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Application to Food Standards Australia New Zealand to amend the minimum L-Histidine requirements in Standard 2.9.1 - Infant Formula Products

May 2012

EXECUTIVE SUMMARY

Nestlé Australia Ltd and Nestlé New Zealand Limited (Nestlé) are proposing a change to the minimum requirement for the essential amino acid, L-histidine, in infant formula and follow-on formula. The current requirement for L-histidine in infant and follow-on formula, as stated in the Australia New Zealand Food Standards Code (ANZFSC) Standard 2.9.1, Table to Clause 22, is minimum 12 mg per 100kJ. We request consideration to reduce the minimum requirement to 10mg per 100kJ. The current L-histidine requirement is higher than the requirements in international regulations [such as Codex Alimentarius (CODEX) and the European Union] and as such, represents a trade barrier, which could potentially be cause for concern for continual supply of some products for this vulnerable population group. Further to this, there is evidence that the proposed minimum level of 10mg per 100kJ of L-histidine is safe and will promote normal growth and development in infants.

The amino acid minimum requirements in Australia New Zealand Food Standards Code (ANZFSC) are based on the breast milk composition findings from the FAO/WHO commissioned Expert Consultation on Protein Quality Evaluation (1989). Since that time, the FAO/WHO commissioned a report by the ESPGHAN International Expert Group to provide a proposal on nutrient levels in infant formula, based on scientific analysis. The recommendations from this report (Koletzko et al., 2005) with regard to amino acid minimum levels have been adapted into Annex I of the revised CODEX Standard on Infant Formula (2007). This includes the requirement for L-histidine levels to be 41mg per 100kcal (9.8 mg per 100kJ) based on the mean of human milk studies. Nestlé is proposing implementing a level of 10mg per 100kJ which would more closely align the ANZFSC with CODEX and European Union requirements. This would also align with the Council of Australian Governments Best Practice Regulation[1] principles of best practice regulatory process "to recognise the effect of regulation on individuals and the cumulative burden on business" and to "have regard to whether the existing regulatory regimes of other jurisdictions might offer a viable alternative".

Nestlé sources infant and follow-on formula for the Australian and New Zealand markets from Europe, and the different L-histidine requirements result in additional cost and risk of supply into the market, particularly with respect to paediatric speciality products such as those required for infants with metabolic, immunological, renal, hepatic and malabsorptive conditions. Paediatric speciality

[1] Council of Australian Governments, Best Practice Regulation, A Guide for Ministerial Councils and National Standard Setting Bodies, October 2007

products represent 11.2% of the value of the total formula market in Australia[2]. These smaller volume products in the Australian/New Zealand market benefit from sharing recipes and hence manufacturing volumes, with other markets. For Nestlé, harmonised L-histidine requirements would allow the same recipe to be used for both CODEX-compliant as well as European Union markets and the Australian/New Zealand market.

There is evidence to suggest that the proposed minimum of 10mg of L-histidine per 100 kJ of infant formula is safe and will promote normal growth and development in infants. The minimum required for CODEX and EU respectively is 9.8mg and 10mg of L-histidine per 100 kJ. These values are used in European countries and all other countries that follow CODEX regulations. To the best of our knowledge, there are no known reports of inadequate normal growth and development due to insufficient L-histidine in any of these countries, where millions of non-breastfed infants have been consuming infant formula products where regulated minimum L-histidine levels are lower than that of Australia and New Zealand.

Additionally, recent international studies using lower protein levels in infant formula, and with L-histidine levels ranging between 9.6 – 10.5mg per 100kJ have all been shown to promote normal growth which is equivalent to that of the breastfed infant (Raiha 2002; Hernell 2003; Turck 2006; Sandstrom 2008; Trabulsi 2011). Some of these studies have also shown that the plasma amino acid concentrations at 2, 4, and 6 months of feeding are within normal limits and indeed slightly higher than the levels in the breastfed controls (Hernell 2003; Sandstrom 2008; Trabulsi 2011). This again emphasises that 10mg per 100 kJ of L-histidine is adequate to support infant growth and development.

It should be noted that, for the purposes of ease and speed of approval, we are requesting only a change to the L-histidine values. Similar arguments could be applied to other amino acid minimums which may be relevant when Standard 2.9.1 Infant Formula Products is next reviewed.

[2] AC Neilsen, Combined MAT Report, Period Ending 12/02/2012

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GENERAL REQUIREMENTS

(as per requirements of The Application Handbook, 1 August 2011, Section 3.1)

Applicant Details

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[redacted]

[redacted]

(f) Nestlé is a manufacturer and importer of a wide variety of foods for the Australian and New Zealand markets and is globally one of the largest manufacturers of infant formula. Nestlé currently imports and markets infant formula products, including paediatric speciality formulas for infants with specific nutritional needs, into Australia and New Zealand.

