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By Federal Express

April 20, 2020

Office of Food Additive Safety (HFS–200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740-3835

Re: GRAS Notice for the Use of L-Carnitine-L-Tartrate (LCLT) in Term Infant Formula

Dear Sir or Madam:

On behalf of our client Ausnutria B.V. ("Ausnutria"), we hereby submit the enclosed GRAS notice for L-Carnitine-L-Tartrate (LCLT) as an ingredient in term infant formula (IF). LCLT is intended for use as a source of L-Carnitine in term infant formula for infants up to 12 months of age. The maximum intended use of LCLT in term infant formula for infants up to 12 months of age is 0.0011 percent of the IF blend weight by volume. Ausnutria's conclusion of GRAS status for the intended use of LCLT in term infant formula is based on scientific procedures in accord with 21 CFR §170.30(a) and (b).

LCLT is not intended for use in any products that would require additional regulatory review by the United States Department of Agriculture. The GRAS notice does not contain any designated confidential business information. In accordance with the Agency's guidelines, we have enclosed Form 3667, one original copy of the GRAS notice, and one complete electronic copy of the GRAS notice on a compact disk (CD).

We are committed to cooperating with the Agency and believe an open dialog is one of the most effective ways to accomplish that objective. If any questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

If you have any questions, please contact us.

Sincerely,

Martin J. Hahn
martin.hahn@hoganlovells.com
202 637 5926

Xin Tao
xin.tao@hoganlovells.com
202 637 6986

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE (GRAS) NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 09/30/2019
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: 2019/03/12

4 For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☒ No If yes, enter the date of communication *(yyyy/mm/dd)*: _____

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier	Name of Contact Person Leoniek Robroch		Position or Title Manager Regulatory Affairs	
	Organization *(if applicable)* Ausnutria B.V.			
	Mailing Address *(number and street)* P.O. Box 50078			
City Zwolle	State or Province n/a	Zip Code/Postal Code LB 8002	Country Netherlands	
Telephone Number +31 88 11 63 631	Fax Number	E-Mail Address leoniek.robroch@ausnutria.nl		
1b. Agent or Attorney *(if applicable)*	Name of Contact Person Martin Hahn		Position or Title Partner	
	Organization *(if applicable)* Hogan Lovells US LLP			
	Mailing Address *(number and street)* 555 13th Street, NW			
City Washington	State or Province District of Columbia	Zip Code/Postal Code 20004	Country United States of America	
Telephone Number 202 637 5926	Fax Number 202 637 5910	E-Mail Address martin.hahn@hoganlovells.com		

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

L-carnitine-L-tartrate

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☒ Electronic files on physical media

☒ Paper

If applicable give number and type of physical media

1 CD

3. For paper submissions only:

Number of volumes 1

Total number of pages 111

4. Does this submission incorporate any information in CFSAN's files? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for conclusions of GRAS status *(Check one)*

☒ Scientific procedures *(21 CFR 170.30(a) and (b))* ☐ Experience based on common use in food *(21 CFR 170.30(a) and (c))*

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

SECTION D – INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

L-carnitine-L-tartrate will be used as a source of L-carnitine in term infant formula. LCLT is non-hydroscopic which facilitates dry-blending and precise dosing. LCLT will be added to IF within the levels recommended by LSRO of 1.2 mg/100 kcal - 2.0 mg/100 kcal, adjusted to account for the L-Carnitine that may be present in the IF from other sources.

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☒ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☒ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete – PART 1 is addressed in other sections of this form)

- [x] PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).
- [x] PART 3 of a GRAS notice: Dietary exposure (170.235).
- [x] PART 4 of a GRAS notice: Self-limiting levels of use (170.240).
- [x] PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).
- [x] PART 6 of a GRAS notice: Narrative (170.250).
- [x] PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

- [ ] Yes
- [x] No

Did you include this other information in the list of attachments?

- [ ] Yes
- [x] No

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that Leoniek Robroch *(name of notifier)*

has concluded that the intended use*(s)* of L-carnitine-L-tartrate *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. Leoniek Robroch *(name of notifier)* agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so; agrees to send these data and information to FDA if FDA asks to do so.

P.O. Box 50078, 8002 LB Zwolle, The Netherlands *(address of notifier or other location)*

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

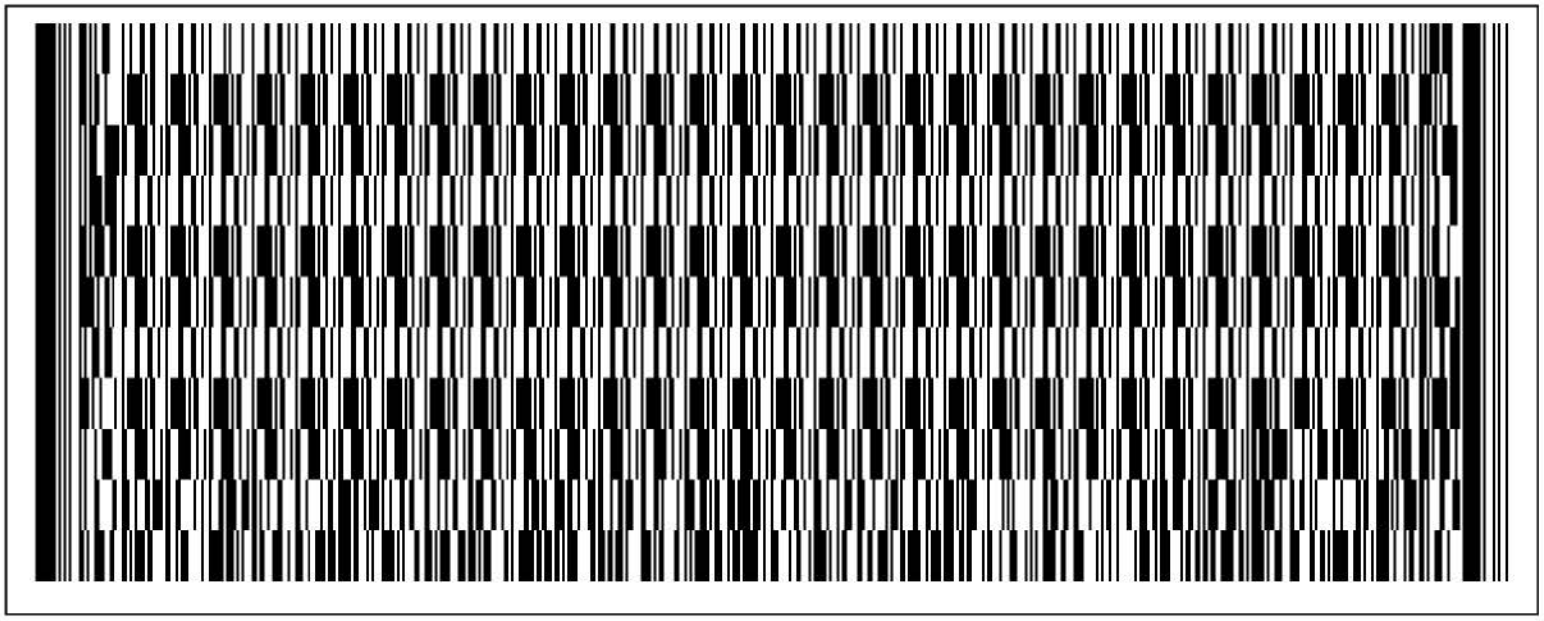
3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
	Martin Hahn, Partner	04/20/2020

SECTION G – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Attachment A_Schmidbaur H, Schier A and Bayler A (1998). The solution and solid state structure of L-carnitine-L-tartrate. Zeitschrift für Naturforschung 53 b, 788-79	LCLT GRAS Submission; 4 pages.

OMB Statement: Public reporting burden for this collection of information is estimated to average 170 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, PRAStaff@fda.hhs.gov. (Please do NOT return the form to this address). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



GRAS Notification of L-Carnitine-L-Tartrate in Term Infant Formula

Ausnutria B.V.
Zwolle, The Netherlands
April 2020

Authors: Charlotte ‘t Hoen, MSc
Hiskias Keizer, PhD

Content

FOREWORD

A thorough review of the scientific literature related to the nutritional, chemical, and toxicological properties of L-Carnitine-L-Tartrate (LCLT) is presented in this document. In addition, the practical rationale for this compound's use as a stable, organoleptically-neutral, and non-hygroscopic salt of L-Carnitine in powdered infant formula is discussed. When the infant formula powder is mixed with water in preparation of an infant feeding, the compound completely dissociates into its sub-components, L-Carnitine and L-tartaric acid, which are both currently permitted and present in infant formula marketed in the U.S. Furthermore, analysis of Ausnutria's intended use of L-Carnitine-L-Tartrate in infant formula demonstrates that the estimated dietary exposure levels of its subcomponents are below available recommendations.

Ausnutria provided detailed information about the identity, manufacturing, and specifications of LCLT. A summary regarding the safety of and exposure to LCLT is provided.

The L-Carnitine from LCLT is safe to use for humans. In none of the studies conducted in humans thus far, any serious adverse effects of exposure to LCLT were observed. A human tolerance up to 3 grams per day for LCLT has been established in adults. L-Carnitine is considered a compulsory component in infant formula by the EFSA and Codex Alimentarius and LCLT can be used to provide L-Carnitine.

The L-tartaric acid from LCLT is safe to use and maximal exposure to this ingredient in this GRAS notice falls within the FAO/WHO acceptable daily intake.

In further support of Ausnutria's determination that LCLT is GRAS for use in term infants, Ausnutria convened an Expert Panel whose members reviewed the data and information in this dossier and any other information that they considered pertinent and concurred with Ausnutria's conclusion that the use of LCLT in term infants, when used as discussed in this dossier, is GRAS. The report of the Expert Panel members is attached in Exhibit 1.

EVALUATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-Carnitine-L-Tartrate AS A FOOD INGREDIENT in Term Infant Formula

Part 1. SIGNED STATEMENTS AND CERTIFICATION

1.1. Basis for GRAS Conclusion

Ausnutria B.V. (Ausnutria), with its principal place of business located in 8025 BM Zwolle, the Netherlands at Dokter van Deenweg 150, hereby we would like to inform the FDA that L-Carnitine-L-Tartrate (LCLT) is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on Ausnutria's view that LCLT substance is Generally Recognized as Safe (GRAS) under the conditions of its intended use in term infant formula (IF) as a nutrient source for L-Carnitine as described in Section 1.4 below.
This GRAS determination was reached in accordance with 21 CFR Part 170, Subpart E. The basis for this determination is scientific procedures in accordance with 21 CFR 107.30 (a) and (b).

It should be noted that the LCLT, for use in term IF, as discussed in this GRAS assessment, is identical to the LCLT that is GRAS for use in food in the U.S. generally, but is not currently added to IF in the U.S. However, LCLT has been approved for use in food and IF preparations in other countries as a source of L-Carnitine by their respective regulatory bodies.
Ausnutria's determination that LCLT is GRAS for use in term IF is further supported by the use of an independent panel of recognized experts (hereinafter referred to as the Expert Panel) qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients to determine the Generally Recognized As Safe (GRAS) status of LCLT for use as a food ingredient in term IF at a maximum level of 0.0011 g/100 ml.. .
In determining the GRAS status of LCLT in term IF, Ausnutria considered all of the publicly available information, including documents produced by other reputable safety organizations and regulatory bodies such as the European Food Safety Authority (EFSA), Health Canada, Food Standards Australia New Zealand (FSANZ), information related to LCLT in FDA sources, and other publicly available information.
It should be noted that the sole source of food for the term infants will be IF. Therefore, the exposure and safety of LCLT, L-Carnitine and L-tartaric acid is based on exposure from LCLT and other additions to the formula.

A thorough review of the scientific literature related to the nutritional, chemical, and toxicological properties of LCLT is presented in this document. In addition, the practical rationale for this compound's use as a stable, organoleptically-neutral, and non-hygroscopic

salt of L-Carnitine in powdered IF is discussed. When the IF powder is mixed with water in preparation of an infant feeding, the compound completely dissociates into its sub-components, L-Carnitine and L-tartaric acid, which are both currently permitted and present in IF marketed in the US. Furthermore, analysis of Ausnutria's intended use of LCLT in IF demonstrates that the estimated dietary exposure levels of its subcomponents are below available safety recommendations, but sufficient to meet functionally active levels of L-Carnitine in IFs.

