APPLICATION FOR THE APPROVAL OF CHOLINE, SUCCINATE (2:1) SALT SOLUTION AS A NOVEL FOOD IN THE EUROPEAN UNION

Pursuant to

Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on Novel Foods

SUMMARY DOCUMENT

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Application for the Approval of Choline, Succinate (2:1) Salt Solution as a Novel Food in the European Union

This application is for the approval of choline, succinate (2:1) salt solution as a novel food ingredient in the European Union (EU) under Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 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 and specifically under Article 3, point 2(a)(i):

"food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997".

Identity

Chemical name:	Choline, succinate (2:1) salt
Chemical Abstracts Service (CAS) number:	109438-15-5
Synonyms and abbreviations:	Choline, butanedioate (2:1) salt Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, butanedioate (2:1) salt DISU
Molecular and structural formulae; stereochemistry:	$C_{14}H_{32}N_2O_6$ $[(CH_3)_3{}^{+}N\text{-}CH_2\text{-}CH_2\text{-}OH]_2\ {}^{-}O_2C\text{-}CH_2\text{-}CH_2\text{-}CO_2{}^{-}$ achiral
Molecular mass (Da):	324.41 g/mol

Production Process

Choline, succinate (2:1) Salt is made when the starting material choline chloride is reacted with sodium hydroxide in propanol to form the choline hydroxide intermediate. The intermediate is reacted with succinic acid to form choline, succinate (2:1) salt. The technical product is dissolved and filtered, followed by sedimentation, additional filtration, rinsing, and drying to form the pure choline, succinate (2:1) salt.

The manufacturing process controls are well defined and include the following:

1. Control of materials:

Materials that were used for the manufacturing process are provided by audited suppliers. Prior to release for use, each raw material used is subject to testing against its specifications.

2. Control of critical steps and intermediates:

   In-process tests and intermediate specifications.

3. Analysis of finished product against food-grade specifications.

Specification

The specification for choline, succinate (2:1) salt is presented in Table 1 and is supported by analysis results from 5 independent batches that show conformity.

Table 1 Chemical Specifications for Choline, Succinate (2:1) Salt Solution

Description/Definition:		
Choline, succinate (2:1) salt is made when the starting material choline chloride is reacted with sodium hydroxide in propanol to form the choline hydroxide intermediate. The intermediate is reacted with succinic acid to form choline, succinate (2:1) salt followed by dissolution, filtration and drying to form the pure choline, succinate (2:1) salt. The salt is then dissolved in water.		
Specification Parameter	**Method**	**Specification**
Appearance	Clear, colourless or yellowish solution	Organoleptic
Identity	NMR	Complies to Reference Spectrum
Identity Choline	AM0558	Complies to Reference Spectrum
Identity Succinic Acid	AM0558	Complies to Reference Spectrum
Assay Choline (mg/g)	AM0058	273–369
Assay Succinic Acid (mg/g)	AM0058	153–207
Molar Ratio Choline:Succinic Acid	Molar ratio of Choline:Succinate	1.7–2.3
Assay Choline + Succinic Acid (mg/g)		425–575
Water content % (w/w)	KF	42.5–57.5
Calculated sum of Water and Choline and Succinate % (w/w)	Add value of KF determination and value of Choline Succinate assay	85–115
Acetone (mg/kg)	RSSL standard in-house method (Gas Chromatography Flame Ionisation Detector	<300
Porpan-2-ol (mg/kg)	RSSL standard in-house method (Gas Chromatography Flame Ionisation Detector	<600
Chloride (as free anion)	RSSL standard in-house method (TM-136)	≤0.5
Sodium	RSSL standard in-house method (TM-200)	≤0.5
Cadmium	RSSL standard in-house method (TM-201)	<1 mg/kg
Lead	RSSL standard in-house method (TM-201)	<3 mg/kg
Mercury	RSSL standard in-house method (TM-201)	<0.1 mg/kg

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Specification Parameter	**Method**	**Specification**
Microbial Purity	Reference Solus Salmonella Elisa method AFNOR Certificate No SOL 37/01-06/13	*Salmonella* spp. absent in 25 g
	Reference BS EN ISO 4832:2006 AM 2009. Method ESGMM302	Coliforms <10 cfu/g
	Reference ISO 21527-1:2008. Method ESGMM308	Moulds <10 cfu/g Yeast <10 cfu/g
	Microbiology of drinking water Part 7 2012. Method No ESGMM100	Total viable count <1,000 cfu/g

cfu = colony-forming units; KF = Karl Fischer; NMR = nuclear magnetic resonance; RSSL = Reading Scientific Services Ltd.

