FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

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23 May 2007

DRAFT ASSESSMENT REPORT

APPLICATION A532

RATIO OF LONG CHAIN POLYUNSATURATED FATTY ACIDS IN INFANT FORMULA PRODUCTS

DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 4 July 2007
SUBMISSIONS RECEIVED AFTER THIS DEADLINE WILL NOT BE CONSIDERED
(See 'Invitation for Public Submissions' for details)

For Information on matters relating to this Assessment Report or the assessment process generally, please refer to http://www.foodstandards.gov.au/standardsdevelopment/

EXECUTIVE SUMMARY

Food Standards Australia New Zealand (FSANZ) received a joint Application from the Infant Formula Manufacturers Association of Australia and the New Zealand Infant Formula Marketers' Association (the Applicant) on 27 February 2004. The Application has requested an amendment to Standard 2.9.1 – Infant Formula Products of the *Australia New Zealand Food Standards Code* (the Code) such that when long chain polyunsaturated fatty acids (LCPUFA) are added to infant formula, the required ratio of omega 6 to omega 3 LCPUFA be a minimum of one.

The Applicant is seeking to change the omega 6 to omega 3 LCPUFA ratio requirement for infant formula on the basis that more recent and relevant scientific evidence has emerged.

It is also argued that promoting consistency between domestic and international food standards is important, and that the current omega 6 to omega 3 LCPUFA ratio of *approximately 2* may pose a technical barrier to trade for Australian and New Zealand manufacturers and importers.

The Applicant also states that no potential infant formula ingredient provides a natural ratio of 2:1 for arachidonic acid (AA, an omega 6 LCPUFA) and docosahexaenoic acid (DHA, an omega 3 LCPUFA).

The specific objectives for the assessment of this Application are therefore to:

- protect the public health and safety of formula-fed infants; and
- promote consistency between domestic and international food standards.

The regulatory options available for Application A532 are to either maintain the *status quo* (Option 1), or amend Standard 2.9.1 such that where LCPUFAs are added to infant formula they must be present in an omega 6 to omega 3 LCPUFA ratio of at least 1 (Option 2).

To meet the above objectives, FSANZ has undertaken a risk assessment of the relevant scientific issues surrounding the addition of LCPUFAs to infant formula. The risk assessment has found that there is little advantage from using one particular omega 6 to omega 3 LCPUFA ratio over another when LCPUFAs are voluntarily added to infant formula.

A cost-benefit analysis has also been undertaken, which shows that Option 1 maintains a unique ratio requirement for Australia and New Zealand, but does not promote consistency between domestic and international food standards. In comparison, Option 2 would continue to protect the health and safety of formula-fed infants and would be more consistent with international food standards. A comparison of options therefore indicates Option 2 provides greater net benefits to all affected parties.

Preferred Approach

Option 2 has been identified as the preferred regulatory approach for Application A532. This approach would result in an amendment to Standard 2.9.1 to require an omega 6 to omega 3 LCPUFA ratio that is *not less than 1*, should LCPUFAs be added to infant formula.

Reasons for the Preferred Approach

The considerations made in reaching FSANZ's preferred approach are as follows:

- the change to the omega 6 to omega 3 LCPUFA ratio does not pose any health and safety risks to formula-fed infants;

- Option 2 is consistent with relevant international regulations currently in place or in draft form; and thus would reduce barriers to trade, increase availability of products and reduce cost for industry and potentially consumers; and

- overall, affected parties will receive a net-benefit from Option 2.

FSANZ therefore recommends the proposed draft variation(s) to the Code that are provided in Attachment 1.

Consultation

FSANZ received a total of 42 submissions over a six week consultation period in response to the Initial Assessment Report. Overall, submitters' views were mixed in relation to a preferred regulatory option. FSANZ has taken these comments into account in preparing the Draft Assessment of this Application.

The majority of submitters supported a change to the current ratio requirement of *approximately 2*. There was a divergence of views in relation to a preferred regulatory option, between retaining some ratio requirement, and deleting subclause 23(d). Of those supporting the retention of a ratio requirement, most favoured a 1:1 ratio.

Public submissions are invited on this Draft Assessment Report.

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INVITATION FOR PUBLIC SUBMISSIONS

FSANZ invites public comment on this Draft Assessment Report based on regulation impact principles and the draft variation/s to the Code for the purpose of preparing an amendment to the Code for approval by the FSANZ Board.

Written submissions are invited from interested individuals and organisations to assist FSANZ in preparing the Final Assessment of this Application. Submissions should, where possible, address the objectives of FSANZ as set out in section 10 of the FSANZ Act. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant studies, research findings, trials, surveys etc. Technical information should be in sufficient detail to allow independent scientific assessment.

The processes of FSANZ are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of FSANZ and made available for inspection. If you wish any information contained in a submission to remain confidential to FSANZ, you should clearly identify the sensitive information and provide justification for treating it as commercial-in-confidence. Section 39 of the FSANZ Act requires FSANZ to treat in-confidence, trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

Submissions must be made in writing and should clearly be marked with the word 'Submission' and quote the correct project number and name. Submissions may be sent to one of the following addresses:

Food Standards Australia New Zealand
PO Box 7186
Canberra BC ACT 2610
AUSTRALIA
Tel (02) 6271 2222
www.foodstandards.gov.au

Food Standards Australia New Zealand
PO Box 10559
The Terrace WELLINGTON 6036
NEW ZEALAND
Tel (04) 473 9942
www.foodstandards.govt.nz

Submissions need to be received by FSANZ by 6pm (Canberra time) 4 July 2007.

Submissions received after this date will not be considered, unless agreement for an extension has been given prior to this closing date. Agreement to an extension of time will only be given if extraordinary circumstances warrant an extension to the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.

While FSANZ accepts submissions in hard copy to our offices, it is more convenient and quicker to receive submissions electronically through the FSANZ website using the Standards Development tab and then through Documents for Public Comment. Questions relating to making submissions or the application process can be directed to the Standards Management Officer at the above address or by emailing slo@foodstandards.gov.au.

Assessment reports are available for viewing and downloading from the FSANZ website. Alternatively, requests for paper copies of reports or other general inquiries can be directed to FSANZ's Information Officer at either of the above addresses or by emailing info@foodstandards.gov.au.

INTRODUCTION

Food Standards Australia New Zealand (FSANZ) received a joint Application from the Infant Formula Manufacturers Association of Australia and the New Zealand Infant Formula Marketers' Association (the Applicant) on 27 February 2004. The Applicant has requested an amendment to Standard 2.9.1 – Infant Formula Products of the *Australia New Zealand Food Standards Code* (the Code). This Draft Assessment Report discusses issues with the proposed amendment, and seeks comment from stakeholders particularly in relation to expected regulatory impact(s), to assist FSANZ in making an assessment of this Application.

1. Nature of the Application

1.1 Basis of the Application

The Applicant initially requested the removal of subclause 23(d) from Standard 2.9.1 of the Code. This subclause requires that if long chain polyunsaturated fatty acids (LCPUFAs) are voluntarily added to infant formula and follow-on formula, then the omega 6 and omega 3 LCPUFAs must be present in a ratio of *approximately 2*. Subsequent to the Initial Assessment, the Applicant modified their original Application so that it now seeks an amendment of subclause 23(d) such that if LCPUFAs are added to infant formula the omega 6 to omega 3 LCPUFAs must be present in a ratio of a minimum of one.

The Applicant's initial request was based on the view that recent scientific evidence no longer supports the requirement for a ratio of omega 6: omega 3 when LCPUFA are added to infant formula.

The Applicant also contends that subclause 23(d) could represent a technical barrier to trade because no proposed international legislation or existing overseas legislation requires such a ratio.

However, the Applicant's position has changed due to a further shift in the scientific debate on LCPUFA additions to infant formula, notably at an international level.

1.2 Scope of Application

This Application pertains solely to infant formula and follow-on formula. Infant formula and follow-on formula are defined in Standard 2.9.1 as follows:

> *Infant formula - means an infant formula product represented as a breast milk substitute for infants and which satisfies the nutritional requirements of infants aged up to four to six months.*
>
> *Follow-on formula - means an infant formula product represented as either a breast milk substitute or replacement for infant formula and which constitutes the principal liquid source of nourishment in a progressively diversified diet for infants aged from six months.*

This Application does not affect 'infant formulas for special dietary use' (e.g. formulas for premature infants and/or those with specific medical conditions).

Clauses 25 and 27(1) of Standard 2.9.1 already provide infant formulas for special dietary use with an exemption from Clause 23(d), by allowing manufacturers to specifically formulate these products to meet unique medical requirements. Therefore, the Applicant's request will not impact on the current regulatory requirements for these products.

This Application also excludes 'formulated supplementary foods for young children' (i.e. a formulated supplementary food for children aged one to three years) otherwise known as 'toddler milk'.

For the purpose of this Report, the term 'infant formula' relates to both infant formula and follow-on formula.

2. Background

LCPUFAs are unsaturated fatty acids with a chain length greater than or equal to 20 carbon atoms[1], and include fatty acids with omega 6 and omega 3 chemical structures. Arachidonic acid (C20:4 omega 6) (AA) and docosahexaenoic acid (C22:6 omega 3) (DHA) are the predominant LCPUFA added to infant formula. The ratio of omega 6 to omega 3 LCPUFAs is 1.5 – 2 in currently available infant formulas.

Humans can only generate omega 6 and omega 3 LCPUFAs from fatty acid precursors. AA can be synthesised from linoleic acid (C18:2) (LA), while DHA is synthesised from alpha-linolenic acid (18:3) (ALA). However, infants appear to have omega 6 and omega 3 LCPUFA requirements that are greater than their LA and ALA conversion processes can provide[2]. It is for this reason that many infant formula manufacturers add LCPUFAs to their products. Also, humans cannot interconvert omega 6 and omega 3 fatty acids (including LCPUFAs), and so a dietary imbalance in these fatty acids can potentially result in a state of nutritional insufficiency[3].

The combination of the inability to interconvert with the potentially higher LCPUFA requirements for infants has produced significant debate over the correct omega 6 to omega 3 LCPUFA ratio that is required in an infant's diet.

2.1 Current Standard

2.1.1 Domestic Regulations

Standard 2.9.1 of the Code regulates the compositional and labelling requirements of infant formula products[4,5]. Subclause 23(d) of Standard 2.9.1 states:

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1 Across the scientific literature, there is variation in the carbon chain length that is used to define 'long chain polyunsaturated fatty acids'. Consistent with Standard 2.9.1 of the Code, LCPUFA are those fatty acids with a chain length of $\geq$ 20 carbon units.

2 Simmer, K. (2001) Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane.Database.Syst.Rev.* (4):CD000376.

3 Mahan, K. and Escott-Stump, S. (2000) Krause's Food, Nutrition and Diet Therapy. 10th ed, Pennsylvania, USA.

4 Infant formula product (as defined in Standard 2.9.1) means a product based on milk or other edible food constituents of animal or plant origin which is nutritionally adequate to serve as the principal liquid source of nourishment for infants.

5 'Infant formula products' refers to all food regulated by Standard 2.9.1.

The fats in infant formula and follow-on formula must –

(d) have a ratio of total long chain omega 6 series fatty acids (C>=20) to total long chain omega 3 series fatty acids (C>=20) of approximately 2 in an infant formula or follow-on formula which contains those fatty acids; and

In addition, the Table to clause 23 prescribes maximum limits for omega 6 LCPUFA, omega 3 LCPUFA and AA of 2%, 1% and 1% of total fatty acids respectively.

2.1.2 Overseas and International Regulations

The European Union have recently revised their infant formula regulations which include requirements on the voluntary addition of LCPUFAs to infant formula and follow-on formula. Clause 5.7 of Annex 1 of the European Commission Infant Formula Directive (2006/141/EC) states that the DHA content of infant formula should not exceed the total content of omega 6 LCPUFA when LCPUFAs are voluntarily added.

Codex Alimentarius is in the process of finalising a draft infant formula standard (ALINORM 05/28/26 Appendix IV at Step 8 [6]). The draft standard currently proposes that if DHA is added to infant formula, then at least the same amount of AA should be added. Codex Alimentarius has a separate standard for 'follow-up formulas' that does not include this requirement.

Aside from European Union and Codex Alimentarius, there are no other overseas or international requirements specific to the LCPUFA contents of infant formula.

2.2 Current Market

2.2.1 Domestic Market

Infant formulas with added LCPUFAs are readily available in Australia and New Zealand. Four major brands supply the market, and all of these brands of infant formula are provided with and without added LCPUFAs. Two of these brands are manufactured in New Zealand using locally produced milk powder, and are subsequently sold in both Australia and New Zealand. The remaining two brands are manufactured overseas and imported into Australia and New Zealand.

The word 'gold' is often used in the product title of infant formulas suitable for term infants, (as sold in Australia and New Zealand) to differentiate products that contain added LCPUFAs and, in some cases, other optional substances such as nucleotides. The cost of these infant formulas is greater than for formulas that do not contain LCPUFAs. Recent national grocery retail sales information indicates Gold products are among the top selling infant formula, with a Gold product ranked at number one in Australia[7].

