ 20130206	M0336501/ 20130306	M0376501/ 20130512	M04066501/ 20130515
Clarity of solution, % transmittance	99.3	99.3	99.5	99.3	99.2
Heavy metals					
Lead, mg/kg	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
Arsenic, mg/kg	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Cadmium, mg/kg	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Mercury, mg/kg	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Microbiological specifications					
Total plate count, CFU/g	< 10	< 10	< 10	< 10	< 10
Yeast, CFU/g	< 10	< 10	< 10	< 10	< 10
Mould, CFU/g	< 10	< 10	< 10	< 10	< 10
Coliforms, CFU/g	< 10	< 10	< 10	< 10	< 10
Salmonella sp., in 25 g	Negative	Negative	Negative	Negative	Negative

CFU: colony-forming unit.

The Panel considers that the information provided on the composition of the NF is sufficient and does not raise safety concerns.

3.4.1. Stability

The applicant provided a summary of stability studies on D-ribose powder tested in its standard commercial package at room temperature for 24 months (proposed shelf life of Bioenergy Ribose™). The test parameters included purity, colour, appearance, moisture content, bulk density and microbial counts. The product settled and became slightly yellow during storage. The bulk density and purity of the product decreased slightly. All the microbial counts remained consistent and within the limits of specifications.

At the request of the Panel, the applicant has provided a study report, including the specification of the methods used to test the parameters, assessing the stability of three additional production lots. The report provides data on purity, loss on drying, clarity and bulk density at different time points over 24 months. All lots were in line with the previous assessment apart from one lot being slighty below the expected clarity at the end of the observation period.

The Panel considers that the data provided sufficient information with respect to the stability of the NF.

3.5. Specifications

The specifications proposed for the NF are indicated in Table 2. They include physical and chemical parameters as well as chemical and biological contaminants.

Table 2: Specifications of the NF

Parameter	Specification	Method
Appearance	Dry with powdery texture, white to slightly yellow in colour	Visual inspection
Specific rotation $[\alpha]_D^{25}$	−19.0 to −21.0°	Polarimetry
D-ribose purity	98.0–102.0% dry basis	HPLC/RI
Ash	< 0.2%	Residues on ignition
Loss on drying (moisture)	< 0.5%	Vacuum oven
Clarity of solution	≥ 95% transmittance	Spectrophotometry UV Vis
Heavy metals		
Lead	≤ 0.1 mg/kg	AOAC 993.14
Arsenic	≤ 0.1 mg/kg	AOAC 993.14
Cadmium	≤ 0.1 mg/kg	AOAC 993.14
Mercury	≤ 0.1 mg/kg	AOAC 993.14

Parameter	Specification	Method
Microbiological specifications		
Total plate count	≤ 100 CFU/g	AOAC 990.12
Yeast	≤ 100 CFU/g	AOAC 995.21
Mould	≤ 100 CFU/g	AOAC 995.21
Coliforms	≤ 10 CFU/g	AOAC 991.14
Salmonella sp.	Negative/25 g	AOAC 992.11

AOAC: Association of official analytical communities; HPLC/RI: High-performance liquid chromatography coupled with refractive index detection.

The Panel considers that the information provided on the specifications of the NF is sufficient and does not raise safety concerns.

3.6. History of use of the NF and/or of its source

3.6.1. History of use of the source

The process for the production of the NF which is the subject of the application employs *B. subtilis* ATCC 21951. This non-genetically modified *Bacillus* strain was obtained through UV mutagenesis and cannot utilise D-ribose due to a lack of transketolase activity (de Wulf and Vandamme, 1997). D-ribose accumulating *Bacillus* strains cannot form spores because two metabolites, ribitol and teichoic acid, derived from D-ribose, are necessary for spore formation. Due to the inability to form spore, D-ribose-accumulating cells of this *Bacillus* strain are more easily killed by heat and dryness than those of wild-type *Bacillus*.

B. subtilis is included in the list of Qualified presumption of safety (QPS)-recommended biological agents intentionally added to food or feed with the qualification 'Absence of toxigenic activity' (EFSA BIOHAZ Panel, 2017).

The applicant provided a review of the scientific literature on the *B. subtilis* species concluding that this species is non-toxigenic and non-pathogenic, and that antibiotic resistance would not be expected as there are no known plasmids in *B. subtilis* that encode for antibiotic resistance. According to the applicant's review, *B. subtilis* has a long history of safe use in foods and for production of various chemicals including ribose, riboflavin and other metabolites and food ingredients. *B. subtilis* is involved in the production of certain fermented food products including soy sauce, tofu, soybean paste and other foods.

The identification of the bacterial strain used to produce Bioenergy's D-ribose was based on cellular morphology, physical-chemical characteristics and 16S rRNA and gyrB gene sequences. In response to an EFSA request regarding the identification of producer microorganism at strain level, the applicant provided data of the transketolase and transaldolase gene sequences. These genes that encode two enzymes of the pentose phosphate pathway (PPP) showed multiple point mutations that allow the differentiation of the strain from reference strains. It was explained that these mutations lead to loss of enzymatic activity and, thereby, to D-ribose accumulation.

The production lots presented in Table 1 were also analysed for the presence of the bacterial lipopolysaccharide (LPS), which is a membrane component of Gram-negative bacteria that could act as endotoxin, according to the US Pharmacopeia method based on the use of amoebocyte lysate from the horseshoe crab (USP35-NF30, 2012) and all the samples analysed tested negative. The Panel notes that for *Bacillus* species other than the *Bacillus cereus* group, a cytotoxicity test should be made to determine whether the strain produces potentially cytotoxic non-ribosomal synthesised peptides (EFSA FEEDAP Panel, 2014). In response to EFSA's request, the applicant evaluated the effect of cell-free culture supernatants of *B. subtilis* ATCC 21951 on permeability of Vero cell cultures using a propidium iodide uptake test in line with the EFSA guidance (EFSA FEEDAP Panel, 2014), without detecting significant changes, indicating the absence of toxigenicity.

3.6.2. History of use of the NF

D-ribose is naturally occurring in all living cells and it is synthesised endogenously from the conversion of glucose via the PPP. Ribose is a component of RNA as well as adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NADH) and other molecules important to cellular metabolism. Ribose serves as a precursor for the synthesis of purine nucleotides. Cyclic ADP ribose is also involved as a messenger in insulin secretion.

According to the applicant, at the time of submission of this application to the UK authority (2013), approximately 1,900 metric tonnes of Bioenergy Ribose™ have been sold in the USA since 2004, equivalent to approximately 1.3 billion servings. A total of 31 adverse reactions were reported in that timeframe through the applicant's post-marketing surveillance programme. All the adverse reactions reported where in relation with the consumption of food supplements containing D-ribose, while no adverse reactions were reported for foods fortified with D-ribose. The adverse reactions reported, ordered by frequency, were upset stomach (5); transient-elevated blood sugar in diabetic customers (4); transient racing heart (3); rash (3); itching (3); diarrhoea (3); constipation (2); swollen leg (2); felt funny (1); weakness/fatigue (1); headache (1); light-headedness (1); excess gas (1); muscle tightness (1).

3.7. Proposed uses and use levels and anticipated intake

3.7.1. Target population

Upon request of the Panel, the applicant specified that the target population for the consumption of D-ribose would be adults and adolescents above 14 years of age.

3.7.2. Proposed uses and use levels

The proposal for intended uses and use levels of D-ribose provided by the applicant is summarised in Table 3. Proposed uses are based on the food group classifications detailed within the UK National Diet and Nutrition Survey (NDNS) report (NatCen Social Research, 2013).