Ausnutria provided detailed information about the identity, manufacturing, and specifications of LCLT. A summary regarding the safety of and exposure to LCLT is provided. This information was augmented with a search of the scientific literature of LCLT.

The L-Carnitine from LCLT is safe to use, and no "No-Observed-Adverse-Effect Level" (NOAEL) in humans has been estimated (Odle, Adams et al. 2014). A human tolerance up to 3 g per day for LCLT has been established in adults as in humans at this dose and below, no adverse effects were reported in literature (Odle, Adams et al. 2014). L-Carnitine,. is considered a compulsory component in IF by the EFSA and Codex Alimentarius, and LCLT can be used as a source of L-Carnitine

The L-tartaric acid from LCLT is safe to use and within the FAO/WHO acceptable daily intake (ADI). In practice, many IFs already contain L-tartaric acid from the ingredient Choline Bitartrate. The Choline concentration in IFs is more than 10 times higher than the L-Carnitine concentration, whereas for each Choline molecule 2 molecules of L-Tartrate are added and for each molecule of L-Carnitine just one molecule of L-Tartrate is added. This implicates that adding carnitine as LCLT to an IF in which Choline is present as Choline Bitartrate, would increase the tartrate dose by less than 5%.

Choline Bitartrate is currently widely used in IF in the U.S. Choline Bitartrate behaves in a similar manner as LCLT in that, when dissolved in water, it dissociates into Choline and L-tartaric acid. Free choline is immediately available from the commonly supplemented choline salts, such as choline bitartrate or choline chloride (Modinger, 2019). Choline Bitartrate, although without specific FDA approval for use in IF, has a long history of safe use in IF. The example of an IF as taken up in this GRAS Notice results in a total dietary exposure to L-tartaric acid that is in accordance with the FAO/WHO ADI.
Ausnutria accepts responsibility for the GRAS Notice that has been made for LCLT as described herein. The Expert Panel, independently, and collectively, reviewed the information provided, and any other information that they deemed necessary and appropriate, after which the Expert Panel conferred and unanimously agreed to the conclusion described in the Expert Panel report. Ausnutria is also of the opinion that other qualified and competent scientists, reviewing the same publicly available toxicological and safety information, would reach the same conclusion. The Expert Panel's report is attached in Exhibit 1.

Ausnutria hereby certifies, that to the best of its knowledge, this GRAS Notice is a complete, representative, and balanced, submission that includes all favorable and unfavorable information known to Ausnutria that is pertinent to the evaluation of the safety and the GRAS

status of LCLT and its intended use in term IF. Therefore, Ausnutria is of the view that LCLT is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetics Act (FD&C Act) based on the conclusion that LCLT is GRAS under the conditions of its intended use.

This GRAS conclusion for the use of LCLT as a food ingredient in term IF has been reached in accordance with the requirements in 21 CFR 170.220.

1.2. Name and Address of Organization

Ausnutria B.V.
Dokter van Deenweg 150
8025 BM Zwolle
The Netherlands+31 (0) 88 11 63 600

1.3. Common Name of Notified Substance

The common name of the substance of this GRAS assessment is L-Carnitine-L-Tartrate (LCLT). The CAS Registry No. is 36887-82-8.

Other names frequently used for LCLT are L carnitine L tartrate, L-Carnitine tartrate and carnitine tartrate. Less frequently used is the chemical name ß-hydroxy-γ-trimethyl aminobutyrate, L-Tartrate.

1.4. Conditions of Intended Use

Ausnutria intends to use LCLT as a source of L-Carnitine in term IF for infants up to 12 months of age. LCLT will be added at a maximum level of 0.0011% (w/v) of the IF. The resultant IF will provide levels of L-Carnitine required for compliance with Codex Standard 72-1981 (CODEX, Amended 2011) and is typical of the amount of L-Carnitine added to IFs in the U.S.

1.5. Statutory Basis for GRAS Conclusion

This GRAS conclusion is based on scientific procedures in accordance with 21 CFR 170.30(a) and 170.30(b).

1.6. Claim of Exclusion from the Requirement for Premarket Approval

Ausnutria has concluded that LCLT is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that LCLT, meeting the specifications cited herein, and when used as a food ingredient in term IF, is GRAS and is therefore exempt from the premarket approval requirements.

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that LCLT, when used as described in this dossier, is GRAS based on scientific procedures.

1.7. Availability of Data and Information

The data and information that serve as the basis for this GRAS Notice will be maintained at the office of Ausnutria (address below) and will be made available during customary business hours.

Ausnutria B.V.
Dokter van Deenweg 150
8025 BM
The Netherlands
+31 (0) 88 11 63 600

The data and information that are the basis for this GRAS conclusion will be made available to FDA upon request by contacting Leoniek Robroch, Ausnutria B.V. at the address above. The data and information will be made available to FDA in a form in accordance with that requested under 21 CFR 170.225(c)(7)(ii)(A) or 21 CFR 170.225(c)(7)(ii)(B).

1.8. Data Exempt from Disclosure:

Ausnutria certifies that no data or information contained in this document are exempt from disclosure under the Freedom of Information Act (FOIA). There is no privileged or confidential information such as trade secrets and/or commercial or financial information in this document. Therefore, if needed, all of the information contained in this dossier can be made publicly available.

1.9. Certification

Ausnutria certifies that, to the best of its knowledge, this GRAS conclusion is based on a complete, representative, and balanced dossier that includes all relevant information, available and obtainable by Ausnutria, including any favorable or unfavorable information, and pertinent to the evaluation of the safety and GRAS status of the use of LCLT in term IF. Ausnutria accepts responsibility for the GRAS conclusion that has been made for LCLT in term IF as described in this dossier.

1.10. Name and Position/Title of Responsible Person Who Signs Dossier

The name and title of the individual signing off on this GRAS Notice is:

---

ir. Leoniek Robroch
Manager Regulatory Affairs at Ausnutria B.V.
Dokter van Deenweg 150
8025 BM Zwolle
The Netherlands

Signature [redacted]

April 6th 2020

1.11. FSIS/USDA – Use in Meat and/or Poultry

Ausnutria does not intend to add LCLT to any meat and/or poultry products that come under USDA jurisdiction. Therefore, 21 CFR 170.270 does not apply.

Part 2. IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

LCLT is a salt comprised of L-Carnitine (Figure 1) and L-tartaric acid (Figure 2) and is intended to be used as a substitute for L-Carnitine in term IF. It is prepared by reacting L-Carnitine with L-tartaric acid. L-Carnitine is a quaternary ammonium salt (like Choline) that occurs naturally in all animals and bacteria. It is essential in fatty acid metabolism. L-Carnitine occurs naturally in foods, and the richest source is red meats. L-Tartaric acid occurs naturally in fruits and wines. L-Tartaric acid and its salts are also approved for use as food additives. LCLT (Figure 3) does not occur naturally in foods. The LCLT carnitine salt is highly water soluble and dissociates into its components, L-Carnitine and L-tartaric acid in water and in the gastrointestinal tract.

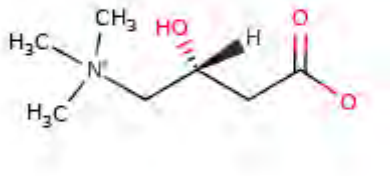


Figure 1. Obtained from (ChemIDplus 2019), chemical structure of L-Carnitine.

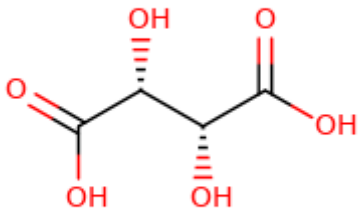


Figure 2. Obtained from (ChemIDplus 2019), chemical structure of L-tartaric acid.

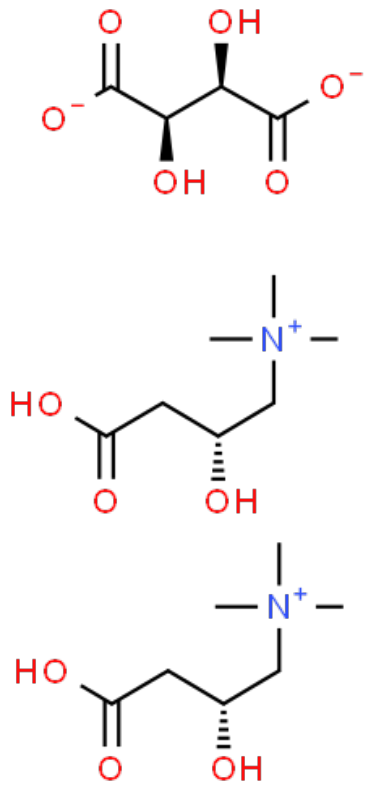


Figure 3. Obtained from (ChemSpider 2015), chemical structure of LCLT.

2.1. Background on the Chemical Properties of L-Carnitine-L-Tartrate

LCLT is a salt of L-Carnitine (68%) and L-tartaric acid (32%) and is intended to be used as a substitute for L-Carnitine in food products and, in this document, as a source of L-Carnitine in term IF. Currently, only L-Carnitine and L-Carnitine hydro chloride are used in IF in the U.S. Practical imitations of the use of L-Carnitine free base and its hydro chloride salt are their fishy, ammoniacal odor and hygroscopicity. The hygroscopicity of L-Carnitine causes a lack of storability of the solid substance and of simple powder mixtures prepared therefrom. The hygroscopicity can cause problems in production of food products such as inadequate flowability and mix-ability during further formulating, processing, and manufacturing of orally administrable dosage forms of powdered mixtures containing L-Carnitine such as IF. Adding L-Carnitine as LCLT salts assures proper mixing. This assures that different fractions of a batch of LCLT containing infant formula contain carnitine at the intended dose level.

In 1991, Lonza developed and patented LCLT, which solved all odor, stability and quality problems. LCLT (U.S. Patent 5073376 and other international patents) is the most commonly used form of L-Carnitine. It is a stable, white crystalline, free-flowing salt of L-Carnitine and natural GRAS L-tartaric acid and contains the highest L-Carnitine concentration of all available salts. LCLT has a pleasant citric taste, it is non-hygroscopic and, therefore, is the optimal form for all powdered and solid products including capsules, tablets, bars, etc. (Schmidbaur, Schier et al. 1998). It perfectly fulfils the needs of contract manufacturers (absolutely free-flowing, non-hygroscopic, no dust) and marketing companies (bright white crystals, long-term stability, pleasant taste, odorless, etc.). Even more so, the physiological properties of the L-Carnitine

component are not altered by the tartrate “complexation” (Schmidbaur, Schier et al. 1998, Walter and Schaffhauser 2000). Aqueous solutions and solid state structure analysis have shown that LCLT completely dissociates into L-Carnitine and L-tartaric acid in aqueous solution (Schmidbaur, Schier et al. 1998). This is important as the safety of L-Carnitine in LCLT is based on the existing safety of the free L-Carnitine where the safety is well established and documented.

Conclusion: LCLT is very soluble in water. In water LCLT dissociates into its individual components, L-Carnitine and L-tartaric acid, and no other byproducts are formed. In its intended use for this notification LCLT will be used in IFs only. As powered IFs are always prepared by adding water this means that LCLT already dissociates into L-Carnitine and L-Tartrate even before it is dosed to infants.

2.2. Chemical Identity of the Ingredient

Ausnutria will obtain its LCLT from Kaiyan Hengtai Chemical Co., Ltd. The LCLT from Hengtai has similar specifications as the LCLT from Lonza (Table 1a and 1b). The production of LCLT takes place in China by Kaiyuan Hengtai Chemical Co., Ltd. at No. 18 Yihe Road, Kaiyuan, Tieling City, Liaoning Province. The facility has several quality certifications, namely ISO 9001, ISO 14001, ISO 2200, Kosher and Halal. The FDA facility number of Hengtai is 1361416074.

