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By email:
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Proposal P1028 – Infant Formula

On 23 February 2016, Food Standards Australia New Zealand called for submissions in relation to Proposal P1028, Infant Formula [05-16].

Lonza Ltd (Lonza) is a Swiss-based company that serves the global pharmaceutical, healthcare and nutrition industries. Its products and services span its customers' needs from research to final product manufacture. Lonza is one of the world's largest manufacturers/suppliers of vitamin B_3 (niacin and niacinamide), arabinogalactan (from larch tree), and L-carnitine. Lonza is headquartered in Basel, Switzerland and is listed on the SWX Swiss Exchange.
Lonza wishes to provide input to the consultation in relation to L-carnitine and L-carnitine L-tartrate and will only address questions related to these substances in this submission. Our responses are provided in Attachment 1 to this letter.

Please do not hesitate to contact the writer should you require further information.

Yours sincerely
Lonza Ltd

[redacted]

ATTACHMENT 1: Lonza responses to P1028

Q1.27 Do you support inclusion of a mandatory requirement for L-carnitine in infant formula? Please provide your rationale.

We support FSANZ's preliminary view that L-carnitine should be listed as a mandatory substance in infant formula.
We also support a mandatory minimum level and agree with the proposed level of 0.3 mg/100 kJ which is higher than the current value specified in the revised Australia New Zealand Food Standards Code for Special Purpose Foods – Schedule 29 - Standard 2.9.1 - Infant Formula Products, which lists L-carnitine under S29-5 as permitted nutritive substance for infant formula products in a dose range from 0.21 mg – 0.8 mg/100 kJ [i].

We do not think that setting a mandatory maximum level is necessary, although the proposed value of 0.8 mg/100 kJ seems reasonably high.

Review of current recommendations around the globe

Codex Alimentarius
The proposed minimum value is in line with the recommendations by Codex Alimentarius (STANDARD FOR INFANT FORMULA AND FORMULAS FOR SPECIAL MEDICAL PURPOSES INTENDED FOR INFANTS of 2015, originally established in 1981 and revised in 2007 [ii]), which lists a minimum L-carnitine content of 1.2 mg/100 kcal (=0.3 mg/100 kJ) for infant formula prepared ready for consumption. This is similar to the L-carnitine content of breast milk. A maximum level has not been specified in this Codex Standard thanks to the excellent safety profile of L-carnitine.

LSRO
In 1995, the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences was asked to develop a report for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA) and the Health Protection Branch of Health Canada [iii]. The LSRO Expert Panel recommended a minimum L-carnitine content of infant formulas of 1.2 mg/100 kcal (=0.3 mg/100 kJ), a level similar to that found in human milk, and a maximum L-carnitine content of infant formulas of 2.0 mg/100 kcal (=0.5 mg/100 kJ), a value similar to the upper limit reported for human milk**.** The Expert Panel was unaware of any studies in which a NOAEL or LOAEL 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.

Scientific Committee on Food
In 2003, the Scientific Committee on Food recommended maintaining requirement in the EU to add L-carnitine to infant formula based on protein hydrolysates and soy protein isolates to achieve a content of at least 1.2 mg/100 kcal (7.5 µmol/100 kcal or 0.3 mg/100 kJ). No maximum amount of L-carnitine was specified [iv].

ESPGHAN

In 2005, an international expert group coordinated by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published their recommendations in a global standard for the composition of infant formula [v], taking into consideration also previous expert reviews by ESPGHAN [vi, vii], the Life Sciences Research Office Report [iii]and the Scientific Committee on Food [iv]. ESPGHAN recommends a mandatory minimum level for L-carnitine of 1.2 mg/100 kcal (=0.3 mg/100 kJ), without the need to set a maximum level.

American Academy of Pediatrics

For soy protein-based infant formulas, the American Academy of Pediatrics specifies the protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45 – 2.8 g/100 kcal or 1.65 – 1.9 g/dL [viii, ix].

Scientific Rationale: L-carnitine in infants

L-carnitine synthesis in newborns is less efficient than in adults and appears to be insufficient to meet the requirements. Therefore, L-carnitine is regarded as a conditionally essential nutrient for infants [x, xi, xii]. L-carnitine is synthesized in the liver and kidneys from the essential amino acids lysine and methionine. The activity of gamma-butyrobetaine hydroxylase, the final enzyme in the L-carnitine biosynthetic pathway, has been suggested to be age-dependent [xiii, xiv, xv]. Hepatic activity of gamma-butyrobetaine hydroxylase in infants was reported to be only 12% of that found in adults. By 2.5 years of age the activity rises to 30% and by 15 years of age it is within the standard deviation of the adult mean [xvi].

Adequate blood and tissue concentrations of L-carnitine may be important in enhancing utilization of fat and energy, and in promoting growth in neonates [xvii]. The elevated L-carnitine levels of breast milk seem to be a factor enhancing the metabolic adaptation of the newborn to the utilization of fatty acids [xviii].

Breast milk represents the only natural source of L-carnitine for the newborn infant unless meat is introduced into the infant's diet [xix]. L-carnitine concentration in breast milk is highest during the first week's post-partum (80-100 nmol/mL) and decreases to around 60 nmol/mL thereafter [xx]. After birth, L-carnitine content in breast milk is even higher than in maternal plasma, and active secretion by the mammary glands has been suggested [xxi].