Table 3: Summary of the individual proposed food uses and use levels for D-ribose

Food category	Proposed use	D-ribose per serving (g)	Serving size (g)[a]	Use level (g/100 g)
Biscuits	Cereal bars	0.62	31	2.00
Buns, cakes, pastries and fruit Pies	Muffins	2.20	70	3.14
Chocolate confectionery	Chocolate confectionery (excluding chocolate bars)[b]	0.68	40	1.74
Flavoured Drinks[c]	Carbonated soft drinks, not low calorie (non-cola)	1.00	250	0.40
	Milk drinks (excluding malts and shakes)	0.80	200	0.40
	Ready-to-drink soft drinks, not low calorie	1.00	250	0.40
	Reduced calorie beverages[d]	1.00	250	0.40
	Sports, isotonic and energy drinks	3.00	250	1.20
Foods intended for particular nutritional uses	Meal replacement beverages	1.00	250	0.40
	Meal replacement bars and energy bars	3.00	60	5.00
Fruit and vegetable juices	Fruit juice	0.50	160	0.31
	Vegetable juice	0.50	240	0.21
Sugar confectionery	Hard and soft confectionery	0.70	35	2.00
Tea, coffee and water	Instant and herbal teas only	1.33	190	0.70
Yogurt, fromage frais and dairy desserts	Yogurt (including frozen yogurt; excluding yogurt drinks)	1.50	125	1.20

(a): Serving sizes are based on the UK Food Portion Sizes handbook (FFSA, 2002) and from manufacturers' websites.
(b): This includes chocolate confectionery, such as chocolate-coated nuts, fruit, caramels, chocolate eggs, bonbons, etc., but excluding chocolate bars.
(c): Flavoured drinks do not include any sugar-free or low-calorie varieties as these beverages were found to have very low carbohydrate content, and therefore not a target for D-ribose.
(d): Reduced calorie beverages are only included if they have a carbohydrate content > 0.2 g/100 mL.

In addition to its proposed uses in fortified food, the applicant proposes to use D-ribose as a food supplement at a level of up to 10 g per day.

3.7.3. Anticipated intake of the NF

In a tiered approach, the applicant provided estimates of the anticipated intake of the NF based on the summary statistics from the EFSA Comprehensive European Food Consumption Database, which generally leads to an overestimation of anticipated daily intakes. For a refined intake estimate of the NF, the applicant used individual data from the UK NDNS rolling programme covering the period 2008–2012.

In the evaluation of the intake estimates for D-ribose, a new intake assessment was performed by EFSA based on the individual European Union (EU) data from the EFSA Comprehensive Food Consumption Database (EFSA, 2011a). The full details of the exposure assessment for the intake of D-ribose from fortified foods are provided in Appendix A.

For the estimation of the intake, the Panel considered the uses proposed by the applicant as reported in Table 3. For the purpose of the exposure assessment, these food categories were recodified according to the FoodEx classification system (EFSA, 2011b).

The ranges of the estimated daily intake of D-ribose from fortified foods in the different population groups considered, based on the EFSA Comprehensive European Food Consumption Database, are reported in Table 4.

Table 4: Summary of the ranges of the estimated daily intake of D-ribose from fortified foods by population group based on the EFSA Comprehensive European Food Consumption Database

Estimated intake (mg/kg bw per day)	Infants (4–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Estimated D-ribose intake from fortified foods						
Mean	4–222 (6)	44–210 (10)	29–137 (18)	17–71 (17)	7–36 (17)	6–28 (14)
High level (P95)	27–829 (5)	136–553 (7)	102–314 (18)	51–154 (17)	32–106 (17)	26–93 (14)

Between brackets the number of surveys considered per population group.

The applicant proposes that D-ribose would be consumed as food supplement at a level up to 10 g a day. Assuming that food supplements would be consumed only by the target population (i.e. adults and adolescents above 14 years of age) and considering the default mean body weight values recommended by the EFSA Scientific Committee (2012) (i.e. 61.3 kg for adolescents above 14 years of age male and females and 70 kg for adult males and females) the derived expected daily intakes from food supplements would be up to 163 mg/kg body weight (bw) per day for adolescents and 143 mg/kg bw per day for adults.

According to the applicant, D-ribose used as a food supplement would typically be taken as an alternative to fortified foods, and therefore, users of D-ribose food supplements would not be expected to consume the food fortified with D-ribose that are detailed in Table 3.

3.7.4. Combined intake from the NF and other sources

Intake from the background diet

D-ribose occurs naturally in the human diet as it is present in all living cells as a component of genetic material and several molecules involved in metabolism. The applicant reported that that low levels of free ribose are consumed daily through the diet, but concluded that the actual levels are difficult to quantify due to the impact of processing on the levels within the various foods.

Ribose is reported to be present in meat in varying amounts, e.g. 1–524 mg/100 g beef meat (Jarboe and Mabrouk, 1974; Gazzani and Cuzzoni, 1985) and 6.4–39.5 mg/100 g chicken meat (Aliani and Farmer, 2002), with these differences probably attributable not only to the origin of the meat but also to differences in sampling or analytical methods. Lilyblade and Peterson (1962) reported that the content of ribose increases post-mortem during storage of chicken meat. The cooking process is reported to reduce the quantity of free ribose as this is involved in Maillard reactions.

RNA and free nucleotides are reported to be degraded in the intestinal tract and free ribose may partially be released by the action of nucleosidases (Uauy-Dagach and Quan, 1994; Carver and Walker, 1995).

Due to the lack of data in the literature, the Panel considers that the intake levels of D-ribose from the background diet are largely unknown.

Endogenous production

Based on the estimated mean daily intake of carbohydrates in the UK, i.e. 252 and 198 g in men and women, respectively, (Department of Health, 2011; UKDA, 2012; NatCen Social Research, 2013) and assuming (i) that 2/3 of these would be composed of glucose, and (ii) that 2–9% of glucose is utilised via the PPP (Magnusson et al., 1988; Delgado et al., 2004), the applicant estimated that the daily endogenous production of D-ribose through the PPP ranges from approximately 3–15 g/day. Additional information on the extent of the daily endogenous production of D-ribose in the literature is lacking. The Panel concludes that the information is insufficient to draw conclusions on the extent of the daily endogenous production of D-ribose.

Combined intake from all sources

The Panel notes the limited information available to estimate the intake levels of D-ribose from the background diet and is therefore not in the position to estimate its contribution to the combined intake of the NF.

The expected intake of the NF from fortified foods only, for the different population groups, is reported in Table 4.

The expected intake of the NF from food supplements in the target population would be up to 163 mg/kg bw per day for adolescents and 143 mg/kg bw per day for adults.

Considering the possible scenario of combined intake of the NF from fortified foods (derived from the EFSA Comprehensive European Food Consumption Database) and from food supplements (estimated using EFSA's default values for body weight (EFSA Scientific Committee, 2012)), the Panel estimated the ranges of intake for the target population groups, i.e. adolescents and adults. The combined intake estimates are reported in Table 5.

Table 5: Summary of the ranges of the estimated combined daily intake of D-ribose from fortified foods and from food supplements for the target population groups, based on the EFSA Comprehensive European Food Consumption Database

Estimated intake (mg/kg bw per day)	Adolescents (10–17 years)[(a)]	Adults (18–64 years)	The elderly (≥ 65 years)
Mean	180–234	150–179	149–171
High level (P95)	214–317	175–249	169–236

(a): According to the applicant, only adolescents above 14 years of age would be part of the target population.

3.8. Absorption, distribution, metabolism and excretion (ADME)

Absorption

In an oral gavage study, rats (body weight: 100–150 g) were administered 2 mL of a 25% sugar solution containing D-glucose, D-ribose, or D-xylose (corresponding to about 5,000 mg/kg bw) following a fasting period of 48 h. Compared to glucose (set to 100%), 74% D-ribose was absorbed within the first hour and 67% in the second hour (Naitô, 1944).