(g) This application is for and on behalf of Nestlé Australia Ltd, and Nestlé New Zealand Limited. There are no other individuals, companies or organisations associated with the application.

Purpose of the Application

The purpose of this application is to seek to amend the minimum L-histidine requirements in Standard 2.9.1 Infant Formula Products, Clause 22 (1) (see Figure 1) from 12mg L-histidine per 100kJ to 10mg L-histidine per 100kJ of infant and follow-on formula.

Figure 1: Food Standards Australia New Zealand – Standard 2.9.1 – Infant Formula products, excerpt from Clause 22.

22 Protein

(1) The L-amino acids listed in column 1 of the Table to this clause must be present in infant formula and follow-on formula at the minimum level specified in column 2 of the Table, subject to subclause 2 and 3.

Table to clause 22

Column 1	Column 2
L-Amino Acid	**Minimum amount per 100 kJ**
Histidine	12 mg

Justification of the Application

The justification for this application is that firstly, there would be no adverse public health or safety issues due to reducing the minimum mandatory requirements for L-histidine, and secondly, that it promotes consistency between ANZFSC and CODEX for L-histidine requirements in infant formula. Ensuring supply through harmonisation and promoting free trade is of paramount importance, especially in the category of infant formula products, where for the non-breastfed infant 0-6 months of age, infant formula would be the sole source of nutrition, and for the non breastfed infant from 6 months of age, follow-on formula, a principle source of liquid nutrition.

ANZFSC Standard 2.9.1 (Clause 22) contains L-amino acid compositional requirements for infant formula and follow-on formula. Division 3 of this Standard contains regulatory requirements for Infant Formula Products for Special Dietary Use. This includes products for metabolic, immunological, renal, hepatic and malabsorptive conditions and allows infant formula products to be specifically formulated for these conditions providing that they comply in all other respects with the Division. Nestlé interprets this to mean that infant formula products for special dietary use are required to comply with the minimum L-amino acid requirements in Clause 22, where a certain level of L-amino acid content is not directly applicable for the dietary management of the condition for which it is formulated. Whilst any change to L-amino acid requirements would affect infant formula and follow-on formula products, Nestlé would find this change particularly useful for products developed for special dietary use (specialty products). Speciality products represent a small percentage of the infant formula market but require significant research and development resources. Harmonisation of the L-histidine requirements would allow the Australian/New Zealand markets to access products developed for the European Union markets which represent the latest science and to which research and development is given priority due to the larger market volume.

Nestlé has no applications with regard to minimum L-histidine requirements in any other country.

i) Safety of proposed change

There is evidence to suggest that a minimum of 10mg of L-histidine per 100kJ of infant formula is safe and will promote normal growth and development in infants. This is the minimum level required in European countries and all other countries that follow CODEX regulations. To the best of our knowledge, there are no known reports of inadequate growth due to insufficient L-histidine in any of these countries.

Nestlé supports the Infant Formula Products Policy Guideline, Specific Policy Principle (h)[3] that the composition of breast milk should be used as the primary reference for determining the composition of infant formula and follow-on formula. However it must be acknowledged that is not necessarily the sole determinant - the composition of breast milk can vary considerably, according to the maternal diet, time of day, stage of lactation and other factors. The mean level of L-histidine found in breast milk across numerous studies conducted in several countries (CODEX STAN 72-1981 Standard for Infant Formula and Formulae for Special medical purposes Intended for Infants, Annex I) is 9.8mg per 100 kJ and the growth of these breastfed infants is viewed as the ideal. It is noted that there is a wide variation in breast milk L-histidine levels, with Villalpando (1998) reporting a level of 7.26mg per 100 kJ in the breast milk of USA mothers, whilst Darragh (1998) showed a mean level of 10.5mg per 100 kJ of L-histidine.

Another consideration is that the age of the breast-fed infant used as an indicator for the purposes of comparison in determining the essential composition of infant formula products should not be beyond six months of age (all of the studies cited in CODEX 2007 involved breast milk fed to infants less than four months of age as the target study group). This is because complementary feeding starts from around 4-6 months and this introduction of solids may introduce a bias into the health and physiological outcome of the infant. For infants around 4-6 to 12 months of age, it becomes significantly more difficult to reliably measure a health outcome due to an increase in the number of confounding factors i.e. breast milk or infant formula is no longer the sole source of nutrition.