2.2.2 International Market

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[6] A draft standard is due to go to the Codex Alimentarius Commission in July 2007 for ratification. This draft document includes a clause that states 'If docosahexaenoic acid (22:6 n-3) is added to infant formula, arachidonic acid (20:4 n-6) contents should reach at least the same concentration as docosahexaenoic acid'.

[7] Ranking Report for Grocery Retail, National AZTEC Information Systems, August 2006

It is preferable for companies to manufacture one formulation for worldwide distribution, for cost advantage purposes. However, it appears that products made in or imported into Australia and New Zealand are sold only in these two countries. One reason for this manufacturing practice is the ratio requirement for added LCPUFAs. In addition, the increased cost of the product, partially related to compliance with the required ratio, may limit the sale of these products outside of Australia and New Zealand.

2.3 Historical Background

Prior to the development of the joint Code, there was no regulation on the addition of LCPUFAs to infant formula in either of the previous Australian[8] or New Zealand regulations[9]. Any addition of LCPUFAs would have occurred via the ability to add fish oil as an ingredient to infant formula.

A Proposal was raised to both harmonise and update the regulation of infant formula within Australia and New Zealand, titled Proposal P93 – Review of Infant Formula. At the Preliminary Inquiry Stage of Proposal P93, the requirements for the addition of LCPUFAs were aligned with the maximum level requirements of the European Commission and the United Kingdom (these were the only infant formula regulations at that time with requirements specific to LCPUFAs). An omega 6 to omega 3 ratio was not included as part of these overseas regulations.

The decision to include a ratio was based primarily on the findings by the United States Life Sciences Research Office (LSRO) (Raiten *et al*., 1998b), which suggested that different omega 6 and omega 3 LCPUFA intakes interfere with the infant metabolism of these fatty acids to varying extents. A specific concern was that the addition of DHA alone to infant formula had been identified with a decrease in the serum levels of AA. Based on the results of studies in preterm infants and animals, the LSRO considered that the addition of LCPUFAs at inappropriate levels could pose a safety risk for clinical outcomes, particularly in relation to growth. Therefore, the LSRO recommended against DHA and AA additions to infant formulas at that time (1998), but agreed to reassess the decision within five years.

To accommodate perceived safety issues with the omega 6 and omega 3 LCPUFAs that were already permitted through addition of fish oil ingredients, the Proposal P93 Preliminary Inquiry Report proposed an additional measure of setting the omega 6 to omega 3 LCPUFA content at a ratio of exactly two. This ratio was based on the level identified from human milk analyses[10]. It was recognised at the time that this additional measure was inconsistent with other overseas and international regulations, but was considered necessary to manage a potential risk in a vulnerable population.

During public consultation, comments were received stating that the ratio of omega 6 to omega 3 LCPUFA in human milk is not always exactly two. Consequently, the requirement for a ratio was retained, although the ratio was changed to '*approximately 2*'.

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[8] *Australian Food Standards Code*, up to Amendment 53. These regulations are no longer in force.
[9] *New Zealand Food Regulations 1984*, up to Amendment 10. These regulations are no longer in force.
[10] Forsyth, J.S. (1998) Lipids in Infant Formulas. *Nutr Res Revs* 11:255-278

3. The Problem

Standard 2.9.1 of the Code prescribes that where LCPUFAs (C ≥20) are voluntarily added to infant formula, they must be present in a ratio of omega 6 to omega 3 LCPUFA of *approximately two*. The Applicant states that no potential infant formula ingredient provides a natural ratio of 2:1 for AA and DHA (including human breast milk).

The Applicant is seeking to change the omega 6 to omega 3 LCPUFA ratio requirement for infant formula on the basis that more recent and relevant scientific evidence has emerged. It is argued that promoting consistency between domestic and international food standards is important, and that the current requirement for an omega 6 to omega 3 LCPUFA ratio of *approximately 2*, may pose a technical barrier to trade for Australian and New Zealand manufacturers and importers.

4. Objectives

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives that are set out in section 10 of the FSANZ Act. These are:

- the protection of public health and safety;
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food; and
- any written policy guidelines formulated by the Ministerial Council.

The specific objectives for the assessment of this Application are to:

- protect the public health and safety of formula-fed infants; and
- promote consistency between domestic and international food standards.

5. Key Assessment Questions

The key assessment questions considered at Draft Assessment are:

- What is the range of LCPUFA ratios naturally occurring in human milk, and how do these ratios compare to the omega 6 to omega 3 LCPUFA ratio prescribed in Standard 2.9.1?

- Are there any differences in the growth and development of infants fed formulas with varying ratios of omega 6 to omega 3 LCPUFA?

- What are the risks associated with feeding infants formula containing the singular addition of DHA or AA?

RISK ASSESSMENT

A risk assessment has been conducted at Draft Assessment to determine the risks arising with a change from the current omega 6 to omega 3 LCPUFA ratio of 2, and in doing so to provide a response to the key assessment questions listed above in Section 5. Particular attention has been given to the influence of formulas with different ratios of omega 6 and omega 3 LCPUFA on infant growth and development. The fatty acid profile of human milk and the impact on serum fatty acid levels has also been assessed.

In undertaking this risk assessment, an extensive review of available literature on the addition of LCPUFAs to infant formula has been conducted. Also, the risk assessment has been peer-reviewed by Professor William McLean of Ohio State University and Dr Clare Wall of Massey University to ensure that the available evidence was considered in an objective manner.

The following section summarises the risk assessment's literature review and subsequent analysis and conclusions. The full details of the risk assessment can be found at Attachment 2.

6. Risk Assessment Summary

FSANZ identified 16 randomised controlled trials examining the feeding of LCPUFA enriched infant formula to term infants, at omega 6 to omega 3 LCPUFA ratios of 0.3 to 4.3 (excluding those that added only omega 3 LCPUFAs to infant formula). These studies were used to determine the role that dietary omega 6 and omega 3 LCPUFAs have in the growth and development of infants.

For the most part, the data obtained from the 16 identified studies show little difference in growth or cognitive outcomes when infants are fed formulas with varying levels of added omega 6 and omega 3 LCPUFAs. In particular, the anthropometric data shows that LCPUFA addition to infant formulas has no effect compared to standard formulation. However, the addition of LCPUFAs to infant formula does appear to have some positive, albeit minor influence on the development of visual acuity in infants compared to standard formulations.

Additionally, the fatty acid profile of human milk (from a wide geographical range) shows great variation in omega 6 to omega 3 LCPUFA ratios, and would appear to suggest that infants can tolerate significant variations to this ratio in their milk source.

Overall, there was a consistent lack of influence on infant growth and development from relative variations in the omega 6 and omega 3 LCPUFA contents of infant formulas. In respect to the singular addition of DHA versus the addition of both DHA and AA to infant formula, the evidence base is currently too small to make a definitive analysis.

Due to the minimal influence of LCPUFAs on infant growth and development, it is concluded that there is little advantage from using one particular omega 6 to omega 3 LCPUFA ratio over another when LCPUFAs are voluntarily added to infant formula.

RISK MANAGEMENT

At Draft Assessment, FSANZ has considered the management of any risks identified through the risk assessment and submissions received during the public consultation period.

7. Safety, efficacy and optimal intakes

FSANZ's risk assessment indicates that the relative quantities of added omega 6 and omega 3 LCPUFAs are unlikely to impact on the growth and development of infants. From the available evidence, it would appear that infants can tolerate significant variations in the omega 6 to omega 3 LCPUFA ratio present in infant formula.

The studies reviewed for the risk assessment undertaken by FSANZ, used formulas with omega 6 to omega 3 LCPUFA ratios ranging from 0.3 to 4.3. Therefore, a ratio within this range is considered appropriate. Also, the risk assessment does not identify any safety issues for formula-fed infants if the required omega 6 to omega 3 LCPUFA ratio is changed from *approximately 2*.

However, it would be prudent for AA to be added concurrently with DHA to infant formula, given that there is some uncertainty regarding the singular addition of DHA versus the addition of both DHA and AA to infant formula.

A majority of submitters supported a change to the current requirement of a ratio of omega 6: omega 3 *of approximately 2* when LCPUFA are added to infant formula. Many submitters also considered there is insufficient evidence to establish the safety of the single addition of AA or DHA.

The inclusion of an upper limit for DHA and AA also maintains a level of safety with LCPUFA additions to infant formula. The Code currently sets maximum levels for various LCPUFAs if these are added to infant formula (Standard 2.9.1 Table to Clause 23).

8. Consistency with international regulations

The recently revised draft Codex standard for infant formula recommends that if DHA is added to infant formula, then AA contents should reach at least the same concentration as DHA. It also includes the footnote 'national authorities may deviate from the above conditions, as appropriate for the nutritional needs', indicating that LCPUFA-enriched infant formulas with a range of omega 6 to omega 3 LCPUFA ratios are considered safe and suitable for infants.

The European Union revised ruling, Commission Directive 2006/141/EU on infant formula and follow-on formula, includes a requirement that the DHA content shall not exceed the content of omega 6 LCPUFA.

Many submitters noted the current ratio requirement of omega 6: omega 3 LCPUFA of approximately 2 is inconsistent with international standards. Some industry submitters also noted the unique ratio requirement for Australia and New Zealand creates trade barriers and adds costs for manufacturers and consumers.

Therefore, amending the omega 6 to omega 3 LCPUFA ratio requirement from *approximately 2* to a ratio of *not less than 1*, in the context of the current maximum levels set in Standard 2.9.1, would align with international recommendations and standards and assist to facilitate trade.

9. Options

As a result of the Applicant's revised position since Initial Assessment, FSANZ is proposing the following two options at Draft Assessment for this Application:

9.1 Option 1 – Maintain *status quo*

Maintain the *status quo* by not amending the Code, and thus retaining the requirement for omega 6 to omega 3 LCPUFAs to be present in a ratio of *approximately 2*, when added to infant formula.

9.2 Option 2 – Amend Standard 2.9.1

Amend Standard 2.9.1 to include a requirement that the omega 6 to omega 3 LCPUFA ratio should be *not less than 1* in infant and follow-on formula when LCPUFAs are added to these products, in place of the current ratio requirement of *approximately 2*.

10. Impact Analysis

10.1 Affected Parties

The parties affected by this Application are: **consumers** being formula-fed infants consuming infant formula with added LCPUFAs and their carers; **industry** being Australian and New Zealand manufacturers and importers of infant formula; and the **Government enforcement agencies** of Australia and New Zealand.

10.2 Cost-Benefit Analysis

This analysis assesses the immediate and tangible impacts of the current food standard under Option 1 and the proposed amendment under Option 2.

10.2.1 Option 1 – Maintain Status quo

10.2.1.1 Consumers

Maintaining the *status quo* is likely to have minimal impact on consumers as infant formula with added LCPUFAs will continue to be available. Thus formula-fed infants would continue to have the choice to use these products to gain any potential benefits from LCPUFAs.

However, the cost of these products for consumers is likely to remain higher than for infant formula without added LCPUFAs, due to the increased costs to manufacture to the omega 6 to omega 3 LCPUFA ratio required specifically for Australia and New Zealand. Industry has noted that if higher costs make a product unacceptable to consumers products may be withdrawn from the market, reducing competition. Without competition, industry has suggested formula supplemented with LCPUFAs may become too expensive for the consumer.

In addition the *status quo* may limit the range of products available for formula fed infants due to barriers to importation of products that do not meet the Code, and therefore limit consumer choice.

10.2.1.2 Industry

Maintaining the *status quo* would continue to impact on industry as it is inconsistent with international recommendations and regulations.

As the requirement to meet an omega 6 to omega 3 LCPUFA ratio of *approximately 2* is unique to Australia and New Zealand, the increased cost burden for industry to produce infant formula with added LCPUFAs for this market would remain, with these costs passed onto the consumer. Industry considers prescriptive ratios to be a cost burden to those that manufacture locally but export to markets where the local regulations are not so prescriptive.

In addition, industry notes that if a product is not accepted by consumers because of the greater cost, then competition in the marketplace could reduce as these products may be withdrawn from the market.

Maintaining the *status quo* would retain the current situation of the ratio requirement being a potential technical barrier to trade due to the inconsistency with overseas and international regulations. Some infant formulas are manufactured for worldwide distribution, and Australia and New Zealand is considered a minor market within this global trade. Therefore the industry experiences difficulties from having to manufacture products with added LCPUFAs that are suitable for both local and export markets.

The lack of harmonisation with international regulations and manufacturing requirements also adds cost and complexity to the importation of infant formula products. Australian and New Zealand importers can experience difficulties when seeking to import products that must comply with the Code. Consequently, the variety of infant formula with added LCPUFAs available in Australia and New Zealand could be reduced.