In a human study, absorption of orally administered D-ribose at doses up to 200 mg/kg per hour for 5 h was reported to range from 87.8% to 99.8% of the plasma levels obtained after application of the same intravenous dose/hour (Gross et al., 1989). The same study reported that serum levels of ribose increased from 1.6 mg/dL (range 0.0–3.5 mg/dL) at baseline to a mean concentration of 4.8 mg/dL at the oral dose of 83 mg/kg per hour, to 32.6 mg/dL at the oral dose of 167 mg/kg per hour and up to around 80 mg/dL at the intravenous dose of 222.2 mg/kg per hour. Both after oral and intravenous administration, a steady state of urinary excretion of ribose occurred after 60–180 min, which was about at the same time as the steady state of the serum concentration of ribose.

Twelve healthy adults (mean body weight 72.7 kg) were administered orally (i) solutions containing 2.5, 5.0 and 10.0 g D-ribose (corresponding to 34, 69 and 138 mg/D-ribose per kg bw) under fasting conditions and (ii) 10.0 g D-ribose under fed conditions with either a high fat (N = 6) or high carbohydrate (N = 6) meal (Thompson et al., 2014). D-ribose was absorbed rapidly (mean T_{max} 18–30 min) and C_{max} and Area under the curve (AUC) increased more than proportionally with dose, indicating saturation of metabolism. Under fed conditions, T_{max} was unchanged; however, C_{max} and AUC decreased with both kind of meals (by 42.6% and 40.8%, respectively, with high fat meals and by 69.1% and 64.9%, respectively, with high carbohydrate meal) indicating that the absorption of ribose decreased during the meals.

Segal and Foley (1958) administered various quantities of ^{14}C-ribose to healthy subjects by intravenous infusion for 15 min. The authors reported a linear disappearance of ^{14}C-ribose from blood when 3 g (43 mg/kg if a body weight of 70 kg is assumed) was injected, but a lag phase prior to the onset of a linear disappearance when doses greater than 3 g were administered, indicating saturation of metabolism.

Distribution

Gonçalves et al. (1969) used ^{3}H-ribose to investigate the fate of D-ribose within the body via autoradiography. Rats were injected either intraperitoneally or intravenously ^{3}H-ribose. After 5–60 min, animals were sacrificed and distribution of radioactivity was analysed by light and electron microscopy. To identify the chemical nature of the label, tissues were treated with RNAse, DNAse and amylase and disappearance of the label was monitored. Radioactivity was broadly distributed in the body, with highest amounts in hepatocytes. Radioactivity was associated with RNA, DNA and glycogen. In addition, amylase resistant radioactivity was detected, especially in cells of secretory glands.

100 mg/kg bw ^{14}C-ribose was injected subcutaneously into rats. 5, 10, 30, 45, 60 and 120 min later the rats were sacrificed and radioactivity was determined in liver, brain and blood. Radioactivity was taken up in liver and brain with the uptake being several fold greater in liver than in brain. Highest radioactivity was found in the liver within 5 min after application. Lower amounts (about half of the values or less per g tissue) were found in the brain and at later time points (Gaitonde and Arnfred, 1971).

Metabolism

Several studies in rats, mice and humans show that D-ribose enters the PPP and is mainly transformed to glucose (Gaitonde and Arnfred, 1971; Hiatt, 1958; Naitô, 1944; Segal and Foley, 1958), which is then used for biosynthesis of glycogen (Naitô, 1944; Hiatt, 1958; Gonçalves et al., 1969), converted to sugar phosphates, amino acids and carboxylic acids (Gaitonde and Arnfred, 1971), glycoproteins (Gonçalves et al., 1969) or is degraded to CO_2 (Segal and Foley, 1958).

Gaitonde and Arnfred (1971) investigated the time course of appearance of metabolites and distribution in liver, blood and brain. Within 5 min after subcutaneous injection of 100 mg ^{14}C-ribose/kg bw to rats, the major metabolite (50%) in blood and liver was glucose, only 1% of the radioactivity was found in ribose. In the liver and blood, ^{14}C was mostly found in free sugars (mainly glucose) during the first half hour after administration, but later more ^{14}C was found in carboxylic acids, nucleotides and sugar phosphates. In the brain in contrast, the majority of ^{14}C was found in amino acids, carboxylic acids, nucleotides and sugar phosphates rather than free sugars.

When ribose was injected subcutaneously to mice, which had been starved for 24 h, the glycogen content in the liver was increased, but more retarded and to a smaller degree as for the same amount of glucose (Naitô, 1944).

Only to a limited extent, D-ribose is used directly as a precursor for the synthesis of RNA and DNA (Gonçalves et al., 1969; Gaitonde and Arnfred, 1971).

Excretion

In clinical studies administering D-ribose to patients either orally or intravenously, Gross et al. (1989), reported that the renal excretion of D-ribose as percentage of intake was on average 5.0%, 15.4% and 16.6% at oral intakes of 83.3, 166.7 and 200 mg/kg per hour, respectively, and 7.9%. 19.3% and 23.1% at intravenous infusion of 83.3, 166.7 and 222.2 mg/kg per hour, respectively.

In the clinical study by Thompson et al. (2014), described above, the amount of D-ribose in urine increased from 4.15% to 7.20% of the administered dose after oral application of 2.5, 5.0 and 10.0 g D-ribose.

After 15 min of intravenous infusion of ^{14}C-ribose, 10% of ^{14}C appeared in the urine, when only the radiolabelled tracer (5 mg) was applied (Segal and Foley, 1958). When 20 g D-ribose (about 285 mg/kg bw, if body weight of 70 kg is assumed) were infused, excretion in the urine rose to 40% indicating saturation of uptake into cells. While the substance excreted in the beginning was ribose, at later time points other (not identified) substances prevailed. In parallel with increased excretion via urine, the amount excreted as CO_2 within the following 6 h decreased from 48% to 16%.

Overall conclusion on ADME

The Panel notes that the information on absorption and excretion of D-ribose in rats is limited. In a study performed in humans, D-ribose is rapidly and nearly completely absorbed when administered at

200 mg/kg bw per hour for 5 h. At dose levels above 3 g (about 40 mg/kg bw) in humans, absorption was faster than metabolism. Application of D-ribose with meals decreases absorption. In the body, D-ribose is converted mainly to glucose via the PPP (rather than to nucleic acid precursors), which then is further used in the metabolism. Part of the ribose and its metabolites is excreted via the urine and the percentage increases with increasing dose.

3.9. Nutritional information

D-ribose is a five-carbon sugar that is ingested with foods as an integral part of RNA and free nucleotides in cells, as well part of riboflavin which belongs to the group of B-vitamins. Orally administered free D-ribose was well absorbed in humans (Gross et al., 1989; see also Section 3.10.4). D-ribose is not an essential nutrient as it is formed from other monosaccharides via the PPP.

The Panel considers that consumption of the NF is not nutritionally disadvantageous.

3.10. Toxicological information

3.10.1. Genotoxicity

A bacterial reverse mutation test was performed in Salmonella Typhimurium strains TA1535, TA1538, TA98, and TA100 as well as *Escherichia coli* strain WP2 *uvr*A (in compliance with OECD TG 471; van Ommen, 1999). Five concentrations of D-ribose were used for each bacterial strain: from 62 to 5,000 μg/plate in the first assay, and from 313 to 5,000 μg/plate in the second assay, both in the absence and presence of a metabolic activation system (S9 mix). D-ribose did not cause a biologically relevant increase in the mean number of revertant colonies compared to the negative control (solvent) in all strains tested, both in the absence and presence of metabolic activation.