While breast milk can be used as a primary reference for the L-amino acid composition of infant formula, we consider that is may not necessarily be the sole determining factor. A paramount consideration is the evidence reflected by effectiveness studies in

[3] AUSTRALIA AND NEW ZEALAND FOOD REGULATION MINISTERIAL COUNCIL, Food Regulation Standing Committee, Regulation of Infant Formula Products [http://www.foodstandards.gov.au/_srcfiles/Infant%20Formula%20May%202011.pdf]Accessed 3rd March 2012

the consuming populations of those countries where infant formulas are regulated by lower minimum L-histidine levels, with no evidence of harm with regard to normal growth and development.

In addition, emerging evidence suggests that high protein levels in infancy may be a risk factor for later obesity (Koletzko 2009), and therefore this area has received considerable recent research focus, with infant growth as the primary outcome in many of the studies. These studies can also be used as supportive to assess the safety of minimum levels of specific amino acids in infant formula.
There are other recent international studies using lower protein levels in infant formula (Raiha et al 2002; Hernell et al 2003; Turck et al 2006; Sandstrom et al 2008; Trabulsi et al 2011), and with L-histidine levels ranging between 9.6 – 10.5mg per 100kJ which have all been shown to promote normal growth and development which is equivalent to that of the breastfed infant. This strongly suggests that adequate L-histidine has been provided to these infants. Each of these 5 high quality studies have been published in the last decade in high impact factor nutrition journals that are globally recognised – namely the Journal of Pediatric Gastroenterology and Nutrition, the American Journal of Clinical Nutrition, and the European Journal of Clinical Nutrition.

Some of these recent studies with infant formula (Hernell et al 2003; Sandstrom et al 2008; Trabulsi et al 2011) have also investigated individual plasma amino acid concentrations at 2, 4, and 6 months of feeding. Their consistent findings are that the plasma amino acid concentrations are within normal limits and indeed slightly higher than the levels in the breastfed controls. This again emphasises that 10mg of L-histidine per 100kJ of infant formula is adequate to support infant growth and development.

In the Sandstrom et al (2008) study an infant formula was used with a reported L-histidine level of between 9.6 – 9.8mg, depending if a factor of 6.38 or 6.25 respectively is used in the calculation. This is the lowest level used in an infant formula study and again demonstrates the safety and adequacy of this level. When the plasma amino acid concentrations were tested at both 4 and 6 months, they were both equal or above the levels of the reference group of breastfed infants (Figures 2 & 3).

Figure 2: Plasma levels of L-histidine after 4 months of feeding with different regimens (Sandstrom et al., 2008)