LCLT is prepared by Hengtai as follows. The L-Carnitine raw material used is produced in-house. The L-tartaric acid raw material is sourced externally. The raw materials used in the manufacturing process are suitable food-grade materials. The L-Carnitine raw material complies to the corresponding United States Pharmacopeia, European Pharmacopoeia (EP) and Food Chemical Codex (FCC; Table 2) specifications. The CAS number of the L-Carnitine raw material is 541-14-1. The L-tartaric acid raw material complies to both its corresponding FCC specification as well as to the Chinese GB specification. The CAS number of the L-tartaric acid raw material is 87-69-4.

General descriptive properties of LCLT are presented in **Table 1**.

Chemical name:	L(-) Carnitine L(+) Tartrate*
Synonym(s):	ß-hydroxy-γ-trimethyl aminobutyrate, L-Tartrate**
Chemical formula:	$C_{18}H_{36}N_2O_{12}$
Molecular weight:	472.49
CAS Reg. Number:	36687-82-8

**There are other names and synonyms for LCLT. Some of these names can be found elsewhere (US national library of medicine).*

***The systematic approved name is: Butanedioic acid, 2,3-dihydroxy- (R-(R*,R*))-, ion(2-), bis((R)-3-carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium).*

Table 1a. Chemical and physical properties of LCLT (Lonza Specifications)

Property	Substance
Common name	L-carnitine-L-tartrate
Other chemical names	β-hydroxy-γ-trimethyl aminobutyrate, L-tartrate; L-carnitine-L-tartrate (2:1)
IUPAC name	1-propanaminium, 3-carboxy-2-hydroxy-N,N,N-trimethyl-, (R)-, salt with (R-(R*,R*)-2,3-dihydroxybutanedioic acid (2:1)
CAS number	36687-82-8
Chemical formula	$2(C_7H_{16}NO_3)\cdot C_4H_4O_6$ $C_{18}H_{36}N_2O_{12}$
Molecular weight g/mol	472.49
Appearance	White crystals or white crystalline powder
Water solubility (g/L at 20°C)	Highly soluble, >1,000
Melting point (°C)	171.1-173.7 (approx. 170 with decomposition)

.

Table 1b. Chemical and physical properties of LCLT (Hengtai Specifications)

Parameter	**Hengtai's specifications**	**Methods**
Appearance	Crystalline powder	USP
Color	White	USP
Melting point	169-175 °C	USP
Assay L-Carnitine	67.2-69.2%	Internal titration method
Assay L-tartaric acid	30.8-32.8%	Internal titration method
D-carnitine	≤ 0.5%	USP
Specific rotation	-11.0 to -9.5°	USP
pH	3.0-4.5	USP
Loss on drying	≤ 0.5%	USP
Residue on ignition	≤ 0.2%	USP
Heavy metals (as Pb)	≤ 10 ppm	USP
Arsenic	≤ 1 ppm	USP
Chloride	≤ 0.4%	USP
Lead	≤ 3 ppm (typical ≤ 0.2 ppm)	USP
Cadmium	≤ 1 ppm	USP
Mercury	≤ 0.1 ppm	USP
Microbiology	**Typical values**	**Methods**

Total plate count	< 1000 cfu/g	USP
Yeast & molds	< 100 cfu/g	USP
E.Coli	Absent	USP
Salmonella	Absent	USP

In addition, Hengtai' LCLT meets the specification of LCLT as listed in the FCC (Table 2). Hengtai states that their LCLT has a self-affirmed GRAS status (Appendix 1). Furthermore, it meets the FCC specifications (Appendix 2). The Safety Data Sheet (SDS) for Hengtai's LCLT is shown in Appendix 3.

Results of analyses performed by Hengtai demonstrate that five batches of LCLT meet the designated specifications, as shown in Table 3. Please note that, even though Hengtai has set the specifications for lead at ≤3 ppm, which is consistent with the Chinese and EFSA specs for heavy metals, Hengtai's analyses show compliance with the FCC specifications for lead.

2.2.1 Chemical Structure of L-Carnitine-L-Tartrate

LCLT is produced as a combination salt of crystalline free base L-Carnitine with L-tartaric acid, and exists as a 2:1 ratio, being two molecules of L-Carnitine to one molecule of L-tartaric acid (Walter and Schaffhauser 2000). See the chemical reaction formula in Figure 4.

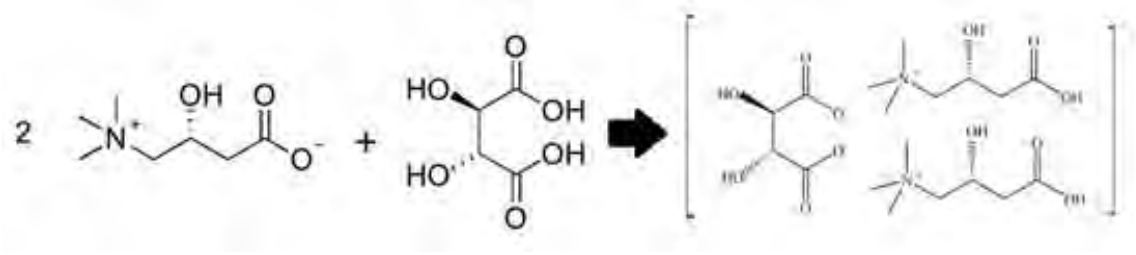


Figure 4. Chemical reaction formula for LCLT.

2.3. Manufacturing Processes

LCLT is produced by combining food grade L-carnitine and L-tartaric acid which are dissolved in deionized water. After this it is concentrated by vacuum drying. Food grade ethanol is added after which the crystallization step takes place and the product is cooled and centrifuged to obtain wet crystals. These wet crystals are then vacuum dried at 58-62 degrees Celsius to obtain the dry crystals. These dry crystals undergo sieving, metal detection, and are finally packaged. The reaction that take place to form LCLT is a neutralization reaction, which is triggered by mixing an acid with a base. The typical particle size of the LCLT is 20-80 mesh. No byproducts are formed.

The production process includes three Critical Control Points (CCPs) as shown in Figure 5. Based on monitoring data, the ethanol residual in the LCLT product complies with the "CMP/ICH/283/95 Impurities: Guideline for residual solvents" for pharmaceutical substances. For ethanol, a limit of 5000 ppm is taken up. A flow chart of the production process can be found in Figure 6.

CCP	Ascertain potential Hazard	CL *
CCP1-Loss on Drying	Ethanol residual	Control temperature, vaccum, time.
CCP2-Sieving	Foreign material	Check the filter integrity before and after filtration.
CCP3-Metal Detectiion	Metal foreign material	Fe2.5mm, Cu5.0mm, Sus4.5mm.

* CL = Critical Limits

Figure 5. The three Critical Control Points (CCPs) during the manufacturing process of L-Carnitine-L-Tartrate at Hengtai

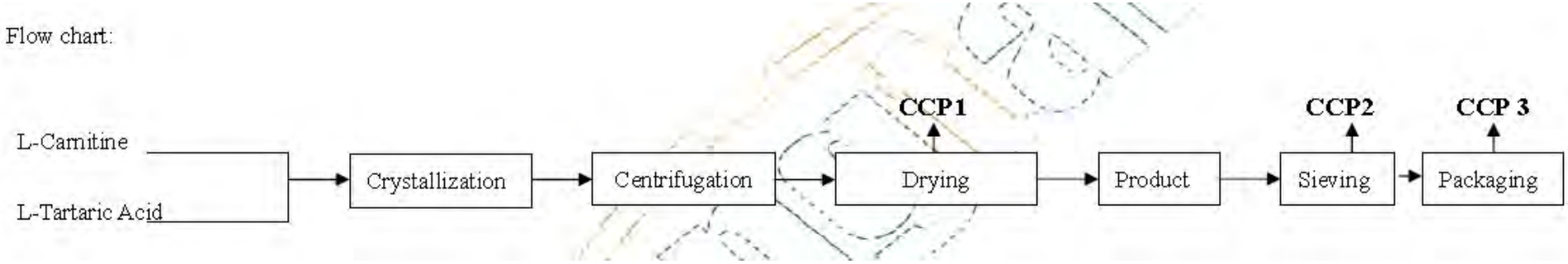


Figure 6. Flowchart of the Manufacturing Process of L-Carnitine-L-Tartrate

2.4. Product Specifications

LCLT is characterized by a L-Carnitine content of 67.2-69.2%, a L-tartaric acid content of 30.8-32.8%, and a specific rotation of -11.0° to -9.5°. The FCC specifications for LCLT are provided in Table 2 below.

Table 2. FCC Specifications for LCLT.

Parameter	**FCC specifications**
Melting point	169-175 °C
Identification	Spectrophotometric identification test
Specific rotation	-11.0 to -9.5°
pH	3.0-4.5
Loss on drying	≤ 0.5%
Residue on ignition	≤ 0.5%
Assay L-Carnitine	67.2-69.2%
Assay L-tartaric acid	30.8-32.8%
Arsenic	≤ 1 mg/kg
Lead	≤ 2 mg/kg

Table 3. Analytical Results for 5 Nonconsecutive Lots of LCLT.

Parameter	**Hengtai's specifications**	**Results of Batch Numbers**					**Average**
		10100220180527	**10100220180630**	**101002201080820**	**10100220190231**	**10100220190414**	
Appearance	Crystalline powder	Pass	Pass	Pass	Pass	Pass	
Color	White	Pass	Pass	Pass	Pass	Pass	
Melting point	169-175 °C	170-171.5	170-171.5	169-170.5	169.5-171	170-171.5	
Assay L-Carnitine	67.2-69.2%	68.1	67.96	68.14	67.74	68.16	68.02
Assay L-tartaric acid	30.8-32.8%	31.74	31.68	31.76	31.79	31.84	31.76
Specific rotation	-11.0 to -9.5°	-10.2	-10.08	-10.05	-10.30	-10.04	
pH	3.0-4.5	3.64	3.66	3.63	3.60	3.64	
Loss on drying	≤ 0.5%	0.3	0.24	0.28	0.16	0.32	
Residue on ignition	≤ 0.5%	0.04	0.04	0.04	0.07	0.05	
Heavy metals (as Pb)	≤ 10 ppm	< 10	< 10	< 10	<10	<10	
Arsenic	≤ 1 ppm	< 1	< 1	< 1	<1	<1	
Chloride	≤ 0.4%	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	
Lead	≤ 3 ppm (typical ≤ 0.2 ppm)	< 3	< 3	< 3	< 3	< 3	
Cadmium	≤ 1 ppm	< 1	< 1	< 1	< 1	< 1	
Mercury	≤ 0.1 ppm	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	
Microbiology	**Typical values**						
Total plate count	< 1000 cfu/g	30	30	30	30	20	
Yeast & molds	< 100 cfu/g	10	10	10	10	10	
Salmonella	Absent	Negative	Negative	Negative	Negative	Negative	

2.5. Physical or Technical Effect

Within this GRAS notice LCLT is intended to be added only to term IF as a dietary source of L-Carnitine. In aqueous solution, LCLT dissociates into L-Carnitine and L-tartaric acid (Schmidbaur, Schier et al. 1998). Therefore, it has been presumed that when LCLT is added to infant formulas and water is added before dosing it to infants, it enters the gastrointestinal tract as dissolved L-Carnitine and L-tartaric acid.

2.6. Regulatory Status of L-Carnitine-L-Tartrate, L-Carnitine, and L-Tartaric Acid

2.6.1. Regulatory Status of L-Carnitine-L-Tartrate

2.6.1.1. U.S. Regulatory History

In the U.S., LCLT has not been approved for use as a food ingredient in IF. L-Carnitine has been voluntarily added to soy-based IF products since 1986 as approved by the FDA and to cow's milk-based products since the mid-1990's (International Formula Council 2011). L-Tartaric acid has been included on the National List of Allowed and Prohibited Substances (United States Department of Agriculture 2019). The use of L-Carnitine and L-tartaric acid in IF supports the fact that these ingredients are safe for use in IF providing the ingredients meets the accepted specifications, i.e., those listed in the FCC, etc.