D-ribose was evaluated for its potential to induce structural chromosomal aberrations in Chinese hamster ovary cells (in compliance with OECD TG 473; de Vogel, 2000a). The cells were incubated with the test substance at concentrations up to 1,500 μg/mL for 4 h in the absence and presence of metabolic activation or 18 h in the absence of metabolic activation. No cytotoxicity was observed. D-ribose did not induce a statistically significant increase in the number of cells with structural chromosomal aberrations at any of the concentrations and time points analysed when compared to control (solvent) values.

In a mammalian gene mutation assay, D-ribose was tested for its ability to induce gene mutations at the TK-locus of cultured mouse lymphoma L5178Y cells (in compliance with OECD TG 476; Steenwinkel, 2000). No cytotoxicity or dose-related increases in mutant frequency were observed following treatment with D-ribose, either in the absence or presence of a metabolic activation system (S-9 mix), at concentrations of 0.21–10 mM. Both in the presence and absence of metabolic activation the mutant frequency was increased not dose dependently at single dose levels in one of two trials. These findings were not reproduced in the second trial.

In an *in vivo* bone marrow micronucleus study, either 2,000 mg D-ribose/kg bw or vehicle control (maize oil) were administered to 10 male and 10 female mice (in compliance with OECD TG 474; de Vogel, 2000b). The mice were sacrificed either 24 or 48 h after treatment. The number of polychromatic erythrocytes per 1,000 erythrocytes in D-ribose-treated mice did not differ significantly compared to negative controls; however, exposure to the bone marrow is evident as D-ribose is absorbed into systemic circulation. The incidence of micronucleated polychromatic erythrocytes per 1,000 polychromatic erythrocytes in mice treated with D-ribose was not significantly higher than those observed in negative controls.

Even though the genotoxicity testing strategy is not fully in line with current EFSA recommendations (EFSA Scientific Committee, 2011), as no *in vitro* mammalian micronucleus test was provided, the Panel considers that there is no concern with respect to genotoxicity of the NF.

3.10.2. Subchronic toxicity

The applicant provided a subchronic (90-day) toxicity study performed with Bioenergy Ribose™ (in compliance with OECD TG 408; Griffiths et al., 2006; Jonker, 2005). Groups of Wistar rats (20 male and 20 female per group) were administered diets containing 0, 5, 10, or 20% D-ribose. Control rats received a basal diet where barley in normal rodent diet was replaced (amounting to 20% of the diet) by 20% pregelatinised potato starch. D-ribose was added at the expense of potato starch to the diet (i.e. 5% D-ribose and 15% potato starch, 10% D-ribose and 10% potato starch, 20% D-ribose).

Based on the food consumption measured during the study, the intake of D-ribose was equivalent to mean daily intakes of 0.0, 3.6, 7.6 and 15.0 g/kg bw per day in males and 0.0, 4.4, 8.5 and 15.7 g/kg bw per day in females.

In the last week of the treatment period, urine was collected in 10 rats per sex. The urine was collected on two subsequent days, the first day under non-fasting condition, and the second day under fasting conditions.

All animals survived to scheduled necropsy apart from one male in the mid-dose group (judged as incidental).

Terminal body weights were lower in all dose groups than in the control group (statistically significant in mid-dose females and in high-dose animals of both sexes). With the exception of the first weeks of treatment, and some time points later, the mean feed consumption and feed conversion efficiency values were comparable across all study groups.

Ophthalmoscopic examination of the animals during the last week of the study did not reveal treatment-related abnormalities.

In haematological analysis, neutrophils were significantly increased and lymphocytes significantly decreased in the male high-dose group. Significantly lower haemoglobin and packed cell volumes in females (all dose levels) were considered as not treatment related, as there was no relation to dose and the control value was unusually high, compared to historical control values.

Clinical chemistry indicated some statistically significant findings. The following parameters were affected: alkaline phosphatase (increased in males in the high-dose group); aspartate amino transferase (increased in mid and high dose females); total protein (decreased in high-dose males and females); albumin (decreased in high-dose males); albumin/globulin ratio (increased in high-dose males and mid- and high-dose females); cholesterol (decreased in high-dose males); triglycerides (decreased in high-dose males); phospholipids (decreased in high-dose males). No changes in glucose serum levels in non-fasted and fasted rats were observed.

Higher water intake and urine volume (statistically significant for the 20% ribose male and female animals) were observed. The statistically significant decrease observed in all parameters in urinalyses for animals in the highest dose group (density, glucose, glucose creatinine molar ratio, pH) was therefore attributed by the authors to the dilution due to the increased urinary volume. In addition, excretion of glucose per 24 h and per mole of creatinine was significantly decreased in mid- and high-dose females. Low-dose females and mid- and high-dose males showed a similar tendency, but the differences from controls were not statistically significant.

Compared to the control, absolute kidney weights were decreased in both high-dose males and females. Relative kidney weights were significantly increased in all treated males. Absolute liver weights were decreased in high-dose males and increased in low- and mid-dose females. Relative liver weights were increased in mid-dose males and all treated females. Both, absolute and relative full caecal weights were significantly higher in both sexes. Absolute empty caecal weights were increased in all dose levels in male and female rats, relative empty caecal weights in the mid- and high-dose animals. Absolute brain weights were decreased in high-dose animals, but relative weights were increased in mid-dose females and high-dose regimens in both sexes. Absolute spleen weight was increased in mid-dose males. Relative spleen weights were increased in both mid- and high-dose animals. Absolute lung weights were decreased in high-dose males and females. Absolute thymus weights were decreased in both sexes in the high-dose group, relative thymus weight in low- and high-dose males. Relative testes weight was increased in high-dose males, relative seminal vesicle weight was increased in low-dose males and absolute epididymis weight was decreased in high-dose males.

At necropsy, no consistent macroscopic pathological findings were noted other than the yellow discolouration of abdominal fur in all mid- and high-dose animals, which was attributed to excessive urinary output of these animals. Microscopic evaluation of numerous tissues revealed no changes that could be attributed to the intake of D-ribose.

The Panel notes the very high-dose levels tested in this study, which makes it difficult to distinguish between nutritional imbalance effects and toxicological effects. The control animals received 20% potato starch replacing the barley of the normal rodent diet to adjust for nutritional imbalances. As no historical control data were provided, it cannot be judged, whether the potato starch in the diet per se also would cause effects, which would mask effects of D-ribose.

The Panel notes that the most prominent findings after application of D-ribose to rats for 90 days are decreased body weight, increases in water intake and urine volume (and dilution of the urine), full and empty caecum weight, liver and other organ weights.

In the 5% group in both sexes, reductions in body weight, compared to the control group are below 5%, in the 10% group in female rats, it is about 7% and statistically significant. The Panel has no information, whether the control diet containing potato starch, compared to the conventional rodent diet containing barley would itself result in reduced body weight. Therefore, a much higher effect of ribose on body weight, compared to conventional diet may be possible.

Increased full and empty caecum weight is a common finding in rats fed high amounts of mono- and disaccharides as well as polysaccharides, e.g. sorbitol, lactose and some starches. These effects, which are not associated with histopathological changes in the caecum, are regarded as physiological adaptation to the presence of incompletely digestible carbohydrates (Leegwater et al., 1974; JECFA, 1978). In the absence of histopathological changes in the microscopic examination of the caecum in the study with D-ribose, the Panel does not consider the observed changes in caecum weight as toxicologically relevant.

Increased water intake is considered a result of osmolar imbalance and leads to dilution of urine. The Panel notes, however, that reductions in the amount of glucose in 24h urine and in relation to creatinine cannot be explained by dilution of the urine. As D-ribose affects the amount of glucose in the blood – as known from studies in humans – this finding may reflect some metabolic changes. Whether these effects are adverse is unknown.