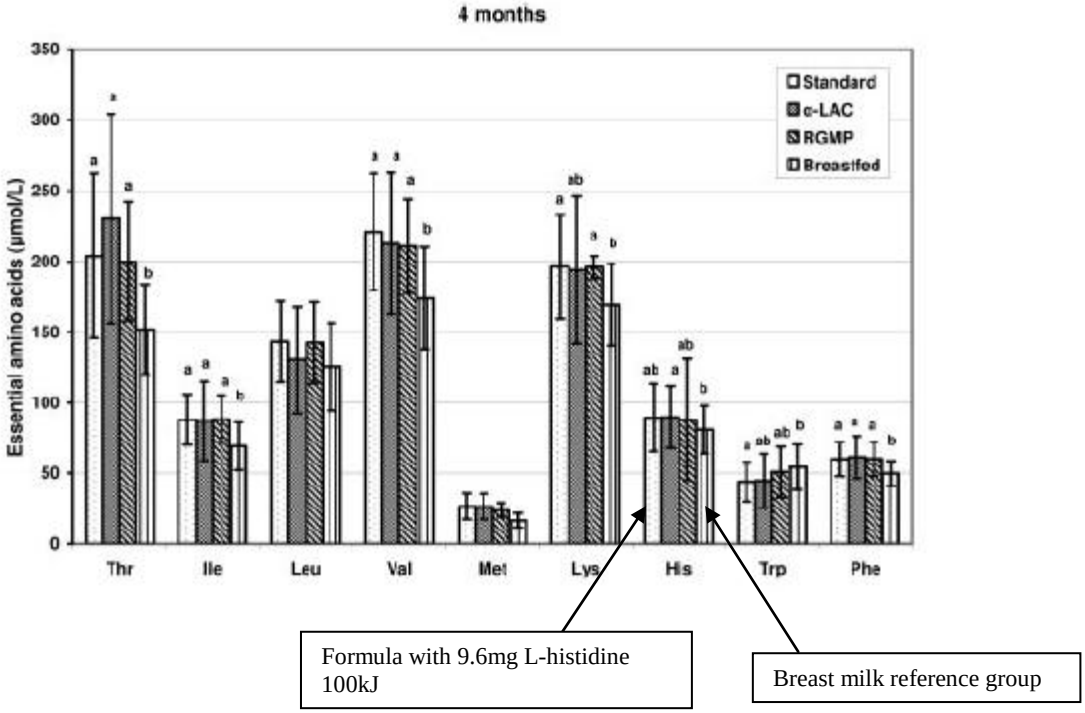
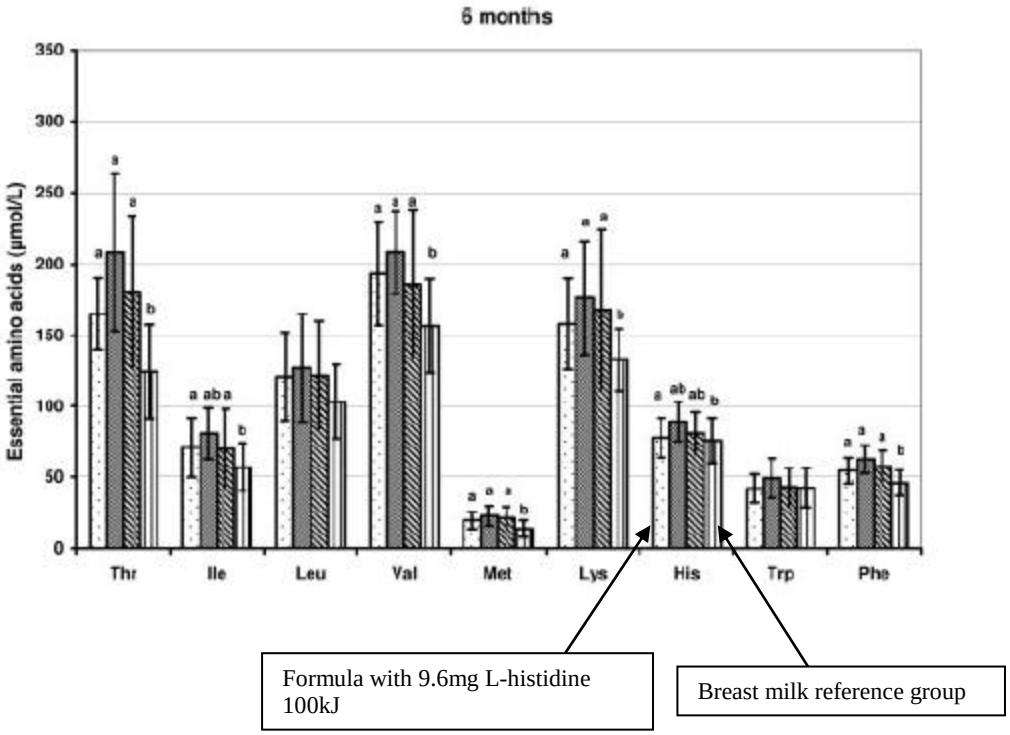


Figure 3. Plasma levels of L-histidine after 6 months of feeding with different regimens (Sandstrom et al., 2008)



It must be noted that in Europe and CODEX markets, 6.25 is now used as the nitrogen conversion factor, whilst Standard 2.9.1 utilises 6.38. The absolute differences were found to be relatively minor. As FSANZ still utilise 6.38, this factor will be the primary one used to report the levels in this submission, but 6.25 will also be mentioned where relevant to allow comparison to the European Union and CODEX.

ii)Promotion of consistency between ANZFSC and CODEX

This application supports the objectives of The Food Standards Australia New Zealand Act 1991 Section 18,(2b) for developing or reviewing of food standards which state that "In developing or reviewing food regulatory measures and variations of food regulatory measures, the Authority must also have regard to... the promotion of consistency between domestic and international food standards"(section 18 (2)).

The proposed change is required to promote ease of trade, international harmonisation and will impose no additional cost or other burden to consumers, industry or regulators. There is evidence to support that the proposed L-histidine levels support normal growth and development in formula fed babies and hence have no negative affect to public health.

As stated above, any change to the L-amino acid requirements in the Table to Clause 22, Standard 2.9.1 would affect infant and follow-on formula as well as specialty formula products. However, for Nestlé, the ability to use a shared recipe for paediatric speciality products with the European Union would improve product offerings for formula fed infants with specific conditions which require speciality products. Existing Nestlé paediatric speciality recipes (shared by the European Union and CODEX markets) are continually being renovated to incorporate the latest research in infant nutrition. Innovations also lead to new products being offered for dietary management of some conditions. We are unable to introduce these new products to the Australian/New Zealand market due to the differing L-histidine requirements, as the higher minimum amount requires most Australian/New Zealand recipes to have L-histidine added as a single amino acid, while CODEX and European Union regulations do not permit addition if the intrinsic (naturally occurring) levels are sufficient. As a result of dis-harmonisation, risks relating to continuation of supply of existing paediatric specialities, as well as introduction of new products, will be challenging. In particular for paediatric speciality products, as these products are required in a relatively small volume for the Australian/New Zealand market so specific recipes are not efficient or possible to produce.