10.2.1.3 Government

The impact of maintaining the *status quo* on the Australian and New Zealand Governments is likely to be minimal, with respect to monitoring and enforcing the omega 6 to omega 3 LCPUFA ratio for infant formula.

10.2.2 Option 2 – Amend Standard 2.9.1

10.2.2.1 Consumers

It is likely that requiring an omega 6 to omega 3 ratio of *not less than 1*, in place of *approximately 2*, would have a minimal impact on the health and safety of consumers of infant formula. Evidence indicates that any impact on growth and development is unlikely to be dependant on the relative quantities of added omega 6 and omega 3 LCPUFAs. Infant formula with added LCPUFAs would continue to be available, consumer choice would remain, and thus enable formula-fed infants to continue to gain any potential benefits from consuming these fatty acids.

As an omega 6 to omega 3 LCPUFA ratio of *not less than 1* would better align with international regulations and could widen trade opportunities, there would be potential for an increased range of products to be available for consumers.

In addition, there may be a cost advantage for manufacturers of infant formula if only one formulation is manufactured for worldwide distribution. This could potentially result in a cost reduction being passed onto consumers.

10.2.2.2 Industry

For industry, replacing the current omega 6 to omega 3 LCPUFA ratio of *approximately 2* with a ratio requirement of *not less than 1* would provide greater harmonisation with the recently proposed Codex recommendations and the current European Union Directive.

The manufacture of one formulation for worldwide distribution provides a cost advantage for companies manufacturing infant formula. The increased costs associated with production of infant formula to meet the current requirements of the Code are likely to reduce as production would not be exclusively for Australia and NZ.

Australian and New Zealand importers may experience less difficulty when seeking to import products that must comply with the Code. Option 2 would reduce manufacturing costs and complexity when importing infant formula products into Australia and New Zealand and allow the importation of a wider range of products.

In addition, infant formula produced locally would be suitable for both local and export markets which will reduce barriers to trade and could potentially increase the sale of these products to countries outside Australia and New Zealand.

10.2.2.3 Government

There is likely to be no impact on the Australian and New Zealand Governments as a result of replacing the current omega 6 to omega 3 LCPUFA ratio of *approximately 2* with a ratio of *not less than 1*.

11. Comparison of Options

A comparison of the Options presented at Draft Assessment indicates that Option 1 would continue to protect the health and safety of formula-fed infants as evidence indicates that an omega 6 to omega 3 LCPUFA ratio of *approximately 2* remains an acceptable ratio. However, as studies show that LCPUFA ratios in breast milk vary and that infants can tolerate significant variations of the omega 6 to omega 3 LCPUFA ratio in their source of milk, there would appear to be no additional benefit in prescribing this specific ratio.

In addition Option 1 is a unique ratio requirement for Australia and New Zealand which does not promote consistency between domestic and international food standards. The omega 6 to omega 3 LCPUFA ratio of *approximately 2* results in trade barriers, increased manufacturing and purchase costs and potentially limits the range of products available to consumers. Overall the costs of maintaining a ratio of *approximately 2* appear to outweigh any benefits.

In comparison, Option 2 would also continue to protect the health and safety of formula-fed infants as evidence indicates an omega 6 to omega 3 LCPUFA ratio of at least 1 is recognised as safe and suitable for infants. Evidence also indicates that any impact on growth and development from LCPUFAs is unlikely to be dependent on the relative quantities of omega 6 and omega 3 LCPUFAs.

Also, a ratio of at least 1 would be more consistent with international food standards, and thus would provide manufacturing, trade and cost benefits to the food industry that would potentially be passed onto consumers.

A comparison of options indicates Option 2 provides greater net benefits than Option 1.

COMMUNICATION

12. Consultation and Communication

FSANZ does not intend to undertake specific communication and consultation work outside of the two statutory public consultation periods. FSANZ will review the nature of the feedback received from submitters to this Draft Assessment, and determine whether additional communication strategies will be required prior to Final Assessment.

12.1 Initial Assessment

FSANZ received a total of 42 submissions[11] in response to the Initial Assessment Report during the six week public consultation period of 31 May to 12 July 2006. A full summary of submissions received and issues raised therein is at Attachment 3.

Submitters' views were mixed in relation to a preferred regulatory option. However, the majority supported a change to the current ratio requirement.

Of the public health and academic submitters (8) a majority favoured the retention of a ratio requirement, with more recommending a 1:1 ratio in preference to the current ratio of *approximately 2*.

Of the industry submitters (12) a majority supported a change to the current requirement in the Code. However, there was a divergence of views between retaining a ratio and the removal of sub-clause 23(d) from Standard 2.9.1. Of those supporting the retention of a ratio, most favoured a 1:1 ratio. Some submitters recommended a different omega 6 to omega 3 LCPUFA ratio for follow-on formula (infants over 6 months of age).

The three Government submitters supported different options including retaining the *status quo*, Option 2, and the retention of an omega 6 to omega 3 LCPUFA ratio that is different to the current requirement of *approximately 2*.

The preferred option of the two consumer submitters differed, but neither supported retaining the *status quo*.

12.2 Draft Assessment

FSANZ is now seeking comment in relation to this Draft Assessment Report. Comments received in response to this report will be used to assist in the development of a Final Assessment Report.

Submitters are invited to provide comment in relation to issues discussed in this report and the proposed regulatory options, and potential impacts in relation to these options.

12.3 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

Currently some relevant international Standards are in place or in development. Modifying Standard 2.9.1 of the Code by reducing the omega 6 to omega 3 LCPUFA ratio from *approximately 2* to at least 1 will make Australian and New Zealand food standards consistent with EU infant formula legislation and the draft Codex infant formula standard**.**

[11] Seventeen submissions were received from university students, most identified as students of Food Science at the University of Auckland, New Zealand. The submissions generally favoured Option 2 supporting the removal of the current clause requiring a ratio of approximately 2.

It is expected that the proposed changes will harmonise Australian and New Zealand regulations with current and future international practices, and therefore will not result in a potential barrier to trade. As such, WTO member nations will not be notified of the proposed amendment to Standard 2.9.1 under either the Technical Barriers to Trade or Sanitary and Phytosanitary Agreements.

CONCLUSION

13. Conclusion and Preferred Approach

Preferred Approach

Option 2 has been identified as the preferred regulatory approach for Application A532. This approach would result in an amendment to Standard 2.9.1 to require an omega 6 to omega 3 LCPUFA ratio that is *not less than 1*, should LCPUFAs be added to infant formula.

The considerations made in reaching this preferred approach are as follows:

- the change to the omega 6 to omega 3 LCPUFA ratio does not pose any health and safety risks to formula-fed infants;
- Option 2 is consistent with relevant international regulations currently in place or in draft form; and thus would reduce barriers to trade, increase availability of products and reduce cost for industry and potentially consumers; and
- overall, affected parties will receive a net-benefit from Option 2.

FSANZ therefore recommends the proposed draft variation(s) to the Code that are provided in Attachment 1.

14. Implementation and Review

Following the consultation period for this document, a Final Assessment of the Application will be completed and considered for approval by the FSANZ Board. The FSANZ Board's resulting decision will then be notified to the Ministerial Council.

Following notification, the proposed draft variation to the Code is expected to come into effect on gazettal, subject to any request from the Ministerial Council for a review of FSANZ's decision.

Attachments

1. Draft variation to the *Australia New Zealand Food Standards Code*.
2. A Review of the Long Chain Polyunsaturated Fatty Acid Content of Infant Formula and its Effects on the Growth and Development of Infants
3. Summary of Submissions from the Initial Assessment Report

Attachment 1

Draft variation to the *Australia New Zealand Food Standards Code*

To commence: On Gazettal

[1] ***Standard 2.9.1*** *of the Australia New Zealand Food Standards Code is varied by omitting from subclause 23(d)* of approximately 2 *substituting –*

that is not less than 1

Attachment 2

A Review of the Long Chain Polyunsaturated Fatty Acid Content of Infant Formula and its Effects on the Growth and Development of Infants

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Executive Summary

Food Standards Australia New Zealand (FSANZ) identified 16 randomised controlled trials examining the feeding of Long Chain Polyunsaturated Fatty Acid (LCPUFA) enriched infant formula to term infants at omega 6 to omega 3 LCPUFA ratios of 0.3 to 4.3 (excluding those that added only omega 3 LCPUFAs to infant formula). These studies were used to determine the role that dietary omega 6 and omega 3 LCPUFAs have in the growth and development of infants.

For the most part, the data obtained from the 16 identified studies show little difference in growth or cognitive outcomes when infants are fed formulas with varying levels of added omega 6 and omega 3 LCPUFAs. In particular, the anthropometric data show that LCPUFA addition to infant formulas has no effect compared to standard formulation. However, the addition of LCPUFAs to infant formula does appear to have some positive, albeit minor influence on the visual development of infants compared to standard formulations.

Additionally, the fatty acid profile of human milk (from a wide geographical range) shows great variation in omega 6 to omega 3 LCPUFA ratios, and would appear to suggest that infants can tolerate significant variations to this ratio in their milk source.

In all measures of assessment, there is a consistent lack of influence on infant growth and development from relative variations in the omega 6 and omega 3 LCPUFA contents of infant formulas. In respect to the singular addition of DHA versus the addition of both DHA and AA to infant formula, the evidence base is currently too small to make a definitive analysis.

It is therefore concluded that there is little advantage from using one particular omega 6 to omega 3 LCPUFA ratio over another when LCPUFAs are voluntarily added to infant formula.

1. Introduction

FSANZ received a joint Application from the Infant Formula Manufacturers Association of Australia and the New Zealand Infant Formula Marketers' Association on 27 February 2004. The Application has requested an amendment to Standard 2.9.1 – Infant Formula Products of the *Australia New Zealand Food Standards Code* (the Code); which is intended to modify the current omega 6 to omega 3 long chain polyunsaturated fatty acid (LCPUFA)[12] ratio of *approximately 2* in infant formula (which contain added LCPUFAs).

To progress this Application, FSANZ has undertaken a review of the available literature on the addition of LCPUFAs to term infant formula. This review will determine the influence on the growth and development of infants from formula with different ratios of omega 6 and omega 3 LCPUFA contents.

In undertaking this assessment, literature has been sourced from the following locations:

- PubMed electronic databases, using the search terms 'infant formula AND long chain AND growth' and 'infant formula AND long chain AND development'; and

- Primary research material from review articles by Makrides *et al.* (2000a), Makrides *et al*. (2005), and Fleith and Clandinin (2005).

From this evidence base, FSANZ has excluded studies conducted on pre-term infants, studies that did not commence formula intervention within two weeks of birth, and those studies that did not include an assessment of either anthropometric, visual acuity or behavioural parameters. These exclusions ensure that the evidence base specifically addresses the health outcomes from the addition of LCPUFAs to formulas for term infants.

Twenty-two published articles were obtained using the above search strategies, and these articles discuss the findings of 16 studies (several articles report different aspects of the same study). These studies had the following characteristics:

- all of the trials compare LCPUFA enriched formula to a control of standard infant formula. The standard formulas were commercially available products that would have met the requirements of the Code at the time of the study;

- allocation to different formula types was random and double-blinded in all trials; and

- for those studies assessing visual acuity and/or neurological development, the parental educational level/socioeconomic status was homogenous across all groups (these data were not collected by studies that assessed anthropometric endpoints only).

Full details of the 16 studies can be found in Tables A1-A5 at the end of this document. The following sections discuss the results of these studies and the implications of this research for the addition of LCPUFAs to infant formula.

[12] Consistent with Standard 2.9.1 of the Code, this report classifies LCPUFAs as polyunsaturated fatty acids with a chain length of $\geq$ 20 carbon units.

2. Findings of studies on the addition of LCPUFAs to infant formula

Of the 16 studies identified by FSANZ, most involved comparisons (over time) between different types of infant formula with either docosahexaenoic acid (DHA) added alone, or DHA added with arachidonic acid (AA) in AA to DHA ratios of 0.3:1 to 4.3:1[13].

Ten of these studies also included a non-randomised group of infants who were breast-fed over the same time period as the formula groups. Because these groups are non-randomised, there are maternal variables associated with the decision to breastfeed that could have potentially contributed to differences between formula-fed and breast-fed groups. These variables include maternal intelligence quotient (IQ), education level, and socioeconomic status; maternal-infant interaction; and the act of breast-feeding itself. However, breast-fed infants are considered to be an important reference group for use in infant feeding studies (Birch *et al*., 2007), and so the human milk results have been discussed below even though it is not the intent of this report to assess the overall performance of infant formula versus human milk.

2.1 The impact on infant growth

Thirteen of the 16 studies reported assessments of infant growth parameters, e.g. weight, length, or head circumference. Nearly all of these studies show that the addition of LCPUFAs to infant formula has no effect on growth (either positive or negative) compared to standard formula, regardless of whether this addition consists of DHA alone, or both DHA and AA (at varying ratios).