Furthermore, increased absolute and relative liver weights at the low- and mid-dose levels can be attributed to adaptation to D-ribose metabolism, while the drop in liver weight at the highest dose level then may reflect a toxic effect. Effects on liver weight are accompanied by slight increases in serum alkaline phosphatase and aspartate aminotransferase and decreases in total protein.

The Panel considers other changes in organ weights rather as secondary to the reduced body weight.

Based on the reduced body weights in combination with the other findings outlined above, the Panel considers that the no observed adverse effect level (NOAEL) for this study in the rats is 5% in the diet corresponding to 3.6 g/kg bw per day.

3.10.3. Reproductive and developmental toxicity

The applicant provided a developmental toxicity study in which 12-week-old albino Wistar rats were mated and the females were administered Bioenergy Ribose™ from gestational day 0 to 21 (in compliance with OECD TG 414; Griffiths et al., 2007; Wolterbeek and Waalkens-Beren, 2005). D-ribose was administered to 28 rats/group at 0, 5, 10 or 20% of the diet. Based on feed consumption this results in an average dose of 0.0, 4.25, 7.94 and 9.91 g/kg bw per day, respectively. Control rats received a basal diet where barley was replaced by 20% potato starch. D-ribose was added at the expense of potato starch to the diet.

All animals survived to the scheduled caesarean section on day 21. Food consumption was decreased in all treatment groups in the first 2 weeks and in the high-dose group in week 3. The mean body weight gain was significantly decreased in the mid- and high-dose groups over each of the first 2 weeks of the study, but then recovered during the third week such that the mean terminal body weights were not statistically significantly different.

The authors reported that gross observations at scheduled necropsy and caesarean section on day 21 were unremarkable. Neither absolute nor relative weight of the liver was affected by treatment at any dose, but caecal weights, both absolute and relative, were significantly increased relative to controls at all three-dose levels.

With regard to reproduction data, the treatment with D-ribose did not affect fecundity index, gestation index, preimplantation loss, post-implantation loss and sex ratio. External observations of foetuses and placentas were also unremarkable in all the study groups. No significant differences were observed, across all viable foetuses between treated and control groups for mean foetal and placental weights. Similarly, observations of visceral malformations, anomalies and variations were unremarkable and did not differ between treated and control groups. Significant skeletal malformations and variations were also not observed between groups.

The incidences for one wavy rib and for two or more wavy ribs did not reach statistical significance when analysing foetuses and litters separately. However, when the incidences of foetuses showing one wavy rib or two or more wavy ribs are grouped together, the incidence of foetuses and the incidence of litters showing one or more wavy ribs was statistically significantly increased in the mid- and high-dose groups ($p < 0.05$). Furthermore, dose dependent and statistically significant differences

between control and treated groups in the incidences of incomplete ossification of the frontal, parietal and interparietal bones were reported.

The Panel notes that besides maternal toxicity (reduced body weight gain), wavy ribs and delayed ossification were detected in the foetuses primarily in the mid- and high-dose groups. Both these foetal effects are observed frequently in developmental toxicity studies and are often secondary to maternal toxicity (Carney and Kimmel, 2007). The NOAEL for maternal toxicity/foetotoxicity is consequently 5% D-ribose in the diet, corresponding to an average intake of 4.25 g/kg bw per day, while the NOAEL for teratogenicity is 20%, the highest level of D-ribose tested.

3.10.4. Human data

The applicant provided human studies on the oral consumption of D-ribose performed with Bioenergy Ribose™ and with D-ribose from other sources.

Studies on oral consumption of D-ribose for several days or weeks

Only one study (Seifert et al., 2008) aimed to assess the safety of D-ribose whereas the others were efficacy studies with the recording of side effects.

In the uncontrolled study by Seifert et al. (2008), 19 healthy adults, 19–25 years, were administered 10 g of Bioenergy Ribose twice daily for 14 days. Haematological and biochemical parameters were analysed at baseline and on days 7 and 14 in fasted states. There were no statistically significant differences from baseline to day 7 and day 14 in all subjects for haemoglobin, haematocrit, white blood cells, platelets, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase. Minor changes were reported at day 7 (but not at day 14) when compared to baseline for gamma glutamyltransferase (18.3 ± 8.62 vs 21.2 ± 13.57 U/L, $p < 0.03$) and for albumin (5.082 ± 0.003 vs. 5.073 ± 0.002 g/dL, $p < 0.01$). Plasma glucose levels slightly declined, though not statistically significantly, throughout the study period (day 0: 3.64 ± 0.80, day 7: 3.55 ± 0.85, day 14: 3.23 ± 1.03 mmol/L). Uric acid levels were non-significantly elevated (within the normal range) in all subjects at day 7 (on average from about 315 μmol/L to 345 μmol/L, read from figure). No adverse physical symptoms, including gastrointestinal problems, occurred in any subject during the study.

In a randomised, double-blind crossover study (Hellsten et al., 2004), eight healthy subjects (25 ± 1.8 years) underwent exercise training for 7 days followed by Bioenergy Ribose™ administration of a total of nine oral doses, each of 200 mg/kg bw over a period of three days (corresponding to 52 g/day for a mean body mass of 86.2 kg) and a subsequent training session 72 h after the last training session ('72-h test'). After the last training session, plasma glucose levels were significantly lower ($p < 0.05$) in the D-ribose group compared to placebo at 30, 60 and 90 min (with lowest values of 3 mmol/L at 60 min) and compared to resting levels at 60 and 90 min but returned to baseline within 2 h. In the D-ribose group, an increase in plasma urate levels (up to 475 μmol/L, read from figure) was also observed compared to levels immediately after training, and to placebo from 10 min after exercise in the 72-h test.

Van Gammeren et al. (2002) reports on a double-blind, placebo-controlled trial in 12 bodybuilders aged 18–35 years in which 5 g Bioenergy D-ribose was consumed 30–60 min before and after training for 4 weeks. No adverse events (i.e. diarrhoea, gastrointestinal distress or muscle cramping) were reported.

In a randomised, double-blind, crossover study, Omran et al. (2003) investigated the effect of consuming 15 g/day of Bioenergy's D-ribose, given in three portions of 5 g with meals for 3 weeks in 15 coronary artery disease (CAD) patients, mean age 61 ± 6 years. No adverse effects were reported.

In a double-blind, placebo-controlled, crossover study, Steele et al. (1966) investigated the effects of 15 g D-ribose, given four times daily after meals for 7 days in five patients with McArdle's disease, age 20–60 years. The symptoms observed were diarrhoea (1), occasional symptoms of hypoglycaemia (1), light-headedness (1) and hunger (1).

Teitelbaum et al. (2006) investigated the effects of CORvalen™ (a ribose-based product produced by Bioenergy) therapy in 41 chronic fatigue syndrome and/or fibromyalgia patients, average age 48 years, in an open-label uncontrolled pilot study. Patients ingested 5 g D-ribose three times daily with food for an average duration of 28 days. Of the five subjects considered non-compliant, three patients withdrew from D-ribose treatment because of a hyperanxious feeling, light-headedness and increased appetite. Among the study completers, one reported transient nausea and 1 reported mild anxiety, but both reactions were reversed by dose reduction.

Gebhart and Jorgenson (2004) reported on a 37-year-old woman diagnosed with fibromyalgia who received 5 g CORvalen™, twice a day for over 2 months with no adverse effects reported during the treatment period.