The minimum L-histidine levels in the ANZFSC are inconsistent with international regulation. For example, CODEX requires the mean to be 41mg per 100kcal (9.8 mg per 100kJ) and European Union requires minimum 10mg per 100kJ (91/321/EEC) for non-hydrolysed infant formulas. The proposed reduction of minimum L-histidine levels requirements in the ANZFSC would improve harmonisation with international requirements. Current infant formulas on the market in European Union and CODEX following countries are the result of global research and development and have been demonstrated to produce adequate growth and development of infants.

Harmonisation, particularly to CODEX, will lead to an efficient and internationally competitive food industry as well as fair trading in this category of products. A regulatory environment that is significantly out of step with international standards will lead to a reduced choice and a less competitive marketplace and could inhibit trade and damage established export business. The development and assessment of high quality infant formula is a very expensive and lengthy process and one that must not be compromised. Non-breastfed infants in Australia and New Zealand benefit from the considerable research that is undertaken not only in Australia and New Zealand, but in other parts of the world too. It's important that our local regulatory environment supports the benefits provided by global research and gives consideration to the impacts on global trade and harmonisation with international food standards.

Further to this, the CODEX requirements for L-histidine are based on more recent scientific studies that were not available when the amino acid requirements were developed for ANZFSC Standard 2.9.1. From our systematic review of the L-histidine literature, there is scientific evidence to suggest that a minimum of 10mg of L-histidine per 100kJ of infant formula is safe and will promote normal growth and development in infants.

Regulatory Impact Information

1. Costs and Benefits

(a) Consumer:
Harmonisation of L-histidine levels would allow Australian/New Zealand markets to access a supply of renovated infant speciality products which take advantage of the latest scientific research. As these products often represent the sole source of nutrition to infants with special nutrition requirements, it is likely that their needs match those of other infants worldwide as they do not have any complementary foods to alter their nutrition requirements.

Harmonisation of international requirements will assist with continuation of supply. For Nestlé, a shared recipe with CODEX and European Union countries will ensure that production schedules will more allow more regular and efficient production of paediatric speciality products making the supply of the product more regular. If there is no change to the L-histidine requirements in Standard 2.9.1, the negative affects to the consumer are more likely to be restricted supply which is important to avoid where infant paediatric speciality products may represent the sole source of nutrition for an infant with a specific condition.

As stated in the above section, the proposed value of L-histidine is shown by scientific evidence to support normal growth and development in healthy infants.

(b) Industry

The effect of harmonisation of regulations, particularly where this is a reduction of a minimum of local requirements, is likely to cause nil or positive financial gain. A reduction in the L-histidine level would warrant a change in the list of ingredients for those products which have this single amino acid added, however, we consider the advantages associated with the opportunity of increased innovation and renovation potential, to outweigh the financial impact to industry.

(c) Government
No financial impact is anticipated.

2. Impact on international trade
The impact of the proposed change to L-histidine levels is unlikely to impact negatively on foods imported into Australia and New Zealand. This change would reflect harmonisation of international requirements, which is generally advantageous to international trade. All formulations would continue to be compliant with FSANZ regulations for infant formula products

Assessment Procedure

We consider this assessment to be Level 2 General Procedure with regard to requirements for assessment.

Confidential Commercial Information

No confidential commercial information is included in this application.

Exclusive Capturable Commercial Benefit

There is no Capturable Commercial Benefit claimed for this application.

International and other national standards

1. International Standards

The relevant regulation for those countries which specify L-histidine levels are shown in Table 1. Note that many other countries such as Canada, United States, Singapore and Thailand do not regulate L-histidine levels.

Table 1: International regulation for L-histidine in infant and follow-on formula.

Regulation	Provision relating to L-histidine	
	Infant Formula	Follow-on formula
CODEX i) Standard For Infant Formula and Formulas for Special Medical Purposes Intended for Infants (CODEX STAN 72-1981) Revision 2007 ii) Standard for Follow-Up Formula (CODEX STAN 156-1987)	41 mg/100kcal (equivalent to 9.8 mg/100kJ) (using 6.25 nitrogen conversion factor)	No specific requirement
European Union Commission Directive 2006/141/EC on infant formulae and follow-on formulae	Minimum 10 mg per 100kJ (using 6.25 nitrogen conversion factor)	Minimum 10 mg per 100kJ (using 6.25 nitrogen conversion factor)
China i) GB10765-2010 Infant Formula ii) GB10767-2010 Older infants and young children formula	36.1 mg per 100 kcal (equivalent to 8.6 mg per 100 kJ)	No specific requirement

INFORMATION TO SUPPORT THE APPLICATION

This application addresses criteria from the FSANZ Application Handbook (1 August 2011):

- Section 3.3.3, Nutritive Substances as this application relates to a request to change the permissions for a currently used nutritive substance (in this application, Sections A-E); and
- Section 3.6.2, Special Purpose Foods as this application relates to a request to change the compositional requirements for Infant Formula Products (Standard 2.9.1) (in this application, Sections F-G).