Three articles (Agostoni *et al*., 1994; Lapillonne *et al*., 2000; Morris *et al*., 2000) did report a significant difference in either weight or head circumferences. In two of these articles (Agostoni *et al*., 1994; Morris *et al*., 2000), the significant differences between study groups occurred only at birth and not at later ages (4 and 12 months); thus there was no demonstrable effect of diet. These differences at birth could reflect a problem with the studies' randomisation processes, although it is more likely that the results reflect the small sample sizes used in both studies (n=15-23 for Agostoni *et al*., and n≈55 for Morris *et al*.).

Lapillonne *et al*. (2000) reported a significant difference ($p<0.05$) of 1.4 cm in the mean head circumference between study groups at 4 months. However, the difference was due to an increased head circumference in the control (standard) formula group compared to the test (DHA modified) formula groups, rather than the reverse. The article also reported that the head circumference results of the test formula group were statistically equivalent to the results for a cohort of breast-fed infants used in the study. The authors of this paper do not give any explanation for the unusual control group results.

2.2 The impact on development of visual acuity

Eight of the 16 studies (reported in 9 articles) have investigated the impact from LCPUFA enriched infant formula on the development of visual acuity in infants (Makrides *et al*., 1995a; Carlson *et al*., 1996; Auestad *et al*., 1997; Birch *et al*., 1998; Jorgensen *et al*., 1998; Hoffman *et al*., 2000; Makrides *et al*., 2000b; Auestad *et al*., 2001; Birch *et al*., 2005).

[13] AA and DHA are the predominant omega 6 and omega 3 LCPUFAs added to infant formula respectively. Other omega 6 and omega 3 LCPUFAs can be added, however their addition is not considered commercially viable.

These eight studies measured visual acuity using either behavioural, visual evoked potential (VEP) or stereoacuity tests[14].

The majority of the eight visual acuity studies did not demonstrate a significant effect of LCPUFA supplementation over standard formula using either behavioural or VEP assessment techniques (Carlson *et al.,* 1996; Auestad *et al.,* 1997; Birch *et al.,* 1998; Jorgensen *et al.,* 1998; Hoffman *et al.,* 2000; Makrides *et al.,* 2000b; Auestad *et al.,* 2001). Also, Birch et al. (2007) conducted a follow-up study of the results presented in Birch et al. (1998), and found that LCPUFA supplementation continued to have no significant impact on the visual acuity of the cohort up to 4 years of age. Singhal et al. (2007) also followed-up an infant cohort previously assessed on anthropometry and neurological development (Lucas *et al*., 1999), and also found that LCPUFA supplementation had no significant impact on stereoactuity up to 6 years of age.

However, there were three studies (Makrides *et al.,* 1995a; Birch *et al.,* 1998; Hoffman *et al.,* 2000; Birch *et al.,* 2005) that reported a positive effect when using VEP techniques. These three studies showed significantly higher ($p<0.05$) changes in VEP of -0.8 to -0.2, -0.3, and -0.14 LogMAR[15] with the consumption of LCPUFA enriched formula at 4, 6 and 12 months of age respectively. Birch *et al*. (2005) also reported a benefit in stereoacuity (of 0.1 LogSec[16]) at 4 months, but not at any other age.

Overall, significant improvements in visual acuity from the use of LCPUFA enriched formula were predominantly identified with the use of VEP techniques, while non-significant results were predominantly associated with behavioural assessments of visual acuity. This pattern may be the result of the problems inherent in the use of behavioural assessments, which rely on an individual's subjective evaluation of an infant and are thus exposed to a greater level of observer error (Birch *et al.,* 1998). The influence of these errors could have overwhelmed any small differences that occurred during the behavioural assessment studies. Because of their increased sensitivity, the VEP derived results are therefore considered to have greater weight than behaviourally assessed results.

2.3 The impact on neurological development

The infant formula research identified by FSANZ has utilised a wide range of techniques for evaluating the neurological performance of infants. The most common of these techniques is the Bayley Scales of Infant Development (Bayley, 1993), which are highly refined and accurate tests on the cognitive, motor, and behavioural development of infants. A similar test designed for Western European languages, the Brunet-Lezine test, was used by Agostoni *et al.* (1994). The MacArthur Communicative Development Inventories have also been used by Scott *et al.* (1998) to assess language development, while Willatts *et al.* (1998) used a means-end problem solving test to evaluate cognitive behaviour.

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[14] In considering the results it should be noted that an improvement in visual acuity, as measured by either a behavioural assessment (e.g. forced preferential looking) or VEP assessment, is reflected by lower values. Improvements in stereoacuity results are, however, reflected by higher values.

[15] Logarithm_{10} of the eye's minimum angle of resolution. The minimum angle of resolution (measured in minutes) can be derived from the reciprocal of a Snellen notation; e.g. 20/25 vision = 1.25 minutes = 0.1 LogMAR.

[16] Logarithm_{10} of an arcsecond

A number of the studies assess neurological endpoints beyond the ages of 0-12 months, as neurological development is more consistent after infancy. At these later ages, the subjects are on a full solid diet, and are no longer consuming the test formulas. However, it is reported that nutrition during infancy can continue to have an effect on neurological performance beyond the immediate time period (Birch *et al.,* 2000), and therefore an assessment of the later age results (12-24 months) has been included in this report.

Of the eight studies assessing cognitive development (Agostoni *et al.,* 1994; Agostoni *et al*., 1997; Scott *et al*., 1998; Willatts *et al*., 1998; Lucas *et al.,* 1999; Birch *et al.,* 2000; Makrides *et al*., 2000c; Auestad *et al.,* 2001), a substantial proportion do not show any difference (at various ages) between infants fed standard formula or formula with added LCPUFAs, even with the use of different omega 6 to omega 3 LCPUFA ratios across the studies. Four studies (Agostoni *et al.,* 1994; Scott *et al*., 1998; Willatts *et al*., 1998; Birch *et al.,* 2000) reported differences between the various formula study groups, but only at single age points.

An assessment of neurological development by Birch *et al.* (2000), using the Bayley Mental Development Index (MDI), showed that at 18 months of age, children who were fed formula in infancy with added LCPUFAs had significantly better scores ($p<0.05$) than those who had been fed standard formula (normative MDI scores of 105.6 and 98.3 respectively). However the psychomotor and behavioural Bayley tests did not show a similar difference. The authors also noted that their assessments of visual acuity at 4 months (see Section 2.2 above) correlated well with the Bayley assessment results at 18 months, suggesting that LCPUFAs could affect cognitive development at an early age.

Using the Brunet-Lezine test, Agostoni *et al.* (1994) showed that at the age of 4 months, infant formula with added DHA and AA resulted in significantly better ($p<0.05$) neurodevelopment than standard formula (normative scores of 105.3 and 96.5 respectively). However, in a follow-up study at 24-months of age (Agostoni *et al*., 1997), the authors found that there was no longer any significant difference in neurological performance between the different study groups.

A study conducted by Scott *et al.* (1998) obtained some disconcerting results with the MacArthur Communicative Development Inventories. It was shown that subjects fed formula with the singular addition of DHA obtained significantly lower scores ($p<0.05$) on the vocabulary comprehension and production components of the test at 14 months of age than subjects fed standard formula. The DHA and AA supplementation group did not, however, differ significantly ($p>0.05$) from the standard formula group or the concurrently studied breastfed reference group.

Willatts *et al.* (1998) took a different approach to assessing neurological development, using a test of problem solving ability rather than focusing on measurements of perception and motor skills. Significant improvements ($p<0.05$) were shown with LCPUFA-enriched formula versus standard formula for the overall test, although this improvement occurred only in one of the three behaviour subsets of the test.

In addition to the above evidence, FSANZ has identified that both Scott *et al.* (1998) and Birch *et al.* (2000) continued to follow their infant cohorts into early childhood (Auestad *et al*., 2003; Birch *et al*., 2007).

The follow-up studies assessed the IQ of their cohorts at between the ages of 3-4 years using standardised techniques, and found no significant difference ($p>0.05$) between the children who had been fed LCPUFA enriched formula and those fed standard formula during infancy.

3. Findings from studies that compare the singular addition of omega 3 LCPUFAs to the addition of both omega 6 and omega 3 LCPUFAs

FSANZ has identified four studies (reported in eight articles) that have directly compared formula containing DHA alone with formula containing DHA in combination with AA in term infants (Auestad *et al*., 1997; Birch *et al.,* 1998; Scott *et al.,* 1998; Makrides *et al*., 1999; Birch *et al.,* 2000; Hoffman *et al.,* 2000; Makrides *et al.,* 2000c).

Three of the four studies, with participant numbers ranging between 58 - 200, did not find any difference in growth, visual acuity or cognitive outcomes up to 2 years of age between infants fed formula with added DHA only or containing both added DHA and AA. Only one study of 68 infants fed a test diet for 17 weeks (Scott *et al.,* 1998) reported a significant difference between the consumption of formula with the singular addition of DHA versus the addition of DHA and AA together (AA to DHA ratio of 3.6:1).

As mentioned in Section 2.3 above, the study by Scott *et al.* (1998) showed that infants fed formula with the singular addition of DHA had lower vocabulary productions scores (MacArthur Communicative Development Inventories) at 14 months of age than infants fed standard formula; a result that did not occur if AA was added with DHA. However, other skills assessed with the MacArthur Communicative Development Inventories, such as gestural communication and the number of phrases understood by the child (vocabulary comprehension), were not adversely affected by the addition of DHA alone compared to the addition of both DHA and AA. Also, Scott *et al.* (1998) assessed subjects at 12 months of age using the Bayley Scales of Infant Development, and found that the type of formula they consumed since birth had no effect on these tests of cognitive development, regardless of the formula's DHA or AA content.

To explain the reasons for their findings, the authors also analysed the serum DHA levels of their subjects. It was found that serum DHA levels were negatively correlated with the vocabulary scores across all feeding regimes. The authors were therefore unwilling to dismiss the results as the product of either chance or the absence of AA from test formulas. Further, results from the follow-up of the Scott *et al.* (1998) cohort at three years of age found that there was no significant difference ($p>0.05$) in cognitive performance between the various feeding regimes (Auestad *et al.,* 2003).

4. Analysis of the findings on omega 6 and omega 3 LCPUFA addition to infant formula

Although a formal meta-analysis was not conducted, the data obtained from the 16 identified studies show little difference in growth or neurological outcomes when infants are fed formulas with varying levels of added omega 6 and omega 3 LCPUFAs. In particular, the anthropometric data show no consistent diet-related effect from the addition of LCPUFAs to infant formula. However, the addition of LCPUFAs to infant formula has been reported in some studies to have a positive influence on the visual development of infants compared to standard formulations. Other studies have not found positive effects on visual acuity.

However, there are exceptions to the visual and neurological development trends that warrant further discussion.

A study of note is that conducted by Auestad *et al.* (2001), which showed no improvement in visual acuity from LCPUFA enriched formula compared to standard formula. This particular study is significant in that it has used the greatest number of subjects (n = 177) of all of the studies that have assessed visual acuity, and thus has the greatest statistical power of these studies. Further, the authors made efforts to remove a number of common methodological errors associated with other infant formula trials, including an analysis of variance to limit errors from the use of multiple examination centres, and the use of two different LCPUFA ingredient sources to ensure that results were not due to the origin of added LCPUFAs. Because of these additional quality controls, the results from Auestad *et al*. (2001) can be considered as highly reliable, even though the study contradicts the positive outcomes from several other studies (Makrides *et al.,* 1995a; Birch *et al.,* 1998; Hoffman *et al.,* 2000; Birch *et al.,* 2005).

An important exception in respect to neurological development is the study by Scott *et al.* (1998). The lower vocabulary production scores of 14 month-old infants fed formula with DHA as its only source of LCPUFAs, compared to 14 month-old infants fed formula containing both DHA and AA, is in contrast to all other studies assessing neurological development and/or comparing these two formula variations. A possible explanation identified by Birch *et al.* (2000) is that the quantity of DHA added to the DHA-only formula (0.23% by weight) was too low; all other studies comparing DHA-only formula to formula with both DHA and AA have used a minimum DHA content of 0.35% by weight in the DHA-only formula. Birch *et al.* (2000) also mentions that another possible reason is that Scott *et al*. (1998) used multiple examiners to conduct the cognitive tests, which could have increased the statistical variability within the study's results. However, it may be that the use of an additional methodology by Scott *et al*. (1998) has identified an effect on a seldom researched aspect of cognition, and therefore is not comparable to other studies on neurological development.

Overall, the quality of research within the evidence base on omega 6 and omega 3 LCPUFA addition to infant formula is high. The main deficiencies encountered can be summarised as:

- The small sample sizes. Most studies had fewer than 20 subjects allocated to each of their feeding regime groups, and only three studies have examined a total subject population of more than 150 subjects (Carlson *et al*., 1999; Lucas *et al*., 1999; Auestad *et al.,* 2001). The reduced statistical power of the evidence base means that there is a greater level of uncertainty associated with the findings from this literature.