Infant formulas containing insufficient L-carnitine produced the symptoms of carnitine deficiency: failure to thrive, nonketotic hypoglycemia (low blood sugar), hypertonia and cardiomyopathy.

Also a recent publication from Japan reported on carnitine insufficiency in infants with milk allergy who were given amino acid formulas or hydrolyzed formulas without L-carnitine. Supplementation with L-carnitine was reported to immediately improve their condition [xxii].

Historical review of L-carnitine's use in infant formula

L-carnitine has been added to soy-based infant formula products since 1986 and to cow's milk based products since the mid 1990's in the US at levels recommended by Codex.

Q.1.28 What is the technological justification can you provide for the use of L-carnitine hydrochloride and/or L-carnitine tartrate infant formula?

L-carnitine is highly hygroscopic and may cause lumping in dry powder mixes or premixes. Especially since the dose to be added to infant formula is so low (around 0.5%), the annual demand for raw material especially for smaller enterprises is not much. It is recommended that a container of raw material is used at once, because every time the lid is opened, powder removed and container closed again the normal humidity of the air results in more lumping.

This problem can be avoided by using L-carnitine L-tartrate which is much less hygroscopic compared to L-carnitine, and the L-carnitine salt form with the highest L-carnitine content commercially available. It consists of 68% L-carnitine and 32% L-tartaric acid. Absorption of L-carnitine tartrate is not altered compared to L-carnitine alone, because in solution, L-carnitine L-tartrate dissociates into L-carnitine and L-tartaric acid.

To assist trade with Australia and New Zealand, L-carnitine L-tartrate as an approved carnitine derivative for infant formula is another reason to consider, since it may already be added to infant formula in other parts of the world.

Q.1.29 If you have provided a technological justification for these forms what evidence to demonstrate safety can you provide for the use of L-carnitine hydrochloride and/or L-carnitine tartrate infant formula?

GRAS
Both L-carnitine and L-carnitine L-tartrate are self-affirmed GRAS in the United States.

JECFA
JECFA (Joint FAO/WHO Expert Committee on Food Additives) have not assessed L-carnitine and L-carnitine L-tartrate, since they do not fall into the scope of JECFA's risk assessments. Both products are regarded as functional ingredients. L-tartaric acid which forms part of L-carnitine L-tartrate was assessed by JECFA in 1977. JECFA established a no-effect level at 7.68% of the diet, equivalent to 3000 mg/kg/day. An ADI for man for L-tartrate (monosodium salt) was reconfirmed at 0 - 30 mg/kg body weight [xxiii].
Tartaric acid is metabolically inert in the human body. When taken by mouth, only about 20% of ingested tartrate is eliminated in the urine; the remainder is not absorbed but metabolized by the human gut microflora [xxiv].

CODEX ALIMENTARIUS
Both L-carnitine and L-carnitine L-tartrate are listed on Codex Alimentarius' Advisory lists of nutrient compounds for use in foods for special dietary uses intended for infants and young children (CAC/GL 10-1979) for infant formula products [xxv].

EFSA
In 2003, the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) of the European Food Safety Authority (EFSA) evaluated the use of L-carnitine L-tartrate as a source of L-carnitine in foods for particular nutritional uses (PARNUTS).

At that time, L-carnitine and L-carnitine hydrochloride were already permitted for use in foods for particular nutritional purposes, including infant formula. The Panel concluded that the consumption of up to 3 g/day of L-carnitine L-tartrate (equivalent to 2 g/day of L-carnitine) presents no safety concerns when used as a source of L-carnitine for use in PARNUTS, provided that the ADI for L-tartaric acid from all sources in the diet is not regularly exceeded [xxvi].

European Union – past and today

Based on the EFSA evaluation published in 2003, L-carnitine L-tartrate was added to the Annex on substances that may be added for specific nutritional purposes in foods for particular nutritional uses of Directive 2001/15/EC in the form of an amendment in 2004 [xxvii]. L-carnitine crystalline was listed in this Annex from the beginning [xxviii].

Since, both L-carnitine and L-carnitine L-tartrate were listed in the Infant Formula Directive (2006/141/EC) which approves their use in infant and follow-on formulas [xxix]. Both products were also regarded as authorized nutritional substances in the Commission Directive 2006/125/EC on processed cereal-based foods and baby foods for infants and young children [xxx].

Both L-carnitine and L-carnitine L-tartrate were listed in the Annex of Commission Regulation (EC) No 953/2009 (valid until June 2016) [xxxi] on substances that may be added for specific nutritional purposes in food for particular nutritional uses under the category “dietetic foods”.

Effective from 20 July 2016, all these regulations will be replaced by Regulation (EU) No 609/2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control [xxxii], which in Article 15 establishes a “Union List” of substances that may be added to one or more categories which are covered by the regulation. L-carnitine, L-carnitine hydrochloride and L-carnitine L-tartrate are all listed in the Annex (Union List) and thus approved for the use in infant formula.

China

L-carnitine and L-carnitine L-tartrate are approved for use in Infant formulae, follow-on formulae and young children at 0.3 mg/100 kJ or 1.2 mg/100 kcal.

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