History of Use

Choline, succinate (2:1) salt has never been consumed itself as a salt in the EU; however, in solution when consumed it may be considered to be nutritionally equivalent to a solution of choline and succinic acid.

Proposed Uses

The proposed uses and conditions of use are summarised in Table 2 below.

Table 2 Proposed Food Uses and Use Levels for Choline, Succinate (2:1) Salt

Specified Food Category [as intended to be included in the Union List]	**Max. Level of Choline, Succinate (2:1) Salt (on a dry weight basis) (mg/100 g or 100 mL unless otherwise specified)**
Unflavoured fermented milk-based products	320
Flavoured fermented milk-based products	320
Edible ices	320
Soft candies	280
Flavoured drinks	280
Meal replacement for weight control	280
Protein products	280
Food Supplements as defined under Directive 2002/46/EC	500 mg/day
Foods for Special Medical Purposes as defined under Regulation (EU) No 609/2013	Case-by-case based on generally accepted scientific evidence.

Intake

Estimates for the intakes of the components of choline, succinate (2:1) salt in EU Member States were based on the proposed food uses and use levels in combination with food consumption data from the European Food Safety Authority (EFSA) Comprehensive Database.

The cumulative intake of choline from proposed uses (i.e. 3.3 g/day) and background sources of choline was estimated to be 3.8 g/day, which is below the upper limit of 7.5 g choline/day.

The cumulative intake of succinic acid based on proposed uses and background sources of succinic acid was determined to be <2 g/day, which is also below the upper safe limit that can be determined based on the available toxicology data.

Risk management measures are in place for food supplements and foods for special medical purposes under

- Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements[1]

- Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009[2] and more specifically regulated under Commission Delegated Regulation (EU) 2016/128 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for food for special medical purposes[3]

Safety

The safety of choline, succinate (2:1) salt solution is based on the fact that it the available safety data on its individual components or the dissociated salt in solution, where the key studies have been summarised. Choline and succinic acid have a long history of human exposure due to their natural occurrence in a variety of foods.

Choline is an essential nutrient and serves as a number of important physiological functions including the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signalling, and lipid and cholesterol transport and metabolism. Although choline can be synthesised *de novo* by the body, production can be become insufficient and thus intake from the diet may be required. EFSA recently established an AI at 400 mg/day (EFSA

[1] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57 (consolidated version: 26/07/2017).
[2] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35–56. Available online: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1533914468695&uri=CELEX:32013R0609 (Consolidated Version: 11/07/2017).
[3] Commission Delegated Regulation (EU) 2016/128 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for food for special medical purposes. OJ L 25, 2.2.2016, p. 30–43. Available online: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1469811508722&uri=CELEX:32016R0128 (Consolidated Version: 14/05/2020).

NDA Panel, 2016a). Choline is found in the diet in a variety of foods, including eggs, meats and fish, whole grains, vegetables and fruits, and fats and oils. Choline is a component of the neurotransmitter acetylcholine, as well as brain and nervous tissue lipids as a component of phosphatidylcholine and sphingomyelin. Other sources of choline are already approved for use in foods in the EU. Choline, choline chloride, choline bitartrate, and choline citrate may be added to food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control in the EU. CDP-choline (or citicoline) has been evaluated as novel food by EFSA and no safety concerns were raised (EFSA NDA Panel, 2013). Choline and choline compounds can also be found in dietary supplements. The cumulative intake of choline based on proposed uses and background sources of choline was estimated to be 3.8 g/day of choline, which is below the upper limit of 7.5 g choline/day.

Succinic acid is an intermediate of the citric acid cycle. Succinic acid is naturally present in foods, with high levels reported in fermented products such as wine. Succinic acid is approved for use as a food additive at levels well above those proposed for use. Based on the NOAEL of 1,250 mg/kg body weight per day for the subchronic study and findings from the 2-year carcinogenicity study of succinic acid, an upper safe limit of intake (acceptable daily intake) of 12.5 mg/kg body weight can be derived. The cumulative intake of succinic acid based on proposed uses and background sources of succinic acid was determined to be <2 g/day, which is also below the upper safe limit that can be determined based on the available toxicology data.

Food supplements containing choline, succinate (2:1) salt are intended for use to provide up to 320 mg/day choline and 180 mg/day succinic acid , which results in intakes that are well below their respective ULs and therefore safe for use in humans.

Together, the weight of the available evidence on choline, succinate (2:1) salt solution supports the safe use of the ingredient at under the proposed conditions of use in food supplement and food/beverages products.