This application is seeking a change to the minimum requirements for L-histidine from 12mg/100kJ to 10mg/100kJ per 100kJ of infant formula. The requirement of L-histidine for normal growth and development of formula fed infants and its safety as a nutritive substance in infant formula is well established. The information below is appropriately limited in some sections where there is a requirement to demonstrate the identity and safety of L-histidine as there is a history of safe and necessary use of this amino acid in infant formula. It will be identified if there is any new information available with regard to L-histidine that is relevant to this application.

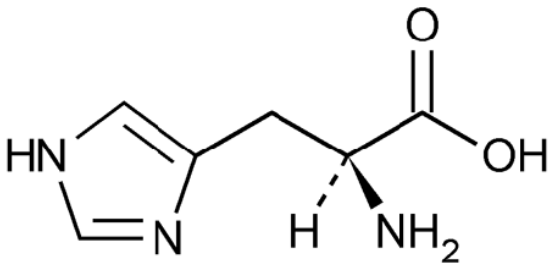
Further, while this is a company-specific application, Nestlé are aware that there is general support from the majority of the infant formula food industry in supporting the principles of harmonisation to CODEX. Specific evidence for this can be seen in the recent Infant Nutrition Council (INC) "Regulatory Position on Food Standards Code, Standard 2.9.1 – Infant Formula Products (dated 15th February, 2012), provided to FSANZ, where L-histidine has been proposed to be included as part of a review to changes to the current Code. Nestlé Australia Ltd & Nestlé New Zealand Limited. are members of the Infant Nutrition Council. The Infant Nutrition Council represents the significant majority of companies marketing and manufacturing infant formula in Australia and New Zealand.

Section A. Technical information on L-histidine

1. *Information to enable identification of the nutritive substance*

i) Chemical name:
L-Histidine (IUPAC)
CAS No. 71-00-1

ii) Structural formula**:** $C_6H_9N_3O_2$



Common name and synonyms**:**
L-Histidine, 2-Amino-3-(1*H*-imidazol-4-yl) propanoic acid, 2-Amino-1*H*-imidazol-4-propanoic acid

iii) Manufacturers code: Not Applicable

iv) Marketing name: Not Applicable

v) CAS registry number**:** 71-00-1

2. *Information on the chemical and physical properties of the nutritive substance*
L-histidine is currently approved for addition to infant formula so further information with regard to this point is not relevant to this Application.

3. *Information on the impurity profile – nature and amounts of all impurities*
L-histidine is currently approved for addition to infant formula so further information with regard to this point is not relevant to this Application.

4. *Manufacturing process*
L-histidine is currently approved for addition to infant formula so further information with regard to this point is not relevant to this Application.

5. *Specification for identity and purity*
L-histidine is currently approved for addition to infant formula so further information with regard to this point is not relevant to this Application.

6. *Analytical method for detection*
L-histidine is currently approved for addition to infant formula so further information with regard to this point is not relevant to this Application

7. *Information on the proposed food label*
L-histidine is a naturally occurring amino acid found in milk, however if the levels naturally occurring in milk used in infant formula are not at sufficient levels then L-histidine will be added as a single ingredient to raise the levels available in the product. In this case, where L-histidine is added as an ingredient, the presence of L-histidine will be declared in the ingredient list (as per requirements of ANZFSC Standard 1.2.4). Where the naturally occurring levels of L-histidine meet the minimum regulatory levels, then L-histidine would not be added as a single ingredient and would not be declared in the ingredient listing. It should be noted that L-histidine amounts in infant formula products are not required to be declared in the Nutrition Information Panel.

Section B. Information related to the safety of L-histidine

L-histidine is an essential amino acid for infants as it is required to meet their physiological needs for tissue deposition and growth. L-L-histidine is currently approved for addition to infant formula therefore safety with regard to addition of L-histidine is not addressed here. The Application requests a decrease in the minimum requirement for L-histidine so we do not consider toxicity associated with maximum levels to be relevant. We would consider safety, for this Application, to be considered in the context of adequate growth and development which has been discussed in preceding sections.

Section C. Information on dietary intake of L-histidine

1. *A detailed list of the food groups or foods proposed to contain the nutritive substance, or changes to currently permitted foods*

This application is relevant to all infant formula products regulated in Standard 2.9.1.