Pliml et al. (1992) studied the effects of four doses of 15 g D-ribose per day for 3 days in 20 CAD patients, aged 45–69 years. Ribose was generally well tolerated, with episodes of slight discomfort (in two patients at 30 min and 2 h, respectively, after the first dose of ribose; the symptoms were not typical of hypoglycaemia) and mild gastrointestinal discomfort (1 on day 3). Three patients had an increase in serum uric acid levels to 410–500 μmol/L (7.4–8.4 mg/dL).

A myoadenylate deaminase deficient patient ingested D-ribose up to 50–60 g D-ribose per day (Zöllner et al., 1986) for an unspecified period. Daily amounts subdivided into 4 g doses were tolerated without side effects, whereas single doses of more than 20 g resulted in diarrhoea.

Salerno et al. (1998) investigated the effects of D-ribose administration in a 13-year-old female patient with adenylosuccinase deficiency. The patient consumed 40 g D-ribose/day in four 10 g doses for 3 months without adverse effects, while higher doses of up to 100 g/day resulted in mild diarrhoea. Uric acid excretion markedly increased. Serum urate levels increased from 0.12 to 0.29 mmol/L and glucose levels decreased from 5.4 to 4.8 mmol/L. In healthy subjects, oral administration of 13 mmol (approx. 1.95 g)/kg bw per day of D-ribose resulted in a 10–20% decrease in serum glucose levels, and a two- to threefold increase in urate and urinary urate-to-creatinine ratio. D-ribose was well tolerated, with the exception of occasional diarrhoea at higher doses, up to about 30 mmol (approx. 4.5 g)/kg bw per day (Salerno et al., 1999).

Studies on the effects of oral single administration of D-ribose

In the double-blind, randomised cross-over study of Thompson et al. (2014) (see Section 3.8), 12 healthy, adult subjects were given oral doses of 2.5, 5.0 and 10.0 g D-ribose under fasting and fed conditions. Serum glucose decreased at fasting in a dose-related manner with respective baseline/post dose values of 86.5/83.1, 85.8/72.6 and 86.8/60.5 mg/dL. Dose-related decreases in serum glucose up to 26.3 mg/dL (30.3% of baseline at the 10 g dose) occurred in the first 60 min post dose and returned to near-normal at 2 h, but remained slightly below predose levels up to the last time point (5 h). Insulin response peaked 15 min post dose. The presence of food did not appreciably affect the lowering of glucose levels compared with the comparable fasting dose. The uric acid levels were virtually unchanged for all fasting doses of D-ribose. The increases in uric acid in the fed state were attributed to the food consumed. D-ribose was generally well tolerated in the dose range studied, though one of the subjects, a 53 kg female for a few minutes experienced mild symptoms of hypoglycaemia 70 min post dose of 10 g ribose in the fasted state.

Fenstad et al. (2000) investigated the effects of D-ribose on resting carbohydrate and purine metabolism in 10 healthy subjects, aged 18–50 years, who were given oral doses of 0, 2, 5 and 10 g of Bioenergy Ribose™ on different days. Blood samples were obtained at 0, 15, 30, 45, 60 and 120 min after the consumption of each dose. A dose-dependent decrease in blood glucose was observed for all D-ribose dosages. Both the 5 and 10 g doses resulted in an acute, temporary state of hypoglycaemia (3 mmol/L and 2.6 mmol/L, respectively), but only with the 10 g dose, the decline reached significance ($p < 0.05$) at 45 and 60 min after ingestion. At any dose of D-ribose, no adverse subjective effects were noted and at 120 min post-consumption, blood glucose had returned to baseline values. A non-significant increase in insulin values was observed for all doses which peaked at 15 min and then declined to or below baseline. Levels of uric acid differed with differing doses of D-ribose (2 g: 297 ± 10 μmol/L; 5 g: 328 ± 0.9 μmol/L; 10 g: 318 ± 0.9 μmol) and paired comparison from 2 g and 5 and 10 g was statistically significant at 30 and 60 min after ingestion ($p < 0.05$).

Gross and Zöllner (1991) administered D-ribose orally after an overnight fast to nine healthy subjects, aged 23–37 years at doses ranging from 83.3 to 166.7 mg/kg bw per hour over at least 4 h, to evaluate the effect on serum levels of glucose, insulin and C-peptide. At 166.7 mg/kg bw per hour, equivalent up to a total amount of 87 g D-ribose, a 25% decline in serum glucose levels was observed and a significant increase in serum insulin concentrations compared to initial levels; however, levels remained within normal ranges for the duration of the study.

In another study by Gross et al. (1989), healthy (n = 8, age 23–37 years) and myoadenylate deaminase deficient (n = 5, age 31–58 years) subjects were administered orally D-ribose at doses up to 200 mg/kg bw per hour for 5 h (corresponding to a total amount of 33–78.5 g for healthy subjects and to 27–74 g for patients). In healthy subjects, the decrease in serum glucose concentrations ranged from 8.9% to 29.5%. All doses were well tolerated, except for 200 mg/kg bw per hour, which resulted in diarrhoea, present in one case also at 166.7 mg/kg bw per hour. No changes in heart rate,

blood pressure, serum uric acid concentrations, uric acid clearance and creatinine clearance were reported before, during or after D-ribose treatment.

Ten healthy subjects, aged 20–30 years, were given orally 1 g/kg bw D-ribose (Ginsburg et al., 1970). Blood samples were taken for 3 h. Following administration, the blood glucose level fell on average 14 mg/dL over the first hour from a fasting mean value of 80 mg/dL, then rose slightly during the second hour and fell again to a mean of 50 mg/dL at 3 h. Plasma insulin levels significantly increased within half an hour of ribose administration, followed by a slight fall and a second increase occurring between 2 and 3 h post-ribose administration. This increase accompanied the secondary decrease in glucose levels. Serum-free fatty acid levels fell by nearly 50% within half an hour of giving ribose (from a fasting mean of 432 meq/L to 250 meq/L at half an hour and fasting levels were regained after a further 2 h. Symptoms reported by subjects included headache (1), marked peristalsis and borborygmi (1) and diarrhoea 3–4 h after ribose ingestion (2).

In ten healthy subjects, aged 21–33 years, who ingested 35 g D-ribose, insulin levels had increased slightly after 15 min, peaked at 20 min to twice the baseline levels and then rapidly declined (Goodman and Goetz, 1970). Blood glucose levels were also decreased with lowest levels not below 75% of baseline values within the follow-up period of 90 min.

Steinberg et al. (1970) administered a single oral dose of D-ribose (15 g to 13 healthy subjects, six probable diabetics, and 15 diabetics), all in the post-absorptive state. Blood samples were collected at 30, 60, 90 and 120 min post-administration. Serum glucose levels decreased in all subjects except for insulin-dependent diabetics. With increasing glucose intolerance, subjects were significantly less responsive to the blood glucose-lowering effect of D-ribose. The mean maximal decrease of 47% (27 mg/dL) was observed in healthy subjects after 60 min. Levels returned towards baseline values at 120 min. No significant changes in insulin levels were observed.

The Panel notes that in studies lasting several days or weeks, except for one study (Steele et al., 1966), which reported symptoms of hypoglycaemia in one patient with McArdle disease at intakes of 60 g/day, no symptoms of hypoglycaemia were observed after oral administration of D-ribose at dosages of 10 g/day up to 1.95 g/kg bw per day in healthy subjects and patients. A non-significant decrease in glucose and increase in uric acid concentration were seen in healthy subjects consuming 20 g/day of D-ribose for 14 days (Seifert et al., 2008). In healthy subjects ingesting 52 g of D-ribose for 3 days, a significant short-term decrease in glucose and increase in uric acid levels was found in relation to a training session (Hellsten et al., 2004). Gastrointestinal symptoms such as discomfort or diarrhoea were reported to occur occasionally at intakes of single doses > 20 g (Steele et al., 1966; Zöllner et al., 1986; Pliml et al., 1992; Salerno et al., 1998, 1999; Teitelbaum et al., 2006).