In 2002, Lonza announced that its LCLT (Carnipure™ tartrate) product is GRAS when used as a functional food based on an independent GRAS determination (Eschenmoser 2002). Based on this determination, LCLT is now available for use in many food products in the U.S. LCLT is listed in the National Foods Association (NNFA) and the Council for Responsible Nutrition (CRN) lists of ingredients that were used in dietary supplements prior to 1994 (pre-DSHEA) and “grandfathered” for use in dietary supplements.

2.6.1.2. European Regulatory History

On the European Union level, the EFSA Scientific Committee evaluated the use of LCLT as a source of L-Carnitine in foods for particular nutritional uses (PARNUTS), including IF. The EFSA concluded that: “L-Carnitine-L-Tartrate is not of concern from the safety
point of view as a source of L-Carnitine for use in foods for particular nutritional uses, provided the Acceptable Daily Intake for tartaric acid from all sources in the diet is not regularly exceeded”. EFSA approved LCLT as source of L-Carnitine for use in IF (EFSA 2003) (Regulation (EU) No. 609/2013), furthermore, L-Carnitine is considered to be an essential component of IF (Regulation (EU) 2016/127).

On a local level, the report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) of 2012 for example proposes a maximum daily amount of L-Carnitine of 2000 mg for adults when using LCLT hydro chloride as sources, and an amount of 3000 mg when using LCLT as a source in food supplements. The Royal Decree 867/2008 (BOE, 2008) regulates the inclusion of certain substances in the basic composition of IFs in Spain and includes the allowance of LCLT.

2.6.1.3. Other Regulatory History

The Codex Alimentarius Commission (CAC) lists LCLT as an allowed source of L-Carnitine in its advisory list of nutrient compounds for use in foods for special dietary uses intended for infants and young children (CAC/GL 10-1979). L-Carnitine is considered an essential component of IF (CODEX STAN 72-1981).

In Canada, L-Carnitine and acetyl-L-Carnitine are permitted novel food ingredients that can be used in a specific class of supplemented foods after obtainment of a Temporary Marketing Authorization Letter from Health Canada on a case-by-case basis (FSANZ 2018). The only types of IFs currently containing LCLT on the Canadian market are soy-based formulas. Health Canada, in a monograph dated December 18, 2018, lists additional uses of L-Carnitine. In this monograph, LCLT and L-Carnitine fumarate are listed as source materials for L-Carnitine (Health Canada 2018).

In China, LCLT is an approved source of L-Carnitine for use in special dietary foods, including IF (GB 14880-2012). L-Carnitine is considered an optional component of IF (GB 10765).

In Japan, LCLT is also approved for use in food by the Japanese Ministry of Health, Labor and Welfare (MHLW). Both L-Carnitine and LCLT can be used in foods and dietary supplements with a maximum daily intake up to 1 g per day or 20 mg per kg body weight per day.

In Australia, L-Carnitine is permitted to be added to IF. However, according to Standard 2.9.1 for Infant Formula Products – Table S29-5 – LCLT is not an approved source to deliver L-Carnitine.

2.6.2. Regulatory Status of L-Carnitine

There is no specific regulation permitting the use of L-Carnitine in IF in the USA. However, L-Carnitine has been added to soy-based IF products since 1986 and to cow's milk-based products since the mid-1990's. The basis for this is presumably the review and recommendations made by the Life Sciences Research Organization (LSRO) where they noted the need for L-Carnitine in infant nutrition and recommended that L-Carnitine be added to term IF at a level of 1.2-2.0 mg/100 kcal (Klein and Heird 2005). The intended amount of L-Carnitine in LCLT containing infant formulas as subject to this GRAS notice falls within this range.

L-Carnitine (synthetic or non-synthetic) is not currently included on the National List of Allowed and Prohibited Substances (hereafter referred to as the National List) of nonagricultural (nonorganic) substances allowed as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))" (7 CFR 205.605). FDA regulations on the nutrient requirements of IF (21 CFR 107.100(a)) do not require the addition of L-Carnitine. The specific function of L-Carnitine is as a "nutrient supplement" according to FDA 21 CFR 170.3(o)(20). L-Carnitine has not been affirmed as GRAS by the FDA as a nutrient and/or dietary supplement (21 CFR 582). However, L-Carnitine

has been determined to be GRAS based on an independent GRAS determination (United states department of agriculture 2019).

2.6.3. Regulatory Status of L-Tartaric Acid

Since 2003, L-tartaric acid has been included on the National List of Allowed and Prohibited Substances as a nonagricultural (nonorganic) substance allowed as an ingredient in or on processed products labeled as “organic” or “made with organic (specified ingredients or food group(s)).” This material is listed both as a non-synthetic allowed substance if made from grape wine (i.e., L-(+) tartaric acid) [7 CFR § 205.605 (a)] and a synthetic allowed (7 CFR § 205.605(b)) substance if made from malic acid (i.e., a synthetic form of L-(+) tartaric acid). Following review of data detailing the manufacture of synthetic L-(+) tartaric acid, it has been determined that the regulatory language (7 CFR 102 § 205.605 (a); 7 CFR § 205.605 (b)) referring to synthetic L(+) tartaric acid should be corrected to say ‘made from maleic acid’ rather than ‘made from malic acid.’ Data included in the FDA GRAS notice for synthetic L-(+) tartaric acid supports this conclusion (United states department of agriculture 2019).

L-Tartaric acid is also affirmed as GRAS under 21 CFR 184.1099 for use in food generally in accordance with 21 CFR 184.1(b)(1). This regulation does not explicitly permit the use of L-tartaric acid in IF. However, L-tartaric acid is present in IF as a result of the use of Choline Bitartrate (Figure 7). Choline Bitartrate is similar to LCLT regarding water solubility and dissociates in aqueous solution into its individual components, Choline and L-tartaric acid.

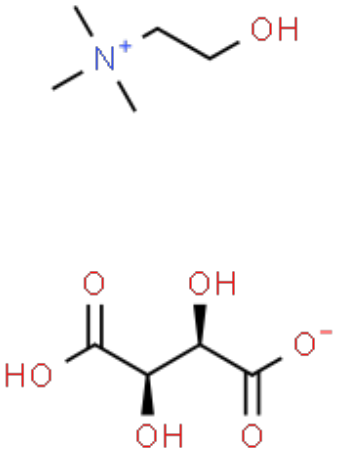


Figure 7. Obtained from (ChemSpider 2015), chemical structure of Choline Bitartrate.

LCLT is similar to the aspartame-acesulfame salt that contains ionically bound aspartame and acesulfame, as they both are organic salts. Aspartame-acesulfame salt has been approved by FDA based on the existing regulations for aspartame (21 CFR 172.804) and acesulfame (21 CFR 172.829). This aspartame-acesulfame salt product is marketed as Twinsweet in the U.S. When dissolved in water, the product dissociates into its individual components, aspartame and acesulfame, similarly as LCLT dissociate into carnitine and tartaric acid. The structure of aspartame-acesulfame salt is shown below in Figure 8.

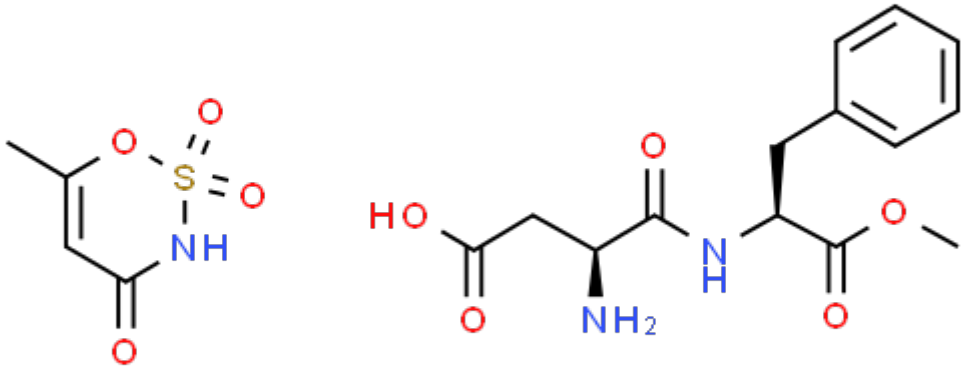


Figure 8. Structure of Aspartame-acesulfame salt

Aspartame-acesulfame salt is also approved in the EU.

2.7. Stability

2.7.1. Stability Data for Hengtai's L-Carnitine-L-Tartrate

Kaiyan Hengtai Chemical Co., Ltd. has conducted both a long-term (36-months) and an accelerated (6-months) stability study on its LCLT. For the long-term (36-months) stability study samples were stored at a temperature of 25 ± 2 °C and a relative humidity of 60 ± 5% during the test period. Over the course of the study, three batches of LCLT were tested for assay (%), specific rotation (°), and water (%) at 0, 3, 6, 9, 12, 18, 24, and 36 months. The data of this study show that LCLT was stable over the entire duration of the study. A summary of the results of this stability study is presented in Table 5.

For the accelerated (6-months) stability study, samples were stored at a temperature of 40 ± 2 °C and a relative humidity of 75 ± 5%. Over the course of this study, three batches of LCLT were tested for assay (%), specific rotation (°), and water (%) at 0, 1, 2, 3, 4, 5, and 6 months. The data of this study show that LCLT was stable over the entire duration of the study. A summary of the results of this accelerated stability study is presented in Table 6.

Table 4. Hengtai's LCLT Long-Term Stability Data.

1.Long - term Stability Test
1.1 Condition T: 25±2° C RH: 60±5%
1.2 Test result

Batch No. \ Item		Specification	Test Date							
			0 months	3 months	6 months	9 months	12 months	18 months	24 months	36 months
20050504	Assay,% *	98.0~102.0	99.68	99.71	99.67	99.77	99.62	99.70	99.64	99.63
	Specific Rotation°	-9.5~-11.0	-10.61	-10.73	-10.62	-10.58	-10.67	-10.72	-10.66	-10.65
	Water,%	≤0.5	0.14	0.11	0.13	0.15	0.12	0.16	0.17	0.14
20050507	Assay,% *	98.0~102.0	99.39	99.34	99.35	99.32	99.42	99.46	99.26	99.29
	Specific Rotation°	-9.5~-11.0	-9.78	-9.75	-9.52	-9.68	-9.84	-9.62	-9.76	-9.65
	Water,%	≤0.5	0.21	0.25	0.19	0.24	0.23	0.22	0.20	0.21
20050509	Assay,% *	98.0~102.0	99.72	99.70	99.78	99.74	99.69	99.87	99.75	99.69
	Specific Rotation°	-9.5~-11.0	-10.11	-10.25	-10.14	-10.24	-10.17	-10.20	-10.23	-10.19
	Water,%	≤0.5	0.26	0.24	0.28	0.27	0.25	0.23	0.26	0.25

* Assay of L-carnitine L-tartrate

Table 5. Hengtai's LCLT Accelerated Stability Data.

2.Accelerate Test
2.1 Condition T: 40±2° C RH: 75±5%
2.2 Test result * Assay of L-carnitine L-tartrate

Item / Batch No.		Specification	Test Date						
			0 months	1 months	2 months	3 months	4 months	5 months	6 months
20050504	Assay,% *	98.0 ~ 102.0	99.68	99.80	99.62	99.75	99.58	99.66	99.72
	Specific Rotation°	-9.5 ~ -11.0	-10.61	-10.63	-10.56	-10.68	-10.49	-10.63	-10.68
	Water,%	≤ 0.5	0.14	0.20	0.18	0.15	0.19	0.18	0.16
20050507	Assay,% *	98.0 ~102.0	99.39	99.47	99.31	99.45	99.40	99.44	99.46
	Specific Rotation°	-9.5 ~ -11.0	-9.78	-9.83	-9.76	-9.81	-9.70	-9.73	-9.83
	Water,%	≤ 0.5	0.21	0.24	0.21	0.22	0.23	0.20	0.19
20050509	Assay,% *	98.0 ~ 102.0	99.52	99.53	99.55	99.50	99.64	99.46	99.48
	Specific Rotation°	-9.5 ~ -11.0	-10.11	-10.17	-10.26	-10.19	-10.21	-10.01	-10.18
	Water,%	≤ 0.5	0.26	0.25	0.28	0.25	0.27	0.24	0.23

Part 3. DIETARY EXPOSURE

3.1. Estimate of Dietary Exposure to the Substance

3.1.1. Intended Use

Ausnutria intends to use Hengtai's LCLT as a source of L-Carnitine in IF formula for full term infants to provide a final level of minimally 1.2 mg L-Carnitine per 100 kcal (= 0.8 mg carnitine/100 ml,) comparable to the L-Carnitine level found in human milk (EFSA 2014), the reference standard for IF. Not all L-Carnitine present in IF necessarily originates from added LCLT, as some LCLT is naturally occurring in the milk source used. Ausnutria intends to supplement its IF based on animal milk protein with a maximum of 1.60 mg LCLT per 100 kcal (1.09 mg per 100 ml IF), resulting in a total L-Carnitine level in IF of 2.10 mg per 100 kcal (1.43 mg per 100 ml IF).