- Inconsistencies in the amount of linoleic acid and alpha-linolenic acid within test formulas (variations of 8.37-34.2% wt and 0.7-5.0% wt respectively). As precursors of DHA and AA, variations in these fatty acids could potentially result in different outcomes when DHA and/or AA are added to test formulas.

- Inconsistencies in the ages for testing, and in the methodologies used to assess study endpoints.

- The lack of correction for baseline anthropometric data.

Even with these deficiencies, the totality of evidence suggests that the addition of LCPUFAs to infant formula has a minimal impact on the growth and development of infants. The only potential benefit from LCPUFA addition would appear to be an improvement in the development of visual acuity, although currently available data remains conflicting on this health outcome. Further, in all measures of assessment, there is a consistent lack of influence on infant growth and development from relative variations in the omega 6 and omega 3 LCPUFA contents of infant formulas.

In respect to the singular addition of DHA versus the addition of both DHA and AA to infant formula, the evidence base is currently too small to make a definitive analysis. What little data there are suggest that the singular addition of DHA to infant formula is as efficacious as the dual addition of DHA and AA to infant formula, and that there is no real effect – either positive or negative – on infant growth and development.

5. Other relevant issues

5.1 Systematic reviews of LCPUFA addition to term infant formula

FSANZ has identified several systematic reviews of the literature on the addition of LCPUFAs to term infant formula (SanGiovanni *et al*., 2000; Simmer, 2001; Makrides *et al*., 2005; Fleith and Clandinin, 2005). These meta-analyses have been conducted using different selections of studies and focus on different aspects of infant growth and development; however they conclude that LCPUFA-enriched formula has no effect on infant growth, and that there is too much uncertainty in the data to demonstrate a positive effect on infant visual and neurological development.

5.2 Human milk omega 6 and omega 3 LCPUFA content

The Australia New Zealand Food Standards Code prescribes an omega 6 to omega 3 LCPUFA ratio of *approximately 2* if LCPUFAs are added to infant formula. This ratio was based on an assumption made by the Life Sciences Research Office (Raiten *et al*., 1998) that the ratio of omega 6 to omega 3 LCPUFAs in human milk remains relatively constant. However, more recent published data does not support that assumption.

Data from 20 separate papers reporting analyses of human milk from different geographical regions (and thus different maternal dietary patterns) shows that AA content varies to a small extent, while DHA content varies to a much greater degree (see Figures A1-A3 at the end of this attachment). The result is an omega 6 to omega 3 LCPUFA ratio that fluctuates widely depending on the diet of the mother and the stage of lactation.

Given the geographical diversity in these data, including representation from both developing and developed nations, it would appear that infants can tolerate significant variations to the omega 6 to omega 3 LCPUFA ratio of their milk source.

5.3 Impact on infant biochemistry

It has been reported that if DHA is used as the only source of added LCPUFAs in infant formula, then the feeding of this formula to infants will produce a significantly reduced red blood cell AA level compared to infants fed standard infant formula (Auestad *et al.,* 1997; Makrides *et al*., 2005).

However, the singular addition of DHA ensures that an infant's red blood cell DHA levels remain at a similar or even higher level than those of breast-fed infants.

The results of many studies show that if AA is added with DHA, then the red blood cell AA can be retained at a level commensurate with breast-fed infants (Fleith and Clandinin 2005).

It is therefore clear that the absence of either omega 6 or omega 3 LCPUFAs from infant formulas will be reflected in the DHA and AA status of infants fed such formulas. However, it is not clear whether variations in the DHA and AA status of infants fed formulas with varying AA to DHA ratios will affect the growth and development of these infants. The only study that has shown an impact on growth and development from differing ratios (Auestad *et al.,* 1997) reported a decrease in the AA status of its DHA alone group versus its DHA and AA group, however the serum AA data were not cross-referenced with the study's growth and development outcomes.

6. Conclusion

The studies identified by FSANZ show that the addition of LCPUFAs to infant formula has no effect on the growth of infants, and at most, a minimal and variable effect on the visual and neurological development of infants. Further, this evidence indicates that any impact on growth and development is unlikely to be dependent on the relative quantities of added omega 6 and omega 3 LCPUFAs (within the ranges studied). It is uncertain what effect, if any, the consumption of formula containing DHA alone has on infants versus the consumption of formula with both added DHA and AA, although the currently available evidence suggests that infants do not experience any adverse health effects from the singular addition of DHA to infant formula.

There does not, therefore, appear to be any advantage from using one particular omega 6 to omega 3 LCPUFA ratio over another within the range of 0.3:1 to 4.3:1, or even from adding AA concurrently with DHA.

Table A1: Methodology and design of studies on the LCPUFA content of infant formulas (0-12 months of age)

Study	Methods	Study Duration	Study Endpoints	Subject Groupings		Infant Dietary Regime Details*				
				Infant Dietary Regime	n	Omega 6 LCPUFA (% wt)	Omega 3 LCPUFA (% wt)	Omega 6: Omega 3 Ratio	Linoleic Acid (% wt)	Alpha-linolenic Acid (% wt)
Agostoni *et al.* (1994; 1995; 1997).	Randomisation into control and LCPUFA formula groups. Breast-fed infants were used as a matched negative control. Randomisation, intervention and assessment were blinded.	0-4 months (Agostoni *et al.,* 1994; Agostoni *et al*., 1995); 4-24 months (Agostoni *et al.,* 1997)	• Assessment of weight, height and head circumference at 4 months. • Assessment of Brunet-Lezine test at 4 and 24 months.	Human Milk	15	n/a	n/a	n/a	n/a	n/a
				Standard formula	21	0	0		11.1	0.70
				Std + DHA + AA	23	0.44	0.35	1.3:1	10.8	0.73
Auestad *et al.* (1997); Scott *et al*. (1998)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months	• Assessment of weight, height and head circumference at 4 and 12 months (Auestad *et al.,* 1997). • Assessment of visual acuity at 4, 6 and 12 months (Auestad *et al.,* 1997). • Assessment of Bayley Scales of Infant Development at 12 months (Scott *et al.,* 1998).	Human Milk	63	1.2	0.9	1.3:1	17.2	1.8
				Standard formula	45	0	0		21.9	2.2
				Standard + DHA	43	0	0.23		20.7	1.9
				Std + DHA + AA	46	0.43	0.12	3.6:1	21.7	1.9

Study	Methods	Study Duration	Study Endpoints	Subject Groupings		Infant Dietary Regime Details*				
				Infant Dietary Regime	n	Omega 6 LCPUFA (% wt)	Omega 3 LCPUFA (% wt)	Omega 6: Omega 3 Ratio	Linoleic Acid (% wt)	Alpha-linolenic Acid (% wt)
Auestad *et al.* (2001)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months	• Assessment of weight, height and head circumference at 4, 6 and 12 months. • Assessment of visual acuity at 2, 4, 6 and 12 months. • Assessment of Bayley Scales of Infant Development at 6 and 12 months.	Human Milk	165	0.51	0.12	4.3:1	16.6	1.3
				Standard formula	77	0	0		22.2	2.6
				Std + DHA + AA (fish/fungal)	80	0.46	0.16	2.9:1	21.0	2.4
				Std + DHA + AA (egg)	82	0.45	0.14	3.2:1	22.4	2.5
Birch *et al.* (1998; 2000); Hoffman *et al.* (2000)	Randomisation into control and LCPUFA formula groups. Intervention and assessment were blinded.	0-12 months; 12-18 months (Birch *et al.,* 2000)	• Assessment of weight, height and head circumference at 4, 6 and 12 months. • Assessment of visual acuity at 4, 6 and 12 months. • Assessment of Bayley Scales at 18 months.	Human Milk	29	0.56	0.29	1.9:1	12.7	0.80
				Standard formula	23	0	0		14.6	1.49
				Standard + DHA	22	0	0.35		15.1	1.54
				Std + DHA + AA	23	0.72	0.36	2:1	14.9	1.53
Birch *et al*. (2005)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	12 months	• Assessment of visual acuity at 4 and 12 months. • Assessment of stereoacuity at 4, 10 and 12 months.	Standard formula	44	0	0		8.48	0.86
				Std + DHA + AA	42	0.43	0.21	2:1	8.37	0.86

Study	Methods	Study Duration	Study Endpoints	Subject Groupings		Infant Dietary Regime Details*				
				Infant Dietary Regime	n	Omega 6 LCPUFA (% wt)	Omega 3 LCPUFA (% wt)	Omega 6: Omega 3 Ratio	Linoleic Acid (% wt)	Alpha-linolenic Acid (% wt)
Carlson *et al.* (1996)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months	• Assessment of weight, height and head circumference at 4 and 12 months. • Assessment of visual acuity at 4 and 12 months.	Human Milk	19	n/a	n/a		n/a	n/a
				Standard formula	20	0	0		21.9	2.2
				Std + DHA + AA	19	0.43	0.1	4.3:1	21.8	2.0
Carlson *et al.* (1999)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months	• Assessment of weight, height and head circumference at 4 and 12 months. • Visual acuity and the Bayley Scales of Infant Development were assessed, however the data was not reported.	Standard formula	104	0	0		n/a	n/a
				Std + DHA + AA	212	0.6	0.3	2:1	n/a	n/a
Decsi and Koletzko (1995)	Randomisation into control and LCPUFA formula groups. Randomisation and intervention were blinded.	0-4 months	• Assessment of weight, height and head circumference at 4 months.	Standard formula	7	0	0		11.1	0.7
				Std + DHA + AA	9	0.4	0.33	1.2:1	13.8	1.0
Innis *et al.* (1996)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-4 months	• Assessment of weight, height and head circumference at 4 months.	Human Milk	26	n/a	n/a		n/a	n/a
				Standard formula	37	0	0		20.5-34.2	2.1-4.8
				Standard + DHA	68	0	0.12-0.24		20.0-32.2	2.1-5.0

Study	Methods	Study Duration	Study Endpoints	Subject Groupings		Infant Dietary Regime Details*				
				Infant Dietary Regime	n	Omega 6 LCPUFA (% wt)	Omega 3 LCPUFA (% wt)	Omega 6: Omega 3 Ratio	Linoleic Acid (% wt)	Alpha-linolenic Acid (% wt)
Jorgensen *et al.* (1998)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-4 months	• Assessment of visual acuity at 4 months.	Human Milk	42	0.65	0.69	0.9:1	11.1	1.3
				Standard formula	11	0.12	0		12.3	1.2
				Standard + DHA	26	0.22	0.77	0.3:1	12.0	1.2
Lapillonne *et al.* (2000)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-4 months	• Assessment of weight, height and head circumference at 4 months.	Human Milk	13	n/a	n/a		n/a	n/a
				Standard formula	12	0	0		17.4	1.6
				Standard + DHA	12	0	0.39		17.6	1.1
Lucas *et al.* (1999)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-18 months	• Assessment of weight, height and head circumference at 4, 6 and 9 months. • Assessment of Bayley Scales of Infant Development at 18 months.	Standard formula	155	0	0		12.4	1.1
				Std + DHA + AA	158	0.3	0.33	0.9:1	15.9	1.4

Study	Methods	Study Duration	Study Endpoints	Subject Groupings		Infant Dietary Regime Details*				
				Infant Dietary Regime	n	Omega 6 LCPUFA (% wt)	Omega 3 LCPUFA (% wt)	Omega 6: Omega 3 Ratio	Linoleic Acid (% wt)	Alpha-linolenic Acid (% wt)
Makrides *et al.* (1995a)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months	• Assessment of weight, height and head circumference at 4 and 12 months. • Assessment of visual acuity at 4 and 12 months.	Human Milk	23	0.5	0.44	1.1:1	13.9	0.9
				Standard formula	19	0	0		16.8	1.6
				Standard + DHA	13	0	1.0		17.4	1.5
Makrides *et al.* (1999); Makrides *et al.* (2000c)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months (Makrides *et al.,* 1999); 12-24 months (Makrides *et al.,* 2000c)	• Assessment of weight, height and head circumference at 4, 8 and 12 months (Makrides *et al.,* 1999). • Assessment of visual acuity at 4 and 8 months (Makrides *et al.,* 2000c). • Assessment of Bayley Scales of Infant Development at 12 and 24 months (Makrides *et al.,* 2000c).	Human Milk	33	0.39	0.29	1.3:1	13.4	1.0
				Standard formula	21	0	0		16.8	1.5
				Standard + DHA	23	0	0.45		16.8	1.2
				Std + DHA + AA	24	0.34	0.34	1:1	16.6	1.0
Morris *et al.* (2000)	Randomisation into control and LCPUFA formula groups. Randomisation, intervention and assessment were blinded.	0-12 months	• Assessment of weight, height and head circumference at 6 and 12 months.	Standard formula	55	0	0		11.8	2.4
				Std + DHA + AA	54	0.4	0.2	2:1	11.6	2.3

Study	Methods	Study Duration	Study Endpoints	Subject Groupings		Infant Dietary Regime Details*				
				Infant Dietary Regime	n	Omega 6 LCPUFA (% wt)	Omega 3 LCPUFA (% wt)	Omega 6: Omega 3 Ratio	Linoleic Acid (% wt)	Alpha-linolenic Acid (% wt)
Willatts *et al.* (1998)	Randomisation into control and LCPUFA formula groups. Randomisation and assessment were blinded.	0-10 months	• Assessment of cognitive performance using a means-end problem solving test.	Standard formula	23	0	0		12.8	0.7
				Std + DHA + AA	21	0.35	0.2	1.75:1	11.4	0.7

n/a = data not available

* = several studies that included a Human Milk group did not collect breast milk samples for analysis of fatty acid contents (data expressed as 'n/a'). Instead, the researchers relied on previously collected human milk composition data that was relevant to their particular population group.