The Panel notes that single oral administration of D-ribose in amounts of 5–87 g consistently resulted in a decrease in plasma glucose levels in healthy subjects or patients with lowest values observed at 45–180 min after D-ribose administration before returning to normal values. The extent of the decline in glucose concentrations reported in the various studies is mixed and ranged between 9% and 47%. As far as reported, insulin levels either non-significantly or significantly increased following D-ribose administration. In these studies, the decrease in glucose levels was not associated with symptoms of hypoglycaemia, except for one study (Thompson et al., 2014) in which short-term symptoms of hypoglycaemia were noted in a low-weight female subject after ingesting 10 g of ribose in the fasted state. Three of these studies reported also on uric acid concentrations with conflicting results. While Fenstad et al. (2000) found significantly higher levels of uric acid (which were, however, still in the normal range) following oral administration of 10 g D-ribose when compared to the dose of 2 g at 30 and 60 min, no changes in serum uric acid concentrations were reported by Thompson et al. (2014) following ingestion of 10 g D-ribose and in the study of Gross et al. (1989), during or after treatment with 27–89 g D-ribose. Gastrointestinal symptoms were noted at single intakes of around 70 g (Gross et al., 1989; Ginsburg et al., 1970).

The studies available on the effects of single administration of D-ribose consistently show a decline in glucose concentrations at doses of 5 g and above in a dose–response manner. This glucose-lowering effect has been observed also in the fed state. In one case, the intake of a single dose of 10 g in a fasted state led to a symptomatic hypoglycaemia. The Panel considers that this blood glucose-lowering effect of D-ribose is adverse, in that it increases the risk of hypoglycaemia.

3.11. Allergenicity

The applicant has provided evidence that the production process results in the absence of microbial proteins in the NF by means of a Bradford assay and Kjeldahl analysis.

In a literature review performed by the applicant, no reports of food allergy resulting from consumption of *B. subtilis*-derived food products were identified. Furthermore, proprietary post-market surveillance data have indicated no allergic reactions to Bioenergy Ribose™ in the USA, where the NF is being marketed since 2004.

The Panel considers that the risk of allergic reactions to the NF is low.

4. Discussion

The Panel considers that the observed effects in the subchronic toxicity study in Wistar rats could be the consequence of nutritional imbalances, but toxicological effects could not be ruled out. Therefore, the Panel derived a NOAEL of 3.6 g/kg bw per day based on this study.

The developmental toxicity study in Wistar rats provided further information on maternal toxicity and embryo/foetotoxicity that support the NOAEL defined in the subchronic study.

Concern has been raised by national competent authorities with regard to the potential of D-ribose intake to cause hypoglycaemia and hyperuricaemia or gastrointestinal symptoms.

In literature, variable glucose levels define hypoglycaemia (3.3, 3.0, 2.8, 2.7, 2.5 and 2.2 mmol/L, where the latter is being used to define severe hypoglycaemia) (Nirantharakumar et al., 2012). In adults without diabetes, a cut-off of 2.8 mmol/L is often used and symptoms related to low blood sugar should confirm the diagnosis (Cryer et al., 2009).

Several studies were provided in the dossier with single oral doses of 2–87 g D-ribose consistently report transient decreases of glucose concentrations within 1–3 h. The transient decrease of glucose concentration was not associated with clinical symptoms of hypoglycaemia, except for one case, where a low-weight female experienced short-term symptoms of hypoglycaemia after ingesting 10 g of ribose in the fasted state. While in this and in most of the other studies, blood glucose levels did not fall below 2.8 mmol/L, a temporary significant decline of blood glucose to 2.6 mmol/L was observed in one study following a single oral dose of 10 g D-ribose. The decrease in blood glucose comes along with increases in insulin levels. The glucose-lowering effect also occurs if meals rich in carbohydrate or fat are ingested before intake of D-ribose.

With regard to a potential impact of D-ribose on increasing serum uric acid, the Panel considers that the available evidence from human studies does not raise safety concern.

With regard to gastrointestinal symptoms, the Panel considers that available studies indicate that these may occur with single intakes exceeding 20 g.

No studies have been provided that investigated intake of D-ribose in infants, young children and adolescents. Whether young age may be of special concern with regard the glucose-lowering effects of D-ribose is not known. However, the Panel considers that children could be particularly vulnerable to glucose-lowering effects of D-ribose (Lang, 2011; van Veen et al., 2011; Ramsden et al., 2017).

The Panel notes that there is a lack of understanding of the mechanisms responsible for the short-term decrease in blood glucose reported in the human studies, only limited data on the dose–response relationship between D-ribose and blood glucose levels, and uncertainty about the risk of symptomatic hypoglycaemia, especially in susceptible persons.

Because the decrease in glucose levels and/or the occurrence of transient symptomatic hypoglycaemia (as reported in one case) is considered adverse, based on the human studies, the LOAEL would be at intakes of 10 g of D-ribose. Concerning the human data, taking the above issues into account, the Panel concludes that 5 g per day, equivalent to 70 mg/kg bw per day, would be the NOAEL with respect to hypoglycaemia that can be considered applicable for adults. For children, the Panel acknowledges the lack of human data directly relevant for this population group.

For the animal study, the Panel considered an uncertainty factor of 100 as sufficient given the nature of the NF and the magnitude of the effects observed. Based on the NOAEL of 3,600 mg/kg bw per day derived from the subchronic toxicity study in rats, an acceptable level of intake would be up to 36 mg/kg bw per day. This is half the NOAEL value identified in the human studies for adults with respect to hypoglycaemia. The Panel concludes that 36 mg/kg bw per day would also take into account the potentially increased sensitivity of certain population groups to hypoglycaemia, including children.

5. Conclusions

The Panel concludes that the NF, D-ribose, is safe for the general population at intake levels up to 36 mg/kg bw per day.

The Panel considers that the safety of the NF at the intended uses and use levels as proposed by the applicant has not been established. Therefore, in line with article 7 of the Commission Implementing Regulation (EU) 2017/2469, the Panel has provided in Appendix A the detailed dietary exposure assessment of the NF.

The Panel reached the conclusion on the safety of the NF under the proposed conditions of use with the data claimed as proprietary by the applicant (oral embryotoxicity/teratogenicity study with D-ribose in rats [TNO report V2657] and subchronic (13-week) oral toxicity study with D-ribose in rats [TNO report V99.1155]).

Steps taken by EFSA

1) Letter from the European Commission to the European Food Safety Authority with the request for a scientific opinion on the safety of D-ribose. Ref. Ares(2017)2556092-19/05/2017.
2) On 1 June 2017, EFSA received a valid application from the European Commission on D-ribose as NF, which was submitted by Bioenergy Lire Science, Inc., and the scientific evaluation procedure started.
3) On 11 September 2017 and 15 January 2018, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
4) On 22 November 2017 and 6 February 2018, additional information was provided by the applicant and the scientific evaluation was restarted.
5) During its meeting on 17 April 2018, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of D-ribose as a NF pursuant to Regulation (EU) 2015/2283.

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Abbreviations

ACNFP	Advisory Committee on Novel Foods and Processes
AOAC	Association of official analytical communities
ATCC	American type culture collection
ATP	adenosine triphosphate
AUC	Area under the curve
bw	body weight
CFU	colony-forming unit
DNA	Deoxyribonucleic acid

GMP	Good manufacturing practice
HACCP	Hazard analysis and critical control points
HPLC/RI	High performance liquid chromatography coupled with refractive index detection
ISO	International Organization for Standardization
LOAEL	lowest observed adverse effect level
LPS	lipopolysaccharide
NADH	nicotinamide adenine dinucleotide
NF	Novel food
NDNS	National Diet and Nutrition Survey
NOAEL	No observed adverse effect level
OECD TG	Organisation for Economic Co-operation and Development – Test Guideline
QPS	Qualified presumption of safety
RNA	Ribonucleic acid

Appendix A – Intake assessment

The intake assessment of D-ribose was performed with the data available in the EFSA Comprehensive European Food Consumption Database (Comprehensive database).