3.1.2. Estimated Daily Intake from Infant Formula

LCLT does not occur naturally in foods, but only in supplemented form. During the first few months of life (up to 4-6 months) when exclusive feeding of human milk and/or IF (American Academy of Pediatrics 2019), the only source of LCLT is IF. During the weaning period, other sources of LCLT may be introduced to the infant's diet. However, the addition of LCLT to "Processed cereal based foods for infants and young children" and "Canned baby foods" is not allowed according to the Codex Alimentarius Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Infants and Young Children (FAO/WHO 2008). Since additional daily exposure to LCLT is unlikely, it is not included in the estimation here.

As many infant formulas contain both L-Carnitine and L-Tartrate from more than one source, the estimated daily intake of infants of both L-Carnitine and L-Tartrate need to be addressed separately.

3.1.2.1. Exposure to L-Carnitine via infant formulas

Ausnutria intends to add 1.09 mg LCLT per 100 ml IF. This equals to an amount of 742 ug of L-Carnitine per 100 ml formula. Ausnutria's formula also contains 690 ug/100 ml L-Carnitine from a natural source.

This results in a total concentration of L-Carnitine in Ausnutria's infant formula of 1.43 mg/100 ml. This is about 1.8 times the minimally regulatory required amount of L-Carnitine of 1.2 mg/100 ml, supporting the choice of this amount of L-Carnitine in the formulation.

As infants are assumed to eat maximally 900 ml (gram) of IF a day (FDA guidance document) their total L-Carnitine intake is 9 x 1.43 mg = 12.9 mg carnitine per day. Assuming 6.3 kg as a representative weight for an infant of the intended age-range, this results in a total daily carnitine exposure of 2.0 mg/ kg body weight (BW).

3.1.2.2. Exposure to L-Tartrate

Tartaric acid is widely distributed in nature, and is classified as a fruit acid. It occurs in many fruits, free and combined with potassium, calcium or magnesium (FDA 1974). Ausnutria intends to add 1.09 mg LCLT per 100 ml IF. This equals to an amount of 346 ug of L-Tartrate per 100 ml formula.

Formulas often also contain L-Tartrate added as counterion for Choline in Choline Bitartrate. Breast milk contains about 6 mg free Choline / 100 ml (Zeisel, Char et al. 1986). If a similar amount of Choline is added to IFs in the form of Choline Bitartrate, then 15 mg of Choline Bitartrate needs to be added to 100 ml of formula. As 15 mg of Choline Bitartrate yields 6 mg of Choline and 9 mg of L-Tartrate, IF may contain up to 9 mg of L-Tartrate per 100 ml of formula when Choline is added as Choline Bitartrate.

When the amount of L-Tartrate coming from LCLT is added to the amount of L-Tartrate possibly already present due to the use of Choline Bitartrate as Choline source, then the total L-Tartrate concentration is 9 mg + 346 ug = 9.35 mg L-Tartrate per 100 ml formula. This value can be considered to be a maximum exposure value as Choline can also partially be added as Choline Chloride, thereby reducing total L-Tartrate exposure.

As infants are assumed to eat maximally 900 gram of IF a day (FDA guidance document), their maximal total L-Tartrate intake is 9 x 9.35 mg = 84 mg L-Tartrate per day. If 6,3 kg is taken as a representative weight for an infant of the intended age-range, this results in a total daily exposure of 13.3 mg of L-Tartrate/ kg BW.

Therefore, if all Choline of an IF would be added as Choline Bitartrate, less than 5% of this Bitartrate exposure results from exposure to LCLT, the rest results from exposure to Choline Bitartrate, which has a long history of safe use in Infant formulas in the USA.

The total exposure to L-Tartrate in IF containing both Choline and L-Carnitine as L-Tartrate salts of 13.3 mg L-Tartrate/ kg BW falls within the ADI range of 0 - 30 mg L-Tartrate / kg BW as defined by the FAO/WHO.

3.1.2.3. Dietary recommendations

Carnitine deficiency is assessed by measuring free and total L-Carnitine concentrations in serum. As reviewed by Crill and Helms (2007), infants fed un-supplemented soy-based formula (which contains little or no L-Carnitine) had lower serum L-Carnitine concentration compared to infants fed carnitine-supplemented soy-based formula suggesting infants lack capacity to synthesize sufficient L-Carnitine. This is possibly related to the fact that neonates and infants lack sufficient activity of gamma-butyrobetaine hydroxylase. This enzyme is important for carnitine biosynthesis but the activity of this enzyme in infants is approximately just 12% of that seen in adults (Rebouche 1986). In addition, higher serum fatty acid concentrations (indicating less utilization of dietary fats for energy) were reported in some studies for infants on un-supplemented formula, although consequences for growth or development is unclear.

Because of the critical role of L-Carnitine in lipid metabolism and the decreased rate of L-Carnitine biosynthesis in infants, L-Carnitine has now been considered to be a necessary addition to infant formula with a minimum amount corresponding to breast milk (Crill and Helms 2007; EFSA 2014).

The U.S. Food and Drug Administration's Center for Food Safety and Applied Nutrition commissioned an Expert Panel of the Life Sciences Research Office (LSRO) for recommendations on IF. This was published in the comprehensive review "Assessment of Nutrient Requirements for Infant Formulas" in 1998. The Expert Panel recommended a minimum L-Carnitine content of IFs of 1.2 mg/100 kcal, a level like that found in human milk. Although the evidence that dietary L-Carnitine is essential for the term infant is not convincing, biochemical changes are noted when infants are fed a L-Carnitine-free diet and there are several anecdotal reports of abnormal clinical manifestations associated with diets low in L-Carnitine. Infants nourished with soy protein-based formula with low L-Carnitine content had lower plasma and urine carnitine levels and evidence of altered lipid metabolism, but no significant differences in rates of growth compared with supplemented infants. The functional significance of these metabolic differences in normal term infants is not known (Raiten, Talbot et al. 1998). The rationale for supplementation is twofold: infants utilize lipids as a primary source for energy and growth after birth, requiring a high rate of mitochondrial oxidation, and the concentration of carnitine in infant circulation and tissues is typically lower without supplementation than in infants fed human milk or IF containing L-Carnitine (Rebouche 2012). The Expert Panel recommended a maximum L-Carnitine content of IFs of 2.0 mg/100 kcal, a value like the upper limit reported for human milk. The Expert Panel was unaware of any studies in which a NOAEL or Lowest Observed Adverse Effect Level had been identified for L-Carnitine exposure in infants. Consequently, in the absence of data the Expert Panel concluded that the maximum should be set at a level comparable to the upper ranges of L-Carnitine concentrations reported for human milk (Raiten, Talbot et al. 1998). In 2002, LSRO (Klein 2002), recommended the addition of L-Carnitine to preterm IF: The Expert Panel recommended that the minimum concentration of L-Carnitine in preterm IF shall be 2.0 mg/100 kcal. This is higher than the average amount present in breast milk but seems to be necessary to support oxidation adequately. The Expert Panel recommended that the maximum concentration of L-Carnitine in preterm IF shall be 5.9 mg/100 kcal (= 4 mg carnitine/100 ml IF).

The L-Carnitine content of IF as proposed by Ausnutria after having supplemented natural L-Carnitine levels from milk with LCLT is 2.1 mg L-Carnitine/100 ml of IF. This value roughly holds the middle between the concentration which is needed for optimal metabolism and which is maximally recommended.

3.1.3. Estimated Dietary Exposure to L-Carnitine via other food

L-Carnitine is supplemented in many IFs worldwide based on recommendations from international health councils and is also allowed in IFs for the U.S. market based on history of safe use. L-Carnitine is also naturally occurring in many food products that can be consumed by infants after weaning. A dietary assessment for infants aged 0-12 months is difficult, partly

due to the unestablished dietary habits for solid foods and deviating portion sizes. For this reason, published data on dietary intake is limited for this age category.

Dietary sources rich in L-Carnitine include meat, poultry, fish, and milk. At the age of 7-8 months; meat, poultry, and fish may be introduced to the infant's diet, whereas regular cow's milk is advised from 12 months onwards (Centers for Disease Control and Prevention (CDC) 2018). An average portion size of meat during infancy was estimated to be 0.08 oz (~2.3 g) (Fox, Reidy et al. 2006). Assuming an average L-Carnitine content of 109 mg per 100 g meat (National Institute of Health (NIH) 2017), this results in a maximum daily intake of 2.5 mg L-Carnitine per day. For an infant weighing 6 kg, this leads to an exposure of 0.4 mg L-Carnitine/kg BW. It is doubtful however, that offering these types of alternative foods to the infants this will lead to an additional exposure to L-Carnitine as the total intake of IF will surely be less if these other foods are eaten by the infants. Estimated natural exposures to other foods during infancy will be even lower and therefore negligible as compared to supplemented sources of L-Carnitine.

3.2. Dietary Exposure to Contaminants or Byproducts

There are no known concerns regarding dietary exposure to LCLT or its products L-Carnitine and L-tartaric acid.

Part 4. SELF-LIMITING LEVELS OF USE

LCLT is intended to be used in IFs only, and LCLT will be present at low and well-defined levels in IFs. As infants maximally can eat about 1200 ml of IF a day (EFSA Scientific Committee 2017), whereas other infants foods like meat and vegetables are less rich in carnitine than IFs, the maximal exposure to LCLT is limited by this amount.

Part 5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

The statutory basis for the conclusion of GRAS status for LCLT in this document is not based on common use in food before 1958. The GRAS conclusion is based on scientific procedures. However, as discussed below, L-Carnitine and L-tartaric acid have been present in the food supply prior to 1958, providing support that the source materials in LCLT has been safely used in food products.

5.1. Other Information on Dietary Exposure

5.1.1. History of Human Food Use

The history of research into carnitine falls into 4 periods: firstly, the period of its simultaneous discovery as a constituent of vertebrate muscle, by Gulewitsch and Krimberg (Figure 8) and by Kutscher in 1905.

Zur Kenntnis der Extraktivstoffe der Muskeln.

II. Mitteilung.

Über das Carnitin.

Von

Wl. Gulewitsch und R. Krimberg.

(Aus dem medizinisch-chemischen Laboratorium der Universität Moskau)

(Der Redaktion zugegangen am 3. Juni 1905.)

Bei der Fortsetzung der Untersuchung des Fleischextrakte-, welche der eine von uns gemeinschaftlich mit Amiradžibi

Figure 9. Manuscript of Gulewitsch and Krimberg from 1905 on the Discovery of Carnitine

Secondly, the period in which its chemical structure was established (1927); and then, the delineation of its major physiological function (1935–1965). Finally, the discoveries of its biosynthetic pathway, transport mechanisms, and primary and secondary carnitine deficiency and syndromes, occurred from 1961 to the present. Investigations of its metabolic role began in the 1940s, as a result of studies by Fraenkel of the nutritional requirements of insects (Wolf 2006).

A literature search, November 2018, in PubMed revealed 45 publications before 1958 describing carnitine. The oldest papers date from 1951 by Fraenkel describing the identification and isolation of vitamin BT now known as L-Carnitine (Fraenkel 1951, Fraenkel and Friedman 1957, Wolf 2006). Between 1955 and 1958 eight articles, all written in French, describe the use of a synthetic complex of carnitine or stable carnitine derivative or bicarnesine or synthetic dicarnitine and carnitine. These synthetic forms of L-Carnitine were used in in vitro and animal

studies, but also in infants and young children to improve weight and growth (Alexander 1956, Chassagne and Jerome 1958).