Table A2: Anthropometric results from studies on the LCPUFA content of infant formulas (0-12 months of age)

Study	Subject groups		Anthropometric Results (mean + sd)[1]																											
			Weight (kg)										Length (cm)										Head Circumference (cm)							
	Type Formula	n	Birth	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd	Birth	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd	Birth	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd
Agostoni *et al.*(1994)	Human Milk	15	3.37	0.49	6.45	0.79							50.4	1.7	63.1	2.6							34.3	1.5	41.8	0.9						
	Standard formula	21	**3.3**[a]	0.46	6.58	0.85							50.2	2.7	63	3.2							34.1	1.1	41.5	1.6						
	Std + DHA + AA	23	**3.22**[b]	0.44	6.36	0.47							50	1.9	62	1.7							34.1	1.4	41.1	1.2						
Auestad *et al.* (1997)	Human Milk	63	3.6	0.46	6.85	0.80					9.95	1.21	50.8	3.1	62.8	2.3					75.3	2.8	34.8	1.5	41.8	1.1					46.6	1.2
	Standard formula	45	3.6	0.47	6.97	0.66					10.23	1.18	50.9	2.9	62.9	2.2					75.4	3	34.8	1.5	41.9	1.1					46.7	1.3
	Standard + DHA	43	3.57	0.46	6.76	0.88					10.16	1.22	51	2.3	62.8	2.2					75.3	2.6	34.9	1.7	41.6	1.1					46.5	1.2
	Std + DHA + AA	46	3.5	0.46	6.79	0.82					10.06	1.26	50.6	2.7	62.9	2.4					75.5	2.6	34.5	1.5	41.8	1.1					46.7	1.2
Auestad *et al.* (2001)	Standard formula	77	3.45	0.44	6.54	0.64					9.78	1	50.8	2.5	63	2.2					75.4	2.7	39.4	1.2	41.8	1.1					46.5	1.2
	Std + DHA + AA	162	3.4	0.47	6.59	0.67					9.67	0.99	50.6	2.6	62.9	1.9					75.2	2.3	39	1.3	41.8	1.2					46.5	1.3
Birch *et al.* (1998)	Standard formula	23			6.89	0.7					9.66	0.52			63.9	2.3					75.5	2.8			42.3	1.1					47	1.3
	Standard + DHA	22			7.1	0.56					10.11	0.92			62.9	2.4					74.7	2.2			42	0.9					46.8	1.2
	Std + DHA + AA	23			7.1	0.58					10.07	1.2			63.4	1.5					74.7	2.5			42.1	1.2					46.6	1.7
Carlson *et al.* (1996)	Standard formula	20	3.33	0.33	6.4	0.72					9.48	1			61.3	2.1					72.5	2.3			41.5	0.8					46.3	1.4
	Std + DHA + AA	19	3.29	0.45	6.32	0.71					10	0.83			61.3	1.1					73.5	1.9			41.3	0.8					46.6	1.1
Carlson *et al.* (1999)	Standard formula	104			6.63	0.74					9.77	1.19			63	2.6					75.4	3			41.7	1.2					46.8	1.4
	Std + DHA + AA	212			6.78	0.75					9.99	1.2			62.9	2.5					75.6	3.1			41.9	1.2					46.7	1.4
Decsi and Koletzko (1995)	Standard formula	7	3.4	0.41	6.41	0.64							54.5	3.7	64.1	2.7							32.2	3.7	40.2	1.1						
	Std + DHA + AA	9	3.55	0.52	6.62	0.48							52.1	4.9	64.9	1.5							35.3	2.3	41.7	1						

Study	Subject groups		Anthropometric Results (mean + sd)[1]																											
			Weight (kg)										Length (cm)										Head Circumference (cm)									
	Type Formula	n	Birth	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd	Birth	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd	Birth	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd
Innis *et al.* (1996)	Standard formula	37			6.62	0.94									63.3	2.9									41.4	1.4						
	Standard + DHA	68			6.68	0.82									62.8	2.8									41.5	1.2						
Lapillonne *et al.* (2000)	Human Milk	13	3.47	0.41	6.6	0.64							50.3	1.4	62.9	1.7							34.8	1.1	41.2	1.1						
	Standard formula	12	3.31	0.45	7.01	0.87							50	2.4	63.3	2.4							35.1	1.4	**42.6**[a]	1.8						
	Standard + DHA	12	3.38	0.43	6.73	0.8							50.7	1.7	64.4	2.4							34.8	1	**41.2**[b]	1.2						
Lucas *et al.* (1999)	Standard formula	125	3.65	0.46			8.00	0.8	9.1	0.9			50.9	1.9			67.3	2.4	72.2	2.4			35.4	1.2			43.8	1.2	45.9	1.4		
	Std + DHA + AA	125	3.54	0.41			7.90	0.9	9.1	1.1			50.5	1.8			67.4	2.5	71.9	2.7			35.3	1.2			43.8	1.1	48.3	1.5		
Makrides *et al.* (1995a)	Standard formula	19	36.5	0.42	6.7	0.79					9.98	1.09	51.2	2.1	62.7	1.5					75.8	2.2	35.2	1.2	42.2	0.9					46.9	1.1
	Standard + DHA	13	32.9	0.53	6.5	0.72					9.94	1.35	50.2	2.8	62.2	2.5					75.8	2.6	34.4	2.2	41.7	1.6					46.3	1.4
Makrides *et al.* (1999)	Standard formula	22	3.55	0.5	6.5	0.53			8.78	0.9	10.62	1.13	51.5	2.6	62.6	2.5			71	2.4	77	2.4	35.3	1.6	41.5	1.1			44.9	1.2	46.9	1.2
	Standard + DHA	25	3.38	0.43	6.53	0.65			8.62	0.99	9.96	1.11	50.8	2	62.2	1.6			70.3	2	75.5	2.3	35.1	1.4	41.8	0.9			44.9	1.2	46.8	1.1
	Std + DHA + AA	24	3.55	0.52	6.65	0.73			8.99	0.99	10.55	1.11	51.3	2.4	62.6	2.5			71	2.4	77	2.4	35.2	1.7	42	1.5			45.6	1.4	47.6	1.5
Morris *et al.* (2000)	Standard formula	55	3.35	0.46			8.13	1.10			10.24	1.31	49.0	2.2			67.8	2.4			75.9	2.7	**34.9**[a]	1.7			43.9	1.6			47.0	1.8
	Std + DHA + AA	54	3.31	0.48			7.94	0.94			9.91	1.13	49.3	2.5			67.9	2.5			75.7	3.1	**34.3**[b]	1.4			43.6	1.3			46.5	1.4

1. Bolded values with different lettered superscripts are significantly different from each other ($p \leq 0.05$), and normal font values without superscripts are not significantly different ($p > 0.05$). Statistical significance is only applied to comparisons between infants fed different study formulas, and not to comparisons with infants fed human milk.

Table A3: Visual acuity results from studies on the LCPUFA content of infant formulas (4-12 months of age)

Study	Subject groups		Visual Acuity Results (mean + sd)[1]																			
			Behavioural Assessment (LogMAR)[2]						Visual Evoked Potential Assessment (LogMAR)[2]								Stereoacuity Assessment (LogSec)[3]					
	Type Formula	n	4 mths	sd	6 mths	sd	12 mths	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd	4 mths	sd	10 mths	sd	12 mths	sd
Auestad *et al.* (1997)	Human Milk	38	0.88	0.13	0.57	0.09	0.52	0.11	0.66	0.13	0.47	0.15			0.34	0.18						
	Standard formula	45	0.90	0.17	0.64	0.09	0.51	0.09	0.64	0.12	0.39	0.15			0.32	0.16						
	Standard + DHA	43	0.92	0.13	0.68	0.09	0.55	0.13	0.69	0.14	0.44	0.16			0.37	0.13						
	Std + DHA + AA	46	0.90	0.16	0.56	0.09	0.51	0.15	0.68	0.09	0.40	0.17			0.32	0.16						
Auestad *et al.* (2001)	Human Milk	165	0.88	0.13	0.57	0.09	0.53	0.13														
	Standard formula	54	0.85	0.13	0.67	0.07	0.51	0.06														
	Std + DHA + AA	123	0.84	0.13	0.57	0.09	0.49	0.03														
Birch *et al.* (1998); Hoffman *et al.* (2000)	Human Milk	29	0.81	0.16	0.74	0.11	0.63	0.14	0.48	0.12	0.32	0.05			0.18	0.08						
	Standard formula	23	0.81	0.17	0.74	0.10	0.63	0.12	**0.54**[a]	0.13	0.38	0.05			**0.33**[a]	0.1						
	Standard + DHA	22	0.88	0.15	0.79	0.12	0.69	0.19	**0.46**[b]	0.08	0.33	0.11			**0.19**[b]	0.12						
	Std + DHA + AA	23	0.88	0.15	0.79	0.17	0.67	0.18	**0.48**[b]	0.1	0.37	0.05			**0.2**[b]	0.11						
Birch *et al.* (2005)	Standard formula	44							**0.56**[a]	0.01					**0.3**[a]	0.01	**2.62**[a]	0.06	2.18	0.05	2.03	0.05
	Std + DHA + AA	42							**0.48**[b]	0.02					**0.15**[b]	0.03	**2.72**[b]	0.05	2.10	0.03	1.87	0.02
Carlson *et al.* (1996)	Human Milk	19	0.69	0.03	0.54	0.02	0.51	0.02														
	Standard formula	20	0.69	0.03	0.60	0.03	0.54	0.02														
	Std + DHA + AA	19	0.75	0.04	0.59	0.03	0.53	0.02														
Jorgensen *et al.* (1998)	Human Milk	17							0.37	0.07												
	Standard formula	11							0.44	0.07												
	Standard + DHA	26							0.4	0.07												

Study	Subject groups		Visual Acuity Results (mean + sd)[1]																			
			Behavioural Assessment (LogMAR)[2]						Visual Evoked Potential Assessment (LogMAR)[2]								Stereoacuity Assessment (LogSec)[3]					
	Type Formula	n	4 mths	sd	6 mths	sd	12 mths	sd	4 mths	sd	6 mths	sd	8 mths	sd	12 mths	sd	4 mths	sd	10 mths	sd	12 mths	sd
Makrides *et al.* (1995a)	Human Milk	23							0.51	0.21	0.1	0.31										
	Standard formula	19							**0.76**[a]	0.1	**0.45**[a]	0.2										
	Standard + DHA	13							**0.56**[b]	0.14	**0.15**[b]	0.35										
Makrides *et al* (2000b)	Human Milk	33							0.73	0.11			0.33	0.20								
	Standard formula	15							0.73	0.11			0.39	0.19								
	Standard + DHA	19							0.77	0.10			0.47	0.18								
	Std + DHA + AA	15							0.74	0.09			0.39	0.17								

1. Bolded values with different lettered superscripts are significantly different from each other ($p \leq 0.05$). Statistical significance is only applied to comparisons between infants fed different study formulas, and not to comparisons with infants fed human milk.
2. Logarithm_{10} of the eye's minimum angle of resolution. Lower values reflect an increased ability to distinguish between two points at a greater distance.

Logarithm_{10} of an arcsecond.

Table A4: Cognitive development results from studies on the LCPUFA content of infant formulas (4-24 months of age)

Study	Subject groups		Cognitive Development Results (mean + sd)[1]																	
			Bayley Mental Development Index (% normal score)								Bayley Psychomotor Development Index (% normal score)								Bayley Behaviour Rating Scale (% normal score)	
	Type Formula	n	6 months	sd	12 months	sd	18 months	sd	24 months	sd	6 months	sd	12 months	sd	18 months	sd	24 months	sd	18 months	sd
Auestad *et al.* (2001)	Human Milk	165	100.8	5.4	100.0	8.7					100.2	10.4	96.6	12.2						
	Standard formula	77	100.4	5	97.8	8.3					99.1	12.3	94.6	12.5						
	Std + DHA + AA	162	99.6	6.1	96.8	9.2					97.8	11.3	94	13.2						
Birch *et al.* (2000);	Standard formula	23					**98.3[a]**	1.94							98.6	1.34			107.3	23.7
	Standard + DHA	22					**102.4[a,b]**	1.81							99.6	0.97			106.4	20.9
	Std + DHA + AA	23					**105.6[b]**	2.7							101.7	0.69			108.1	24.6
Lucas *et al.* (1999)	Standard formula	155					94.2	12.8							94.7	13.4				
	Std + DHA + AA	158					95.8	10.1							96.4	9.1				
Makrides *et al*. (2000c)	Human Milk	33			116	10			120	18			97	18			98	11		
	Standard formula	22			110	12			104	13			102	17			97	15		
	Standard + DHA	25			114	12			108	16			106	18			104	17		
	Std + DHA + AA	24			108	16			102	23			103	22			96	21		
Scott *et al*. (1998)	Standard formula	45			105	14							105	15						
	Standard + DHA	43			104	15							101	14						
	Std + DHA + AA	46			105	12							98	14						

1. Bolded values with different lettered superscripts are significantly different from each other ($p \leq 0.05$), and normal font values without superscripts are not significantly different ($p > 0.05$). Statistical significance is only applied to comparisons between infants fed different study formulas, and not to comparisons with infants fed human milk.