Since 2010, the 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 (EFSA, 2011a). New consumption surveys added in the Comprehensive database were also taken into account in this assessment.

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 represents the best available source of food consumption data across Europe at present.

Food consumption data from the following population groups: infants, toddlers, children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table A.1). Consumption records were codified according to the FoodEx classification system (EFSA, 2011b).

Table A.1: Population groups considered for the exposure estimates of D-ribose

Population	Age range	Countries with food consumption surveys covering more than 1 day
Infants	4–11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers	12–35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children[(a)]	3–9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	10–17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adults	18–64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly[(a)]	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Romania, Sweden, UK

(a): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

For the estimation of the intake, the Panel considered the uses proposed by the applicant as reported in Table 3. For the purpose of the intake assessment, these food categories were recodified according to the FoodEx classification system. Table A.2 provides the list of the food categories used for the exposure assessment of D-ribose.

Table A.2: Food categories used for the exposure assessment of D-ribose based on the FoodEx classification system

Food category	FoodEx name	FoodEx code	FoodEx level	D-ribose use level (g/100 g)
Biscuits	Cereal bars	A.01.06.003	L3	2
Buns, cakes, pastries and fruit pies	Muffins	A.01.07.001.036	L4	3.14
Chocolate confectionary	Chocolate (Cocoa) products	A.10.03	L3	1.7
Chocolate confectionary	Bitter chocolate	A.10.03.001	L3	1.7
Chocolate confectionary	Bitter–sweet chocolate	A.10.03.002	L3	1.7

Food category	FoodEx name	FoodEx code	FoodEx level	D-ribose use level (g/100 g)
Chocolate confectionary	Chocolate, cream	A.10.03.004	L3	1.7
Chocolate confectionary	Chocolate with nuts or fruits	A.10.03.005	L3	1.7
Chocolate confectionary	Chocolate-coated confectionery	A.10.03.006	L3	1.7
Chocolate confectionary	Filled chocolate	A.10.03.007	L3	1.7
Chocolate confectionary	Milk chocolate	A.10.03.008	L3	1.7
Chocolate confectionary	White chocolate	A.10.03.009	L3	1.7
Chocolate confectionary	Pralines	A.10.03.010	L3	1.7
Chocolate confectionary	Cooking chocolate	A.10.03.011	L3	1.7
Chocolate confectionary	Cooking chocolate, white	A.10.03.012	L3	1.7
Chocolate confectionary	Dietetic chocolate	A.10.03.013	L3	1.7
Chocolate confectionary	Chocolate substitutes	A.10.03.014	L3	1.7
Food for particular nutritional uses	Carbohydrate-rich energy food products for sports people	A.18.03.001	L3	5
Fruit and vegetable juices	Fruit juice	A.12.01	L2	0.31
Fruit and vegetable juices	Concentrated fruit juice	A.12.02	L2	0.31
Fruit and vegetable juices	Fruit nectar	A.12.03	L2	0.31
Fruit and vegetable juices	Mixed fruit juice	A.12.04	L2	0.31
Fruit and vegetable juices	Vegetable juice	A.12.06	L2	0.21
Fruit and vegetable juices	Mixed vegetable juice	A.12.07	L2	0.21
Sugar confectionary	Candies, with sugar	A.10.04.001	L3	2
Sugar confectionary	Marzipan	A.10.04.003	L3	2
Sugar confectionary	Caramel, hard	A.10.04.004	L3	2
Sugar confectionary	Caramel, soft	A.10.04.005	L3	2
Sugar confectionary	Toffee	A.10.04.006	L3	2
Sugar confectionary	Fudge	A.10.04.007	L3	2
Sugar confectionary	Dragée, sugar coated	A.10.04.008	L3	2
Sugar confectionary	Sugar cotton	A.10.04.009	L3	2
Sugar confectionary	Foamed sugar products (marshmallows)	A.10.04.010	L3	2
Sugar confectionary	Liquorice candies	A.10.04.011	L3	2
Sugar confectionary	Gum drops	A.10.04.012	L3	2
Sugar confectionary	Jelly candies	A.10.04.013	L3	2
Sugar confectionary	Nougat	A.10.04.014	L3	2
Sugar confectionary	Halva	A.10.04.015	L3	2
Sugar confectionary	Chewing gum with added sugar	A.10.04.016	L3	2
Tea, coffee, water	Herbal tea, infusion	A.13.02.004	L3	0.7
Tea, coffee, water	Instant tee powder, infusion	A.13.02.005	L3	0.7
Tea, coffee, water	Instant tea, liquid	A.13.02.006	L3	0.7
Yoghurt	Yoghurt, cow milk, plain	A.08.06.001	L3	1.2
Yoghurt	Yoghurt, cow milk, with fruit	A.08.06.002	L3	1.2
Yoghurt	Yoghurt, sheep milk	A.08.06.003	L3	1.2
Yoghurt	Yoghurt, goat milk	A.08.06.004	L3	1.2
Flavoured drinks	Soft drinks[a]	A.13.01	L2	0.4
Flavoured drinks	Flavoured milk	A.08.02.001	L3	0.4
Flavoured drinks	Carbohydrate-electrolyte solutions for sports people	A.18.03.002	L3	1.2

(a): Excluding cola drinks.

The contribution of each survey to the estimated intake for each population group is provided as supporting information to this opinion https://doi.org/10.2903/j.efsa.2018.5265.

Table A.3 reports the main food categories contributing to the total intake of D-ribose in the different population groups, estimated from the proposed use levels of D-ribose in fortified foods using the EFSA Comprehensive database.

Table A.3: Range of contribution (%) of D-ribose intake from the different food categories used in the exposure assessment in the EU

Food category	Infants (4–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Biscuits	–	–	–	–	–	–
Buns, cakes, pastries and fruit pies	–	6.6 (1)	6.1–7.8 (2)	9.0–21.4 (2)	10.7–20.3 (2)	5.6–5.7 (2)
Chocolate confectionery	5.5–7.2 (2)	5.2–18.9 (7)	5.0–17.4 (16)	5.6–18.2 (17)	5.7–16.6 (16)	5.4–10.5 (8)
Flavoured drinks	7.4–14.8 (2)	12.1–30.3 (6)	5.2–68.4 (16)	7.8–79.1 (16)	7.2–86.1 (17)	5.5–33.0 (11)
Foods intended for particular nutritional uses	–	–	–	–	–	–
Fruit and vegetable juices	5.3–29.6 (5)	10.0–44.2 (10)	7.6–39.5 (17)	8.3–39.3 (16)	10.8–27.5 (15)	6.1–22.1 (13)
Sugar confectionery	–	6.1 (1)	5.1–14.6 (6)	5.2–16.2 (6)	9.7 (1)	5.9 (1)
Tea, coffee and water	7.3–60.6 (3)	5.0–26.3 (4)	6.7–21.7 (7)	6.5–26.3 (8)	10.1–62.4 (11)	5.7–89.4 (12)
Yogurt	14.6–92.8 (6)	5.6–86.0 (9)	6.1–61.5 (17)	10.1–54.5 (15)	10.1–65.4 (15)	9.0–78.9 (13)

Between brackets the number of surveys where the food category contributes to > 5% to the total mean exposure.