Using Google Scholar, November 2018, 274 manuscripts were obtained about L-Carnitine before 1958. The oldest papers published about L-Carnitine were from 1928 and 1936, and mainly from Germany and in the German language (Linneweh 1929, Kutscher and Ackermann 1936, Strack, Wördehoff et al. 1936). A French paper from 1957 describes the use of carnitine carnitinate to improve growth failure in infants and preterms (Rovinski and Camous 1957). The oldest patent found is a German patent dated 8 December 1938 (Appendix 4). This describes the process for the preparation of the methyl or ethyl ester of acetylated carnitine.

Currently LCLT is commonly used in sports and energy drinks at approximately 750 mg per serving (FSANZ 2018). A Fact Sheet, published by the National Institutes of Health, Office of Dietary Supplements, discussing the uses and benefits of carnitine in adults can be found elsewhere (National Institute of Health (NIH) 2017).

Part 6 not appropriately attributed. Nineteen pages removed.

Part 7. LIST OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE

7.1. List of Abbreviations

Acceptable Daily Intake	ADI
Spanish Agency for Food Safety and Nutrition	AESAN
Codex Alimentarius Commission	CAC
Critical Control Points	CCPs
Critical Limits	CL
Council of Responsible Nutrition	CRN
European Food Safety Authority	EFSA
European Pharmacopoeia	EP
Food Agricultural Organization of the United Nations	FAO
Food Chemical Codex	FCC
US Food & Drug Administration	FDA
Feeding Infants and Toddlers Study	FITS
Freedom of Information Act	FOIA
Food Standards Australia New Zealand	FSANZ
Generally Recognized As Safe	GRAS
Infant Formula	IF
L-Carnitine-L-Tartrate	LCLT
Life Sciences Research Office	LSRO
National Health and Nutrition Examination Survey	NHANES
National Foods Association	NNFA
No-Observed-Adverse-Effect Level	NOAEL
Organization for Economic Co-operation and Development	OECD
Foods for Particular Nutritional Uses	PARNUTS
Reference Daily Intake	RDI
Selected Committee on GRAS Substances	SCOGS
Safety Data Sheet	SDS
United States	U.S.
World Health Organization	WHO

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Appendix 1. Signed Statement By Kaiyuan Hengtai

开原亨泰化工有限公司
KAIYUAN HENGTAI CHEMICAL CO., LTD.

GRAS declaration

Product: L-carnitine L-tartrate
Vaneeghen article number: 31212024

TO WHOM IT MAY CONCERN

The FDA GRAS database does not cover all ingredients already in use as of October 15, 1994. Amongst others, L-carnitine L-tartrate is not listed here.

For the GRAS status identification, FDA says it is company's responsibility.
Since above-mentioned database is not complete, the National Foods Association (NNFA) produced a list (NNFA list) in 1995 to summarize those already marketed product before 1994 and was consequently transferred to the Council of Responsible Nutrition for amendments and the so-called CRN list was brought up.
Only for those ingredients not listed on CRN list, the producer of final product form needs to notify FDA through NDI petition and/or GRAS status submission.

Fortunately, L-carnitine L-tartrate is mentioned both on the NNFA and CRN list.
The ingredients listed on the CRN list would be regarded as grandfathered ingredient and GRAS.
After verification of the GRAS status of this product, we the manufacturer Kaiyuan Hengtai Chemical, confirm it is GRAS (self-affirmed) as well.
Thus to the best of our knowledge, we confirm L-carnitine L-tartrate is GRAS.

Date: 17th of September 2018

(Signature and stamp)

Company: Kaiyuan Hengtai Chemical
Name : Wenju Tang
Function: Vice QU General Manager

Company add.: No.18, Yihe road, Kaiyuan city, Liaoning province, China 112300
Tel: 86-24-73710986 Fax: 86-24-74330516
Office add.: Room 413, No.72 Jianshe East road, Tiexi district, Shenyang city, Liaoning province, China 110021
Sales Tel:13609818883 Service Tel:86-24-25520838 Techsupport Tel:86-24-25510805 Fax:86-24-25524770
Http://www.hengtaichem.com E-mail: sales@hengtaichem.com

Appendix 2. FCC Statement for L-Carnitine-L-Tartrate From the Distributor of L-Carnitine-L-Tartrate

vaneeghen

FCC statement

Product: L-carnitine-L-tartrate
Article number: 31212024

TO WHOM IT MAY CONCERN

We hereby declare that the above-mentioned product, supplied by vaneeghen, has the quality of FCC standard L-carnitine-L-tartrate. Our product is tested by USP methods, but will comply to all FCC parameters when tested for it.

Amsterdam, 21st of August 2018

Van Eeghen
M. Jonker
Quality Assurance Specialist

Appendix 3. Safety Data Sheet for L-Carnitine-L-Tartrate From Hengtai

开原亨泰化工有限公司
KAIYUAN HENGTAI CHEMICAL CO., LTD.

Safety Data Sheet

Section1. Identification of the substance/preparation and of the company/undertaking

1.1. Product identifier

Product name:	L-Carnitine L-Tartrate
CAS	36687-82-8
EINECS number	——
Product code:	101002
Synonyms:	(R)-Bis [(3-carboxy-2-hydroxypropyl) trimethyl Ammonium] L-tartrate

1.2.Relevant identified uses of the substance or mixture and uses advised against.

As supplement for application in food, feed and phamaceuticals

1.3. Details of the supplier of the safety data sheet

Manufacturer
KAIYUAN HENGTAI CHEMICAL CO., LTD.
No.18, Yihe Road, Kaiyuan City, Liaoning Province, China 112300
Tel: +86-24-73710986
Fax: +86-24-73722309

1.4.Emergency telephone number

Emergency tel: +86-24-25520838

Section 2. Hazards identification

2.1.Classification of the substance or mixture

No particular hazards known.

2.2 Label elements

Not available.

2.3 Other hazards

PBT: This product is not identified as a PBT/vPvB substance.

Section 3. Composition/information on ingredients

3.1 Substances

Chemical identity:	L-Carnitine L-Tartrate

CAS number	36687-82-8
EINECS number	——

Section 4. First aid measures

4.1Description of first aid measures

Skin contact:	Remove all contaminated clothes and footwear immediately unless stuck to skin. Wash immediately with plenty of soap and water.
Eye contact:	Bathe the eye with running water for 15 minutes. Consult a doctor.
Ingestion:	Wash out mouth with water. Consult a doctor.
Inhalation:	Remove casualty from exposure ensuring one's own safety whilst doing so. Consult a doctor.

4.2. Most important symptoms and effects, both acute and delayed

Skin contact:	There may be irritation and redness at the site of contact.
Eye contact:	There may be irritation and redness. The eyes may water profusely.
Ingestion:	There may be soreness and redness of the mouth and throat.
Inhalation:	There may be irritation of the throat with a feeling of tightness in the chest. Exposure may cause coughing or wheezing.

4.3. Indication of any immediate medical attention and special treatment needed

None

Section 5. Fire-fighting measures

5.1Extinguishing media

Extinguishing media: Suitable extinguishing media for the surrounding fire should be used.

5.2. Special hazards arising from the substance or mixture

Exposure hazards: In combustion emits toxic fumes.

5.3. Advice for fire-fighters

Wear self-contained breathing apparatus. Wear protective clothing to prevent contact with skin and eyes.

Section 6. Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Personal precautions: Refer to section 8 of SDS for personal protection details. If outside do not approach from downwind. If outside keep bystanders upwind and away from danger point. Mark out the

contaminated area with signs and prevent access to unauthorised personnel. Do not create dust.

6.2. Environmental precautions

Do not discharge into drains or rivers.

6.3. Methods and material for containment and cleaning up

Clean-up procedures: Transfer to a closable, labelled salvage container for disposal by an appropriate method.

6.4. Reference to other sections

Reference to other sections: Refer to section 8 of SDS. Refer to section 13 of SDS.

Section 7. Handling and storage

7.1. Precautions for safe handling

Handling requirements: Avoid direct contact with the substance. Ensure there is sufficient ventilation of the area.

Do not handle in a confined space. Avoid the formation or spread of dust in the air.

7.2. Conditions for safe storage, including any incompatibilities

Storage conditions: Store in well ventilated area. Keep container tightly closed.

7.3. Specific end use(s)

Specific end use(s): No special requirement.

Section 8. Exposure controls/personal protection

8.1 Control parameters

Workplace exposure limits: No data available.

8.2. Exposure controls

Engineering measures: Ensure there is sufficient ventilation of the area.

Respiratory protection: Respiratory protective device with particle filter.

Hand protection: Protective gloves.

Eye protection: Safety glasses. Ensure eye bath is to hand.

Skin protection: Protective clothing.

Environmental: Refer to specific Member State legislation for requirements under Community environmental legislation.

Section 9: Physical and chemical properties

9.1. Information on basic physical and chemical properties

Appearance	White crystalline powder
Odor	None reported
pH	3.0 ~4.5
Melting point /freezing point	169 ~175 °C
Initial boiling point and boiling range	No data available
Flash point	No data available
Evaporation rate	No data available
Flammability (solid, gas)	No data available
Upper/lower flammability or explosice limits	No data available
Vapor pressure	No data available
Vapor density	No data available
Relative density	No data available
Solubility	Soluble in water
Partition coefficient: n-octanol/water	No data available
Auto-ignition temperature	No data available
Decomposition temperature	No data available
Vixcosity	No data available

9.2 Other information

No data available

Section 10. Stability and reactivity

10.1. Reactivity

Stable under recommended transport or storage conditions.

10.2. Chemical

Stable under normal conditions.

10.3. Possibility of hazardous reactions

Not available

10.4. Conditions to avoid

Conditions to avoid: Heat.

10.5. Incompatible materials

Materials to avoid:Strong oxidizing agents,Strong acids.

10.6. Hazardous decomposition products

No data available.

Section 11. Toxicological information

11.1 Information on toxicological effects.

No data available.

Section 12. Ecological information

12.1. Toxicity

No data available.

12.2. Persistence and degradability

No data available.

12.3. Bioaccumulative potential

No data available.

12.4. Mobility in soil

No data available.

12.5. Results of PBT and vPvB assessment

PBT identification: This product is not identified as a PBT/vPvB substance.

12.6. Other adverse effects

Negligible ecotoxicity.

Section 13. Disposal considerations

13.1. Waste treatment methods

Product

Observe all federal, state, and local environmental regulations. Contact a licensed professional waste

disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber.

Contaminated packaging

Dispose of as unused product.

Section 14. Transport information

Transport class: This product does not require a classification for transport.

Section 15. Regulatory information

15.1. Safety, health and environmental regulations/legislation specific for the substance or mixture

Not available

15.2. Chemical Safety Assessment

Not available

Section16. Other information

The information given is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall the company be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if the company has been advised of the possibility of such damages.

Date of issue: Dec.29, 2017; Date of print: Dec.29, 2017

Appendix 4. Oldest (German) Patent on Acetylated Carnitine

DEUTSCHES REICH

AUSGEGEBEN AM
21. APRIL 1942

REICHSPATENTAMT

PATENTSCHRIFT

№ 719891

KLASSE 12q GRUPPE 3201

St 58154 IV c/12 q

* Dr. Erich Strack in Leipzig *
ist als Erfinder genannt worden.

Dr. Erich Strack in Leipzig

Verfahren zur Herstellung des Methyl- bzw. Äthylesters des acetylierten Carnitins

Patentiert im Deutschen Reich vom 8. Dezember 1938 an
Patenterteilung bekanntgemacht am 26. März 1942

Ester des Carnitins, nämlich der Methyl- und Äthylester, sind bekannt. Es wurde nun gefunden, daß die Veresterung des freien alkoholischen Hydroxyls des Carnitinmethyl- bzw. -äthylesters mit Essigsäure neue Stoffe ergibt, die vor den nicht acetylierten Estern besondere Vorteile aufweisen. Diese liegen teils auf chemisch-physikalischem Gebiete, z. B. Löslichkeit, Kristallisation, teils auf physiologischem. So ist nach Beobachtungen am Froschherzen der acetylierte Carnitinsäuremethylester dem nichtacetylierten in der Kontraktion erregenden Wirkung wesentlich überlegen. Der acetylierte Carnitinsäureäthylester vermag die Schlagkräftigkeit des geschädigten Herzens zu erhöhen.