Table A5: Cognitive development results from studies on the LCPUFA content of infant formulas (4-14 months of age)

Study	Subject groups		Cognitive Development Results[1]																	
			Brunet and Lezine Development Quotient (% normal score + sd)				MacArthur Communicative Development Inventories (% normal score + sd)										Means-end Problem Solving[2] (median values)			
							Phrases Understood		Vocabulary Comprehension		Vocabulary Production		Early Gestures		Late Gestures		Entire Test	Barrier component	Cloth component	Cover component
	Type Formula	n	4 months	sd	24 months	sd	14 months	sd	14 months	sd	14 months	sd	14 months	sd	14 months	sd	10 months	10 months	10 months	10 months
Agostoni *et al.* (1994; 1997)	Human Milk	15	102.2	11.5	99.7	7.0														
	Standard formula	21	**96.5**[a]	10.9	99.1	7.1														
	Std + DHA + AA	23	**105.3**[b]	9.4	100.1	10.3														
Scott *et al.* (1998)	Human Milk	60					104	17	101	13	97	17	105	12	102	13				
	Standard formula	42					100	16	**100**[a]	17	**101**[a]	13	105	18	101	15				
	Standard + DHA	38					96	16	**92**[b]	14	**91**[b]	17	102	19	97	16				
	Std + DHA + AA	33					99	12	**98**[a]	15	**99**[a,b]	18	105	14	100	14				
Willatts *et al.* (1998)	Standard formula	23															**11.5**[a]	4.8	4.5	**2.5**[a]
	Std + DHA + AA	21															**14.0**[b]	5.5	5.0	**4.3**[b]

1. Bolded values with different lettered superscripts are significantly different from each other ($p \leq 0.05$), and normal font values without superscripts are not significantly different ($p > 0.05$). Statistical significance is only applied to comparisons between infants fed different study formulas, and not to comparisons with infants fed human milk.
2. This test consisted of relative scores (0, 1, or 2) for different degrees of cognitive awareness exhibited during each component of the test. The three components each have three behaviour subsets that are assessed, resulting in a maximum possible score of 6 for each component and 18 for the entire test.

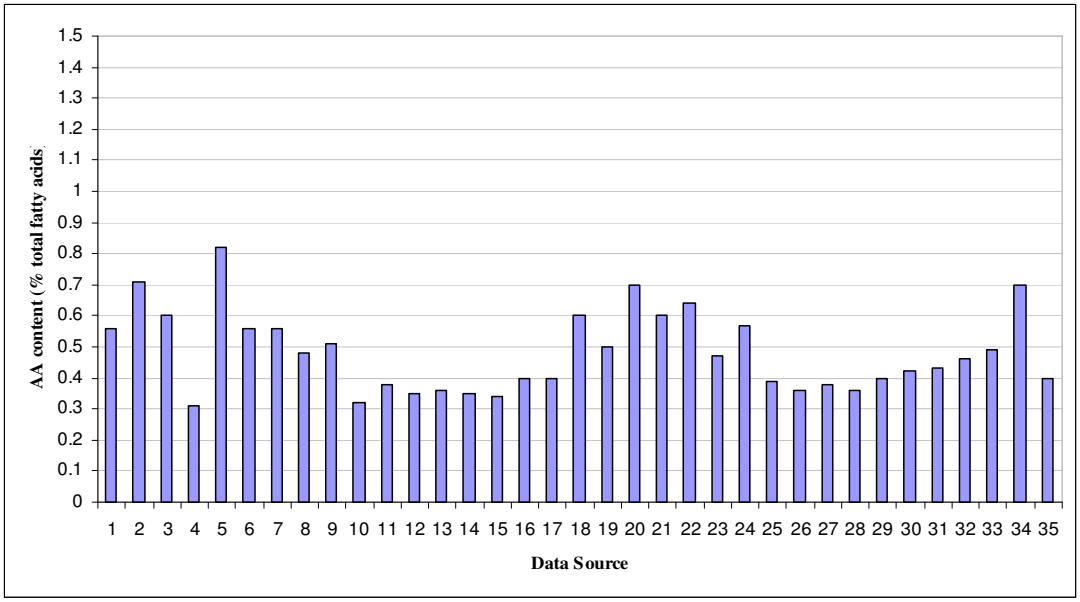

Figure A1: Arachidonic acid content of human milk

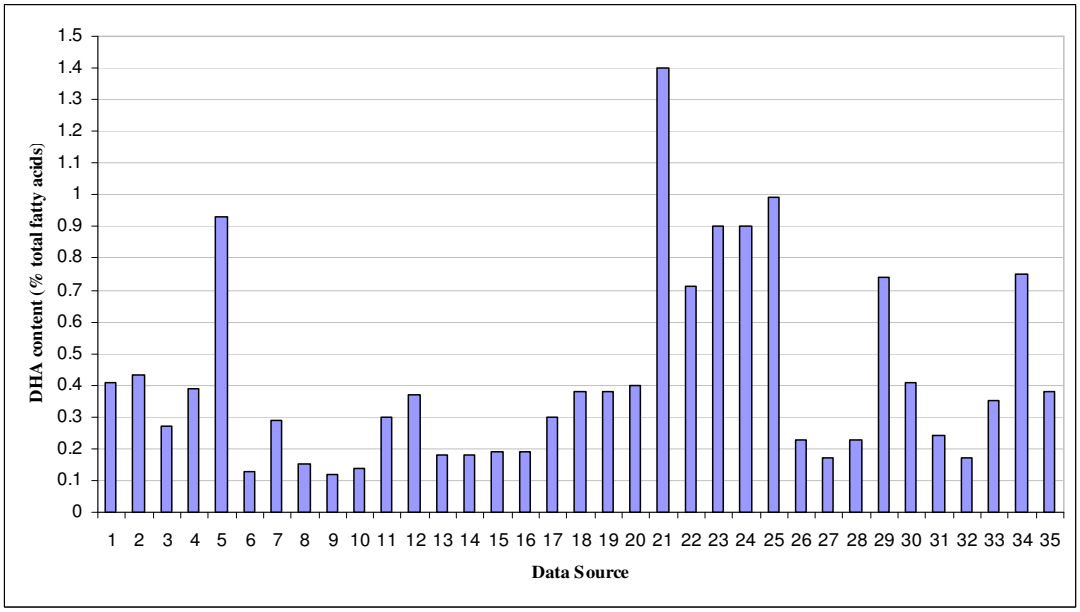

Figure A2: Docosahexaenoic acid content of human milk

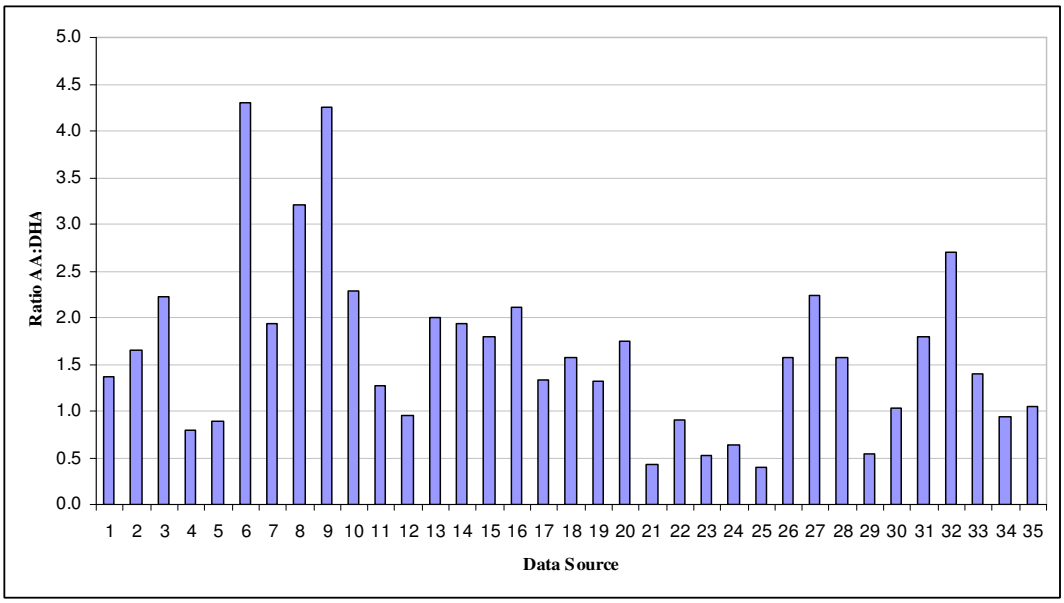

Figure A3: Ratio of arachidonic acid to docosahexaenoic acid in human milk

Data Sources:

1-3: Surinam, Curacao, Tanzania - Muskiet *et al*. (1987)
4: Gambia – Prentice *et al*. (1989)
5: Nigeria – Koletzko *et al*. (1992)
6-9: United States of America – Jackson *et al.* (1994), Birch *et al.* (1998), Auestad *et al.* (1997), Auestad *et al.* (2001) respectively
10-12: United Kingdom (vegan, vegetarian and omnivore) – Sanders and Reddy (1992)
13: Finland - Luukkainen *et al.* (1994)
14. Germany – Koletzko *et al.* (1988)
15: Netherlands – Huisman *et al.* (1996)
16: Australia – Makrides *et al.* (1995b)
17: Sweden – Jansson *et al.* (1981)
18: Israel – Budowski *et al.* (1994)
19: France – Guesnet *et al.* (1993)
20-21: Canada (Vancouver, Inuit) – Innis and Kuhnlein (1988)
22-23: Malaysia (Chinese, Malay and Indian) – Kneebone *et al.* (1985)
24-32: Japan, United Kingdom, Canada, Australia, Philippines, Chile, Mexico, United States of America, China (respectively) – Yuhas *et al.* (2006)
33: Tanzania – Kuipers *et al.* (2005)
34: Denmark – Jorgensen *et al.* (1998)

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Attachment 3

A532 SUMMARY OF SUBMISSIONS FROM THE INITIAL ASSESSMENT REPORT

Executive Summary of submissions

Background

In July 2006 FSANZ received 42 submissions in response to the Initial Assessment Report of Application A532 – Consideration of an amendment to Standard 2.9.1 of the Code to remove subclause 23(d). This subclause requires long chain polyunsaturated fatty acids (LCPUFAs) if voluntarily added to infant formula and follow-on formula to be present in a ratio of omega 6 to omega 3 LCPUFAs of *approximately 2*.

There were two options proposed at Initial Assessment namely:

Option 1 – Maintain the s*tatus quo*;

Option 2 – Amend Standard 2.9.1 by removing subclause 23(d) which requires infant formula to contain omega 6 and omega 3 in a ratio of *approximately 2*, when LCPUFA are added to these products.

Many submissions indicated a preference for a modification of these two Options including:

Modified Option 1 - Maintain a requirement for a ratio of omega 6: omega 3 but not the current ratio of *approximately 2*.

Combination: Option 2 combined with a Modified Option 1 - Amend Standard 2.9.1 to remove subclause 23(d) for Follow-on formula intended for infants more than 6 months of age, but require a ratio of omega 6: omega 3 of a minimum of 1:1 ratio in infants' formula for 0-6 months of age if LCPUFAs are added.

Submitters' views were mixed in relation to a preferred regulatory option, however the majority supported a change to the current requirement.

Of the public health and academic submitters (8) a majority favoured the retention of a ratio requirement, with more recommending a 1:1 ratio in preference to the current ratio of *approximately 2*.

Of the industry submitters (12) a majority also supported a change to the current ratio requirement. However, there was a divergence if views between retaining some ratio requirement, and deleting subclause 23(d). Of those supporting the retention of a ratio, most favoured a 1:1 ratio. Some submitters recommended a different ratio requirement for infant formula for infants under 6 months of age, and for Follow-on formula for those over 6 months of age.

The three Government submitters supported different options including retaining the status quo, Option 2, and the retention of an omega 6 to omega 3 LCPUFA ratio but not the current requirement of *approximately 2*.