The composition of these products with regard to energy, fat, sodium and energy content are regulated in Standard 2.9.1.

2. *The maximum proposed level of the nutritive substance for each food group or food, or the proposed changes to currently permitted levels*

There is no maximum level stipulated in ANZFSC Standard 2.9.1 (Table to Clause 22) for L-histidine. The current Application reflects the status quo, with the proposed variation to lower the current minimum. L-histidine is naturally occurring in milk however it is supplemented by addition where necessary to meet regulatory requirements.

The minimum amounts of L-histidine consumption have been calculated below for formula to show the differences in minimum consumption for a minimum requirement of L-histidine at both the current requirement for 12mg per 100kJ and the proposed requirement for 10 mg per 100kJ. This calculation uses the mean formula consumption of 750mL from birth to six months as per CODEX[4]. The energy requirement used will be as per Standard 2.9.1 – that is of no less than 2500 kJ/L and no more than 3150 kJ/L in the case of infant formula, and no less than 2500 kJ/L and no more than 3550 kJ/L in the case of follow-on formula.

[4] CODEX Stan 72-1981, Annex II, General Principles for Establishing Minimum and Maximum Values for the Essential Composition of Infant Formula [7(a)] states that "In establishing minimum or maximum amounts of nutrients per 100 kcal (or per 100 kJ) of infant formula based on consideration of reference values for the nutrients expressed as units per daily intake or per kilogram of body weight, the following assumptions will be considered

(a) The mean intake of prepared formula for infants from birth to six months of age is 750 mL per day"

Infant Formula: The current requirement for L-histidine is a minimum of 12 mg/100kJ. This is equivalent to 225 – 284 mg of L-histidine consumed per day when 750mL of infant formula is consumed. If the proposed requirement for a minimum of 10 mg/100kJ is used, the consumption is 188-236 mg of L-histidine per day. It is reasonable to assume that infant formula is the sole source of nutrition.

Follow-on Formula: The WHO recommendation is for complementary foods to be added to an infant's diet from 6 months old. The recommendation, for example for a Nestlé infant formula, is for after the 6th month, for 3-4 formula feeds which would be equivalent to 700mL -920mL of formula per day. Complementary foods (dairy, meat, poultry, fish, rice, wheat, soy) would provide increasing dietary sources of L-histidine as the infants complementary food intake increases. To the best of our knowledge, instances of L-histidine deficiency are not reported. L-histidine from follow on formula, based on 700mL of formula consumer per day, would be 210-265 mg of L-histidine. If the proposed requirements for a minimum of 10 mg/100kJ is used, the consumption of L-histidine from formula is 175 -249 mg of L-histidine.

3. *For foods or food groups not currently listed in the most recent Australian or New Zealand Nutrition surveys, information on likely level of consumption*
Indicative consumption levels for infant formula and follow-on formula are included above.

4. *The percentage of the food group in which the nutritive substance is proposed to be used or the percentage of the market likely to use the nutritive substance*
Not applicable.

5. *Information relating to the use of the nutritive substance in other countries*
L-histidine is an amino acid that is naturally occurring in the milk. CODEX and European Union markets regulates quantities of amino acids for infant formula products. The amino acid L-histidine is to be added only if the naturally occurring levels are insufficient to meet the regulated levels. Many other markets (e.g. USA, Canada, Japan) do not regulate amino acid levels.

6. *For foods where consumption has changed in recent years, information on likely current food consumption*
Not applicable. Infant formula is the sole source of nutrition for fully formula fed babies – therefore, we consider that the consumption pattern is not relevant.

Section D. Information related to the nutritional purpose of adding L-histidine to infant formula

L-histidine has been well described as an essential amino acid that is required by infants for normal growth to occur. It is added to infant formula in order to achieve a similar growth outcome as achieved by the breastfed infant. Recent studies that have used a minimum of less than or equal to 10mg L-histidine per 100kJ of infant formula have been shown to support normal growth in infants, comparable to the breastfed control groups. Furthermore, plasma L-histidine levels have been shown to be higher in the formula fed infants as compared to the breastfed infants (Sandstrom et al. 2008).

Section E. Information related to potential impact on consumer understanding and behaviour

Any change to the minimum requirement for L-histidine levels would be unlikely to affect consumer behaviour. L-histidine levels are not declared on the product label in a Nutrition Information Panel, and only in a statement of ingredients where added. Based on passive surveillance, from data collected from Nestlé consumer care lines, we are not aware of any consumer in the last 3 years, to have contacted Nestlé with regard to a query on L-histidine.

Section F. Information related to general compositional requirements

1. Information related to the safety of the proposed compositional change
L-histidine is currently approved for addition to infant formula. Further information with regard to the safety of the proposed compositional is in the 'Justification i) Safety of Proposed Change' section of this Application.