Die Herstellung der acetylierten Ester kann entweder in der Weise erfolgen, daß man Carnitin zunächst nach bekannten Methoden acetyliert und dann in gleichfalls bekannter Weise veräthert oder durch Behandeln der fertig gebildeten Ester des Carnitins mit acetylierenden Mitteln in bekannter Weise acetyliert.

Beispiel 1

Das Chlorhydrat des Carnitinmethylesters wird mit der 5fachen Menge Acetylchlorid übergossen und 2 Tage bei 20° stehengelassen. Das überschüssige Acetylchlorid wird im Vakuum abdestilliert und der Rückstand in absolutem Alkohol aufgenommen. Man kann das Produkt, falls erforderlich, über das Chlorplatinat reinigen.

Beispiel 2

Carnitinäthylesterchlorhydrat wird mit Acetylchlorid 2 Stunden am Rückfluß im Sieden gehalten, die Esterbasen mit Äther gefällt, der Rückstand mit Äthanolwasser aufgenommen

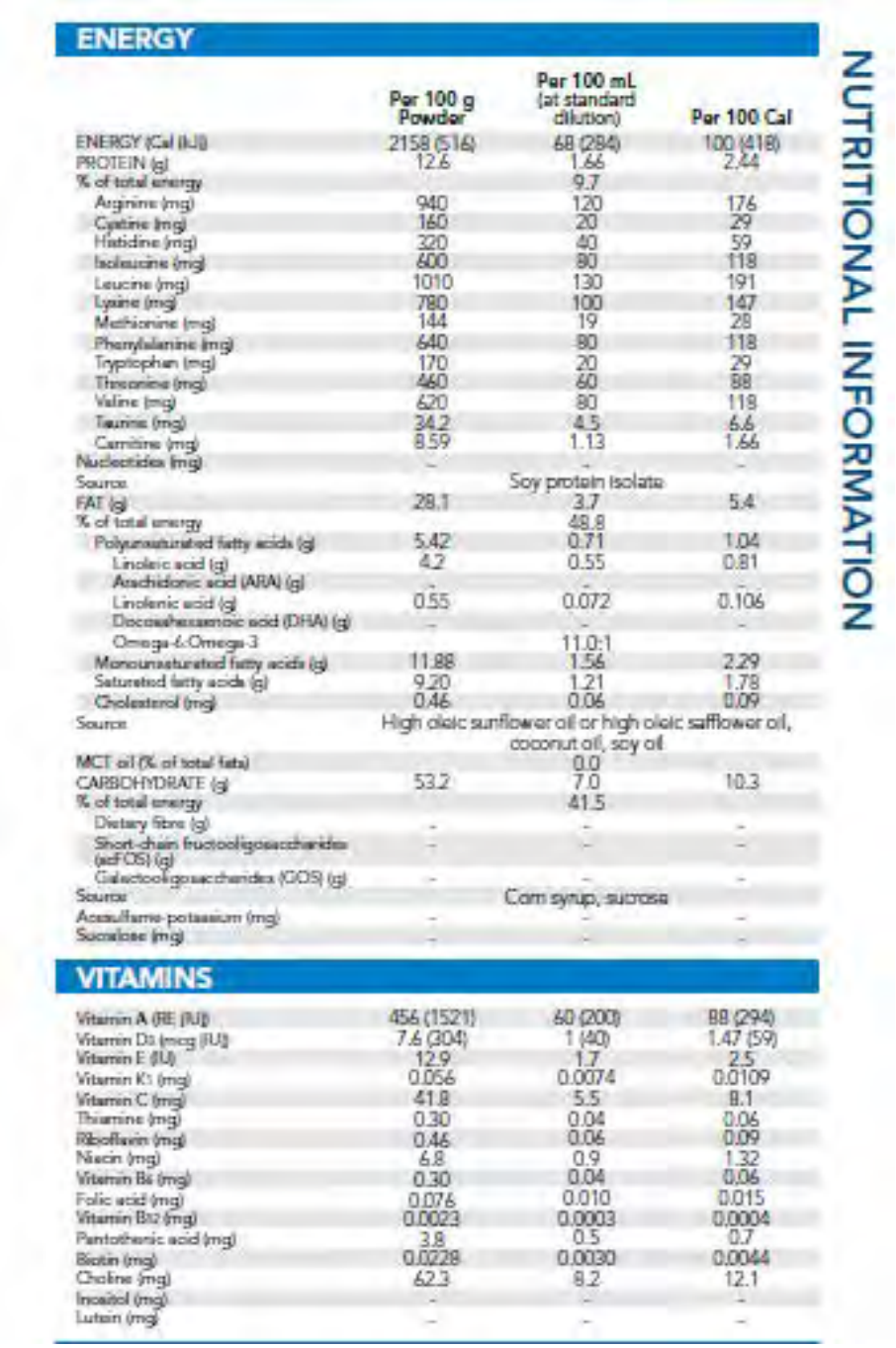
Appendix 5. Recipe Composition of Kabrita Gold Goat Based Infant Formula, China, 2011

Kabrita 1 GOLD M.O. HNC (PD10102 3)	
Base Vronie Goat	73.750
Z-Lactose	20.319
GOS op glucosestroop	2.185
FOS	1.289
AA Powder	1.159
Natriumchloride Suprasel Fijn	0.14916
Zinkpremix	0.08833
IJzerpremix	0.08762
Vitamine C	0.05438
Kalium Chloride	0.03098
Magnesiumchloride	0.02132
Inositol	0.01970
Koperpremix 1.5%	0.01348
Mangaanpremix	0.01316
L-Carnitine L-tartrate	0.00687
Choline Bitartraat	0.00544
Vitamine A	0.00399
Vitamine E	0.00357
Calciumpantothenaat	0.00300
Vitamine D3 Cws 100.000 IU/g	0.00258
Niacine	0.00148
Pre-premix foliumzuur 10%	0.00090
Natrium-Selenaat 1%	0.00089
Pre-premix biotine 1%	0.00089
Vitamine K1 5%	0.00082
Vitamine B1	0.00071
Vitamine B6	0.00017
Vitamine B2	0.00007
TCP Puremin Ca301	0.25000

Appendix 6. Recipe Composition of Goat Milk Based Infant Formula for Clinical Trial

Code	Description	Status	Weight
31038	Base HANNA goat	P	81.50000
31011	GOS on glucose syrup	P	10.52632
30074	Lactose edible (monohydrate)	P	4.53341
31037	ARASCO protein free (Vana-Sana)	P	1.73182
30880	DHASCO powder (Vana-Sana)	P	0.69273
30981	Tricalcium (di) fosfaat	P	0.32796
30160	Fe premix (3%)	P	0.19429
30690	Choline bitartrate	P	0.16557
30161	Zn premix (3%)	P	0.14393
30163	Mn premix (0.1%)	P	0.04735
30165	Taurine	P	0.03190
30162	Cu premix (1.5%)	P	0.02466
30153	Vitamin E (DL-alpha tocopheryl acetate 50%)	P	0.01745
30144	Inositol	P	0.00556
31070	Magnesium carbonate	P	0.01561
30071	Vitamin C (L-ascorbic acid)	P	0.01374
30154	Vitamin A (Retinyl acetate)	P	0.00481
30073	Niacinamide	P	0.00458
30963	KI premix (0.765%)	P	0.00278
30928	L-carnitine L-tartrate	P	0.00412
31127	Vitamin D3 Cws 100.000 IU/g (Cholecalciferol)	P	0.00260
30080	Calcium pantothenate (D-calcium pantothenate)	P	0.00246
31042	Biotin 1% (D-Biotin)	P	0.00157
30193	Vitamin B12 0.1 % (Cyanocobalamin)	P	0.00087
30072	Vitamin K1 5% (Phytomenadione)	P	0.00104
20059	Pre-premix folic acid 10% (Pteroylmonoglutamic aci	P	0.00095
30581	Sodium selenate 1%	P	0.00076
30069	Vitamin B1 (Thiamin hydrochloride)	P	0.00054
30192	Vitamin B2 (Riboflavin)	P	0.00038
30070	Vitamin B6 (Pyridoxine hydrochloride)	P	0.00026

Appendix 7. Nutrition Declaration of Similac Isomil Infant Formula (Abbott), Canada



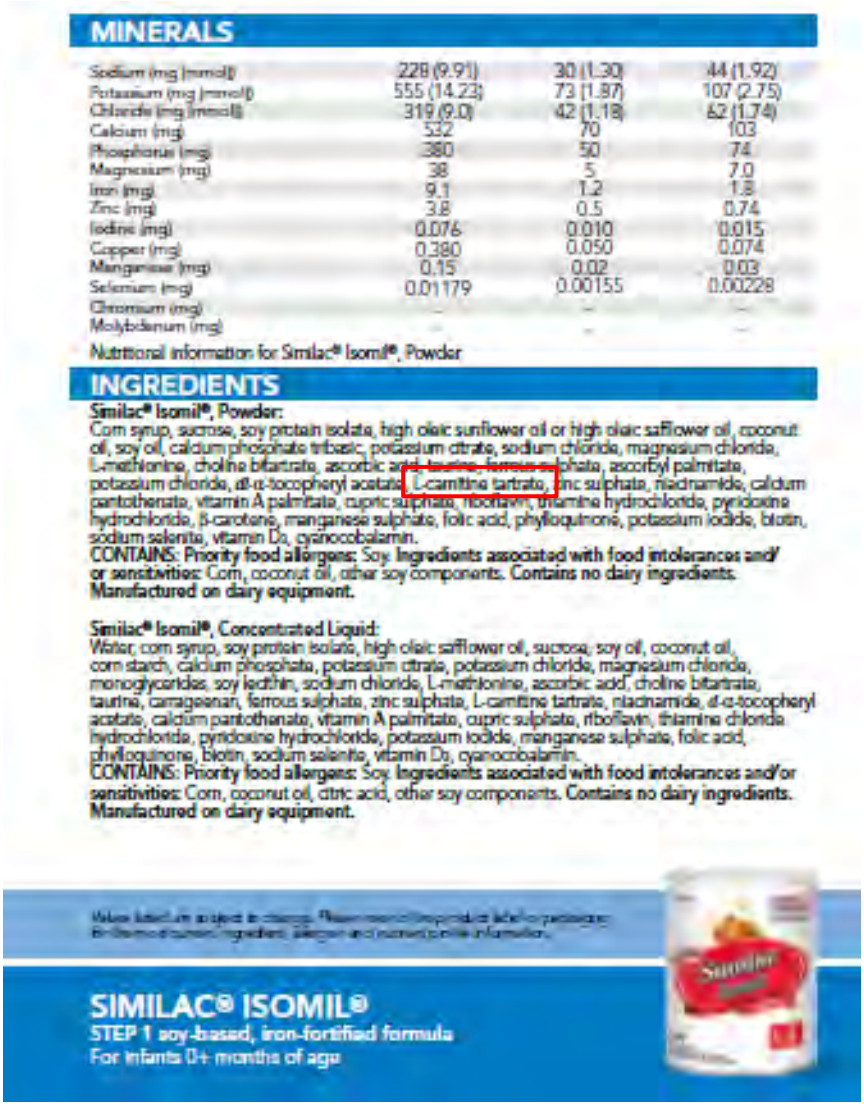
NUTRITIONAL INFORMATION

ENERGY

	Per 100 g Powder	Per 100 mL (at standard dilution)	Per 100 Cal
ENERGY (Cal (kJ))	2158 (516)	68 (284)	100 (418)
PROTEIN (g)	12.6	1.66	2.44
% of total energy		9.7	
Arginine (mg)	940	120	176
Cystine (mg)	160	20	29
Histidine (mg)	320	40	59
Isoleucine (mg)	600	80	118
Leucine (mg)	1010	130	191
Lysine (mg)	780	100	147
Methionine (mg)	144	19	28
Phenylalanine (mg)	640	80	118
Tryptophan (mg)	170	20	29
Threonine (mg)	460	60	88
Valine (mg)	620	80	119
Taurine (mg)	34.2	4.5	6.6
Carnitine (mg)	8.59	1.13	1.66
Nucleotides (mg)	-	-	-
Source		Soy protein isolate	
FAT (g)	28.1	3.7	5.4
% of total energy		48.8	
Polyunsaturated fatty acids (g)	5.42	0.71	1.04
Linoleic acid (g)	4.2	0.55	0.81
Arachidonic acid (ARA) (g)	-	-	-
Linolenic acid (g)	0.55	0.072	0.106
Docosahexaenoic acid (DHA) (g)	-	-	-
Omega-6:Omega-3		11.0:1	
Monounsaturated fatty acids (g)	11.88	1.56	2.29
Saturated fatty acids (g)	9.20	1.21	1.78
Cholesterol (mg)	0.46	0.06	0.09
Source		High oleic sunflower oil or high oleic safflower oil, coconut oil, soy oil	
MCT oil (% of total fats)		0.0	
CARBOHYDRATE (g)	53.2	7.0	10.3
% of total energy		41.5	
Dietary fibre (g)	-	-	-
Short-chain fructooligosaccharides (scFOS) (g)	-	-	-
Galactooligosaccharides (GOS) (g)	-	-	-
Source		Corn syrup, sucrose	
Acesulfame-potassium (mg)	-	-	-
Sucralose (mg)	-	-	-