2. Information related to the nutritional impact or performance impact of the proposed compositional change
Refer to Section C and Section D of this Application.

3. Information related to internationally recognised codes of practice and recommendations/guidelines
Refer to the 'International and Other National Standards ' section of this Application.

Section G. Information related to the dietary intake or dietary exposure

1. *Information on the identity and physical and physiological need of the target population*

The target population affected by this change is formula fed infants. Infants require amino acids to ensure their rapid growth needs are met.

2. *Data to enable the dietary exposure of the target population to be estimated*
Refer to Section C of this Application.

3. *Data on the recommended level of consumption of the special purpose food for the target population*
Refer to Section C of this Application.

REFERENCES

Codex Alimentarius (2007). Standard For Infant Formula And Formulas For Special Medical Purposes Intended For Infants (STAN 72-1981).

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Appendix One: Literature Search

Table One: Search strategy used to systematically search the Medline OVID Database 1948 – 7th October 2011

Term	Number of Abstracts reviewed	Inclusion Criteria	Number of studies reviewed
Search 1: [1] Explode Histidine [2] Explode infant or infant formula Limits: None Combine [1] and [2]	368	Studies were only included in the final review if they: - were conducted in infants or breastfeeding mothers; and specifically examined the metabolism/effects of protein/amino acids or combinations of amino acids of which L-histidine might be one.	7
Search 2: [1] Explode Breast milk or Milk, Human [2] Explode amino acid Limits: None Combine [1] and [2]	664		37
Search 3: [1] Explode toxic [2] Explode histidine [3] Explode amino acid [4] Explode infant Limits: None Combine [1], [2] and [4] Combine [1], [3] and [4]	2		2

Papers Identified by the Literature Search

Search 1:

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CHECKLIST FOR GENERAL REQUIREMENTS

General Requirements (3.1)

3.1.1 Form of application
☑ *Executive Summary*
☑ *Relevant sections of Part 3 identified*
☑ *Pages sequentially numbered*
☑ *Electronic + 2 hard copies*
☑ *Electronic and hard copies identical*
☑ *Hard copies capable of being laid flat*
☑ *All references provided*

☑ 3.1.2 Applicant details

☑ 3.1.3 Purpose of the application

☑ 3.1.4 Justification for the application

☑ 3.2.5 Information to support the application

3.1.6 Assessment procedure
☐ *General*
☐ *Major*
☑ *Minor*

☑ 3.1.7 Confidential Commercial Information
☐ *Confidential material separated in both electronic and hard copy*
☐ *Justification provided*

☑ 3.1.8 Exclusive Capturable Commercial Benefit

☑ 3.1.9 International and Other National standards

☑ 3.1.10 Statutory Declaration

☑ 3.1.11 Checklist/s provided with Application
☑ *3.1 Checklist*
☑ *Any other relevant checklists for Sections 3.2-3.7*

CHECKLIST FOR STANDARDS RELATED TO SUBSTANCES ADDED TO FOOD

Nutritive Substances (3.3.3)

☑	A.1 Identification information	☑	C.2 Proposed maximum levels in food groups or foods
☑	A.2 Chemical and physical properties	☑	C.3 Likely level of consumption
☑	A.3 Impurity profile information	☑	C.4 Percentage of food group to use nutritive substance
☑	A.4 Manufacturing process	☑	C.5 Use in other countries (if available)
☑	A.5 Specification information	☑	C.6 Where consumption has changed, information on likely consumption
☑	A.6 Analytical detection method	☑	D.1 Nutritional purpose
☑	A.7 Proposed food label	☑	E.1 Need for nutritive substance
☑	B.1 Toxicokinetics and metabolism information	☑	E.2 Demonstrated potential deficit or health benefit
☑	B.2 Animal or human toxicity studies	☑	F.1 Consumer awareness and understanding
☑	B.3 Safety assessments from international agencies	☑	F.2 Actual or potential behaviour of consumers
☑	C.1 List of food groups or foods likely to contain the nutritive substance	☑	F.3 Demonstration of no adverse effects on any population groups

CHECKLIST FOR STANDARDS RELATED TO THE COMPOSITION OF FOOD PRODUCTS

Special Purpose Foods (3.6.2)

- ☑ A.1 Safety of proposed compositional change
- ☑ A.2 Nutritional impact of compositional change
- ☑ A.3 Internationally recognised codes of Practice and guidelines
- ☑ B.1 Target population
- ☑ B.2 Dietary exposure information
- ☑ B.3 Level of consumption
- ☑ C.1 Safety and nutritional impact of labelling change
- ☑ C.2 Demonstrated understanding of labelling change (not applicable)
- ☑ C.3 Internationally recognised codes of Practice and guidelines