VITAMINS

Vitamin A (RE (IU))	456 (1521)	60 (200)	88 (294)
Vitamin D3 (mcg (IU))	7.6 (304)	1 (40)	1.47 (59)
Vitamin E (IU)	12.9	1.7	2.5
Vitamin K1 (mg)	0.056	0.0074	0.0109
Vitamin C (mg)	41.8	5.5	8.1
Thiamine (mg)	0.30	0.04	0.06
Riboflavin (mg)	0.46	0.06	0.09
Niacin (mg)	6.8	0.9	1.32
Vitamin B6 (mg)	0.30	0.04	0.06
Folic acid (mg)	0.076	0.010	0.015
Vitamin B12 (mg)	0.0023	0.0003	0.0004
Pantothenic acid (mg)	3.8	0.5	0.7
Biotin (mg)	0.0228	0.0030	0.0044
Choline (mg)	62.3	8.2	12.1
Inositol (mg)	-	-	-
Lutein (mg)	-	-	-



MINERALS

Sodium (mg (mmol))	228 (9.91)	30 (1.30)	44 (1.92)
Potassium (mg (mmol))	555 (14.23)	73 (1.87)	107 (2.75)
Chloride (mg (mmol))	319 (9.0)	42 (1.18)	62 (1.74)
Calcium (mg)	532	70	103
Phosphorus (mg)	380	50	74
Magnesium (mg)	38	5	7.0
Iron (mg)	9.1	1.2	1.8
Zinc (mg)	3.8	0.5	0.74
Iodine (mg)	0.076	0.010	0.015
Copper (mg)	0.380	0.050	0.074
Manganese (mg)	0.15	0.02	0.03
Selenium (mg)	0.01179	0.00155	0.00228
Chromium (mg)	–	–	–
Molybdenum (mg)	–	–	–

Nutritional information for Similac® Isomil®, Powder

INGREDIENTS

Similac® Isomil®, Powder:
Corn syrup, sucrose, soy protein isolate, high oleic sunflower oil or high oleic safflower oil, coconut oil, soy oil, calcium phosphate tribasic, potassium citrate, sodium chloride, magnesium chloride, L-methionine, choline bitartrate, ascorbic acid, taurine, ferrous sulphate, ascorbyl palmitate, potassium chloride, dl-α-tocopheryl acetate, L-carnitine tartrate, zinc sulphate, niacinamide, calcium pantothenate, vitamin A palmitate, cupric sulphate, riboflavin, thiamine hydrochloride, pyridoxine hydrochloride, β-carotene, manganese sulphate, folic acid, phylloquinone, potassium iodide, biotin, sodium selenite, vitamin D3, cyanocobalamin.
CONTAINS: Priority food allergens: Soy. **Ingredients associated with food intolerances and/or sensitivities:** Corn, coconut oil, other soy components. **Contains no dairy ingredients. Manufactured on dairy equipment.**

Similac® Isomil®, Concentrated Liquid:
Water, corn syrup, soy protein isolate, high oleic safflower oil, sucrose, soy oil, coconut oil, corn starch, calcium phosphate, potassium citrate, potassium chloride, magnesium chloride, monoglycerides, soy lecithin, sodium chloride, L-methionine, ascorbic acid, choline bitartrate, taurine, carrageenan, ferrous sulphate, zinc sulphate, L-carnitine tartrate, niacinamide, dl-α-tocopheryl acetate, calcium pantothenate, vitamin A palmitate, cupric sulphate, riboflavin, thiamine chloride hydrochloride, pyridoxine hydrochloride, potassium iodide, manganese sulphate, folic acid, phylloquinone, biotin, sodium selenite, vitamin D3, cyanocobalamin.
CONTAINS: Priority food allergens: Soy. **Ingredients associated with food intolerances and/or sensitivities:** Corn, coconut oil, citric acid, other soy components. **Contains no dairy ingredients. Manufactured on dairy equipment.**

Obtained at 12 December 2018 from: https://static.abbottnutrition.com/cms-prod/similac.ca/img/en-isomil-prodinfo_0.pdf

Appendix 8. Nutrition Declaration of Bubs Goat Milk Based Infant Formula, Australia

Obtained at 5 December 2018 from https://www.bubsaustralia.com/products/goats-milk-formula-stage-1

Exhibit 1. Report of the Expert Panel

EXPERT PANEL OPINION ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS of L-CARNITINE-L-TARTRATE FOR USE IN TERM INFANT FORMULA

The undersigned, an independent panel of experts, qualified by their scientific training and expertise (the Expert Panel), was convened by Ausnutria to specifically conduct a critical and comprehensive evaluation of the safety and "generally recognized as safe" ("GRAS") status of the proposed use of L-Carnitine-L-Tartrate (LCLT) in term infant formula (IF). The Expert Panel members have, independently and collectively, reviewed the information in this GRAS document and other information that they deemed appropriate. Following its independent critical evaluation of the available information, the Expert Panel convened by teleconference on June 26, 2019, thoroughly discussed the document, and agreed to the suggested revisions and edits. The Expert Panel unanimously concluded, without any reservation, that the intended use of LCLT in term IF, meeting appropriate food-grade specifications, and manufactured using current Good Manufacturing Practices (cGMP), is GRAS for use as a food ingredient in term IF.

Ausnutria ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety, toxicology, chemistry, and microbiology. Efforts were placed on identifying conflicts of interest or relevant 'appearance issues' that could potentially bias the outcome of the deliberations of the Expert Panel. No such conflicts of interest or 'appearance issues' were identified. The Expert Panel received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel were not contingent upon the outcome of their deliberations.

The Expert Panel consisted of qualified experts whose names and signatories appear below. The curriculum vitae of the expert panel members are attached in an Annex to this document. The Expert Panel has prepared a summary statement of its conclusions, which is provided below.

GRAS (Generally Recognized as Safe) Panel Statement Concerning the Generally Recognized as Safe GRAS Status of the Proposed Use of L-Carnitine-L-Tartrate in term infant formula

We, the members of the GRAS (Generally Recognized As Safe) Panel (Expert Panel), qualified by scientific training and relevant experience to evaluate the safety of food and food ingredients, have performed a comprehensive and critical review of the available information and data on the safety and GRAS status of the use of L-Carnitine-L-Tartrate in term infant formula. The data and information reviewed are summarized in the attached GRAS document ("Generally Recognized As Safe (GRAS) Notice: L-Carnitine-L-Tartrate in term infant formula"), and other information that the panel members determined to be pertinent to the use.

Based upon our review of the information and data available, we have determined, using scientific procedures, that the amount of LCLT consumed for the intended use in term IF, has been shown to be safe and GRAS.

The intended use of LCLT in term IF has been determined through the application of scientific procedures to be safe as described under 21 CFR 170.30 (b) and is supported by the following:

1. LCLT is a salt of L-Carnitine and L-tartaric acid and is used as a source of L-Carnitine. LCLT is soluble in water and dissociates into L-Carnitine and L-tartaric acid in the gastrointestinal tract. Thus, the safety of LCLT can be based on the safety of L-Carnitine and L-tartaric acid individually, and the safety of which is well established and accepted.

2. L-Carnitine has been added to term infant formula in the U.S. since 1985. LCLT has been added to IF since 2004, but not in the U.S.
3. There are sufficient published scientific animal and human studies and publicly available reports and monographs by several regulatory authorities that support and document the safe use of LCLT in foods, including the use of LCLT as a source of L-Carnitine in term IF. A risk assessment supports the use of LCLT at a maximum level of 2250 mg/day which is equivalent to 1550 mg/day of L-Carnitine.
4. L-Tartaric acid occurs naturally in fruits and wine. L-tartaric acid is currently present in IF through the use of Choline Bitartrate, a salt of Choline and L-tartaric acid, which behaves similarly to LCLT in that Choline Bitartrate also dissociates into its individual components, Choline and L-tartaric acid.
5. The resultant minor increase in exposure of L-tartaric acid from the use of LCLT in IF does not present a safety concern.
6. Independent GRAS determinations have been made for the use of L-Carnitine and LCLT in food, including IF, in the U.S.
7. LCLT will be added to IF within the levels recommended by LSRO of 1.2 mg/100 kcal – 2.0 mg/100 kcal, adjusted to account for the L-Carnitine that may be present in the IF from other sources.
8. LCLT is non-hydroscopic which facilitates dry-blending and precise dosing.
9. LCLT has been established to be safe by EFSA as a safe source of L-Carnitine for use in IF.
10. The EFSA recommends the amount of L-Carnitine in IF to be at levels of at least 1.2 mg/100 Kcal. There is no evidence of adverse safety events associated with the use of LCLT in term IF when used at the level of 1.2 mg/100 kcal – 2.0 mg/100 kcal, adjusted to account for the L-Carnitine that may be present in the IF from other sources, and used consistent with current good manufacturing practice.

The Expert Panel critically evaluated the documentation of the safety of LCLT in this document and other available data and information that members of the Expert Panel deemed to be pertinent to the safety of LCLT under the conditions of its intended use. In addition, the Expert Panel critically evaluated the specifications for LCLT, analytical data, conditions of its intended use as an ingredient in IF, the production process, and the estimated dietary exposure to LCLT resulting from the intended use. After an independent review, the Expert Panel convened again on March 23, 2020 and thoroughly discussed the document, and agreed to the suggested revisions and edits. The Expert Panel then independently, jointly, and unanimously, concluded that the intended use of LCLT, when used in IF at a level of 1.2 mg/100 kcal – 2.0 mg/100 kcal, and consistent with current good manufacturing practices, meeting appropriate food-grade specifications, when used as discussed in this document, is safe and GRAS, based on scientific procedures. Therefore, based on a consideration of the totality of the evidence, it is also the opinion of the Expert Panel that other qualified experts would concur with these conclusions.

CONCLUSION

We, the undersigned expert panel members have, individually and collectively, critically evaluated the information described in this document, and other pertinent information and data, related to the safety of the proposed use of LCLT in term IF as a food ingredient at a level of 1.2 mg/100 kcal – 2.0 mg/100 kcal, and unanimously conclude that the intended use of LCLT in IF is safe and GRAS based on scientific procedures.

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have concluded that LCLT, when used as described, is GRAS.

Signatures

This declaration has been made in accordance with FDA's standard for food ingredient safety, i.e., reasonable certainty of no harm under the intended conditions of use.

[redacted]

Robin Guy, M.S.

April 6, 2020
Date

[redacted]

Prof. Jon A. Vanderhoof

Apr 6 - 2020
Date

[redacted]

Karin Ricker, Ph.D.

April 6, 2020
Date

Annex. Resumes of Expert Panel Members

Thirty pages of Curriculum Vitae removed in accordance with the Privacy Act of 1974.