Student submissions (17) generally favoured Option 2 supporting the removal of the current clause requiring a ratio of *approximately 2*.

The two consumer submitters preferred Options differed but neither supported retaining the status quo.

Two submitters did not indicate a preferred option.

KEY ISSUES IDENTIFIED FROM SUBMISSIONS

1. Regulatory options

Reasons for and against each of the regulatory options included:

1.1 Maintaining the status quo

Support:
- Insufficient evidence to establish the safety of removing of AA in infant formulas that contain DHA. Consider international consensus is that DHA should be combined with AA when LCPUFA are added to infant formula.
- Studies are difficult to compare and additional studies are required.
- A full risk assessment and peer review is needed before decisions can be made.

Against:
- No scientific evidence to support retaining the ratio of *approximately 2*.
- The current ratio is inconsistent with international standards e.g. draft CODEX standard.
- The unique requirement for Australia and NZ increases costs for manufactures and consumers, creates trade barriers and reduces product variety.

1.2 Option 2: Amending Standard 2.9.1 by removing the requirement for infant formula to contain omega 6 and omega 3 in a ratio of approximately 2, when LCPUFA are added to these products.

Support:
- Recent evidence does not support a fixed AA to DHA ratio of *approximately 2.*
- Recent studies show variations in breast milk ratios are suitable for growth and development of infants.
- Would support harmonisation with international standards e.g. CODEX draft standard.
- Would reduce manufacturing costs and allow industry to trade competitively on the international market.

Against:

- Could result in the single addition of DHA or AA. Considers there is insufficient evidence to establish the safety of this, it would not align with international consensus and breast milk contains both DHA and AA.
- Not requiring a set ratio would create inconsistencies with international recommendations and manufacturing practice.
- Additional evidence is required and studies are difficult to compare.
- A full risk assessment and peer review is needed before decisions can be made.

1.3 *Modified Option 1: retain a ratio requirement when omega 6; omega 3 are added to infant formula, but not a ratio of approximately 2.*

This alternative option was presented by submitters at Initial Assessment and is assessed in addition to the options presented by FSANZ.

Support:

- Evidence does not support a fixed AA to DHA ratio of *approximately 2*.
- Given the variation in breast milk a ratio of approximately two is excessively stringent.
- Insufficient evidence to remove regulation as this would allow manufacturers to add any ratio of LCPUFA.
- The addition of DHA without AA is not supported by current scientific knowledge. There is a lack of clinical studies / data on the addition of AA without DHA.
- Would align with expert recommendations FAO/WHO; ESPGHAN; European commission; EU; draft CODEX standard for infant formula.

1.4 *Combination: Modified Option 1 (for 0-6 mths age) and Option 2 (for Follow-on formula)*

This alternative option was presented by submitters at Initial Assessment and is assessed in addition to the options presented by FSANZ.

Support:

- Would align with CODEX draft standard which permits a ratio of omega 6: omega 3 in Infant formula at a minimum of 1:1
- Would align fully with CODEX draft standard which recognises Follow on formula as a separate standard which does not require a ratio when LCPUFAs are added.

Ref	Submitter	A532 Submission Comments
	Consumers and Consumer & Community Organisations	
	A Henderson Individual	**Modified Option 1** Does not support Option 2. Suggests an alternative regulation be implemented, such as the recommendation by the European Scientific Committee on Food (ESCF) that infant formula with LCPUFA added should contain omega 6 (AA) not less than the omega 3 (DHA) content. ***Science, Health and Safety*** Considers there is not yet enough understanding to remove regulation as manufacturers could add any LCPUFA ratio. Considers the ratio should be kept as close to breast-milk as possible. Considers the current required ratio of 2 may be excessively stringent given the variation in breast-milk. Considers there is a lack of data on addition of AA without DHA, and notes the requirement for AA to maintain the levels observed in breast milk. Concerned that the addition of DHA alone results in a 25% average reduction in serum AA. Notes that while there is still no evidence that a reduction in serum AA poses an immediate risk, theoretically eicosanoid metabolism may be altered, in addition to limited or altered immune function. (Field, Clandinin MT., & Van Aerde J.E.,2001). Considers because of the contradictive in-vivo mechanisms of omega 3 and omega 6, it is likely that the addition of AA alone will have a similar, opposite effect to the 25% reduction in AA following supplementation of DHA, observed by Makrides et al (2005). Notes a review paper by Simopoulos (2002) reported ratios as high as 5 have shown to protect against asthma.
	Food Industry	
I1	Australian Food and Grocery Council (AFGC) Kim Leighton Australia	**Supports Option 2** ***Science, health, safety*** Considers there is no scientific evidence to support retention of this ratio. Notes science has progressed since the Application with further data and knowledge available regarding the ratio. Recommends FSANZ discuss with the applicant whether there is a need to amend the application in light of this new evidence.

Ref	Submitter	A532 Submission Comments
		Ministerial guidelines Considers the current standard does not meet the FSANZ objective regarding minimum effective regulation. ***International*** AFGC supports harmonisation with international standards. Recommends FSANZ considers the recommended position of the Codex Committee in a recent report.
I2	Banks Consultancy Robyn Banks Australia	**Supports Combination of Options: Modified Option 1 for 0-6 months and Option 2 for Follow 0n formula** Supports (IFMAA and Nestle) submissions that suggest adoption of the Codex draft requirements for products from 0-6 months. Supports removal of the ratio 2:1 for infant formula products for infants aged over 6 months. ***Science, Health and Safety*** Considers the scientific evidence demonstrates that there is no requirement for the ratio 2:1 to be retained. ***International*** Considers the ratio is inconsistent with international standards. Notes there have been recent developments in the international regulatory process in relation to the addition of LCPUFAs. Notes the proposal from the Codex committee for Nutrition and Foods for Special Dietary Uses 2005, that when DHA is added then the AA level should be at least the same as DHA. Notes the Codex standard for follow on formula does not require such levels of AA when DHA is added. ***Trade*** The current standard is inconsistent with Codex draft standard so is a technical barrier to trade. ***Impact on industry.*** *Status quo*: as a LCPUFA ratio of 2:1 is not replicated internationally infant formula must be manufactured specifically for Australia and NZ with increased costs which are passed on to consumers. *Removal of ratio:* International harmonisation would result in economies of scale for manufacturers and could increase availability of products at a more competitive cost to consumers. ***Impact on Government.*** Considers there would be no negative impact on Government enforcement. FSANZ would not incur TBT objections from other countries.

Ref	Submitter	A532 Submission Comments
	Ocean Nutrition, Australia Kevin Mall, GM Australia / NZ	**Supports Option 2** Considers the imposition of a formal omega 6 to omega 3 ratio is clinically unwarranted. ***Impact on Industry*** The unique existence of this requirement for Australia and NZ adds a significant cost burden for manufacturers. ***International*** No similar restrictions apply in other regulated global markets e.g. EU Directive 96/4/EC contains no specific ratio requirements, but imposes upper limits – this was reconfirmed in 2003. Notes in 2004 the FAO/WHO Codex Committee on Nutrition and Foods for Special Dietary Uses published a draft standard for infant formula. This contained no specific ratio for omega-6 and omega-3 fatty acids, but proposed maximum levels each set at 2% of total fatty acids. Supports harmonisation of Australia NZ Food Standards Code with other international standards.
	Nutricia, Australia Mike Sharp	**Supports Option 2** ***Impact on Consumers*** Notes access to specific internationally available products is currently restricted for infants. In Australia and NZ local demand does not total sufficient cases to justify individual production volumes to satisfy this current regulation.
	NZIFMA and IFMAA, NZ and Australia Julie Dick	**Submission supports Option 2 but also supports the recent draft Codex revised standard.** **NB.** *The Applicant subsequently confirmed support for the direction taken by Codex in adopting a ratio of 1:1 for Omega 6: Omega 3 when added to infant formula, therefore* ***supports a Modified Option 1.*** While supporting Option 2, the Applicant's submission refers to recent developments within Codex for infant formula with regard to the ratio of addition of LCPUFA. The Applicant believes it is important to use the best international opinion and be consistent with international regulation. Notes, in line with current scientific opinion and to align with the intention of Codex in relation to their revised Infant Formula Standard, the applicant would support an amendment to Standard 2.9.1 Clause 23d to permit a ratio of LCPUFAs omega 6 : omega 3 at a minimum of 1:1, with a maximum of 0.5% total fatty acids for DHA in Infant Formula. (0-6 months) Also notes that CODEX recognises Follow-on formula for infants from 6 months of age as a separate standard and would support Option 2 for this age group.

Ref	Submitter	A532 Submission Comments
		Science, heath and safety Supports the scientific research presented in the application including the summary given by Dr Makrides. Considers current evidence suggests that addition of DHA alone for follow on formula is acceptable. ***Impact on industry*** Removal or amendment of the LCPUFAs ratio requirement will allow industry to trade competitively on the international market, and encourage industry innovation which will benefit consumers. ***Trade*** The status quo is a prescriptive ratio inconsistent with international standards. The status quo will continue to pose a trade barrier for companies marketing infant formula in Australia and New Zealand and will continue to add a cost burden on consumers who choose infant formula with added LCPUFAs. ***Impact on consumers*** Removal or amendment of the current ratio requirement would increase consumer choice as industry could offer a wider variety of formulas without unnecessary expense. ***International*** Considers the status quo does not promote consistency with the revised CODEX standard whether they do, or do not, proceed with this latest consideration at Step 6. The removal of clause 23(d), or aligning with Codex would enable FSANZ to achieve consistency with proposed international standards. ***CBA*** Considers any form of prescriptive ratio poses a cost burden to companies that manufacture locally and export to markets where local regulations are not prescriptive e.g. in Asia and parts of Europe. Notes these markets permit the sale of infant formula products containing DHA without added AA.
	Fonterra Co-Operative Group Ltd. Roger Hall	**Supports Option 2** ***Science , health, safety*** Considers there is no real nutritional reason to stipulate a ratio. A maximum level is still present in Std 2.9.1 so from a nutritional view the amendment is justifiable. ***International*** Notes internationally no ratio is currently applied so this would remove any barrier to trade.

Ref	Submitter	A532 Submission Comments
	Food Technology Assn of Victoria Inc., Australia David Gill	**Supports Option 2** No supporting information provided but requests future reports.
	WYETH Australia Pty Limited Dr Jeanette Fielding	**Supports a Modified Option 1.** WYETH was not a signatory to the application. Remains opposed to the proposal on the basis that it disagrees with the rationale, especially the focus on growth as the primary endpoint, therefore failing to take account of the roles of AA and DHA beyond simply growth. ***Recommend alternative proposal:*** That when DHA is added to infant and follow-on formula that AA be added at a ratio of least 1:1. Considers this ratio is supported by the international scientific community, meets the established nutritional needs of infants, and meets the objectives of FSANZ. Believes follow-on formulas should continue to re required to meet the current ratio or amended ratio of at least 1:1 to support normal growth and development. A required ratio of AA to DHA of at least 1:1 would assist industry to reduce costs, and harmonise with international regulations, while meeting nutritional needs of formula fed infants. ***Science, health and safety*** Notes the current ratio requirement of approximately 2 is provided by breast milk, which provides the model for infant formula. Refers to a study of 9 countries where the mean AA to DHA ratio is 1.63:1 and other studies with a ratio of 1.65:1 and 3.16:1. Considers AA and DHA can be added to infant formula from non-fish sources to achieve the ratio 2:1. Considers there is scientific evidence to support a ratio of AA to DHA of approx. 2:1. Also considers there is wide consensus amongst the scientific community that if DHA is added to infant formula, that AA be added at a ratio of at least 1:1. Provides a table summarising these recommendations. Notes that AA levels are relatively consistent in breast milk despite maternal diet, while DHA levels change. This suggests AA has a specific function in infant development and growth and that its inclusion in infant formulas is essential. Notes several studies that support that DHA and AA have functions beyond growth e.g. decreased incidence of respiratory illness.

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		Also notes DHA and AA influence each others synthesis – the presence of DHA with no AA affects AA synthesis and tissue levels of AA. *Tissue levels* Notes evidence that insufficient or imbalanced AA levels can affect tissue accretion levels as well as cognitive and immune functions. Notes AA concentrations in the brain maintain a constant range regardless of AA intake, but AA concentrations in other tissues such as heart and liver are depleted with insufficient dietary AA. *Cognitive functions* Refers to studies relating to the role of AA in infant vocabulary, memory, problem solving, social skills and language. Also refers to a study showing AA supplementation improved brain function in elderly men. Considers all these studies support the argument that AA functions beyond that of simply growth. *Immune and organ functions* Refers to new findings presented at the 2006 International Society for the Study of Fatty Acids and Lipids (ISSFAL) conference. Notes the consensus that while the scientific community may not understand all the functions of AA, it is in breast milk at specific concentrations therefore if LCPUFAs are added to infant formula AA should be added. Notes AA is the predominant precursor to eicosanoids which have extensive biological activities. Infants receiving formula with DHA and AA had decreased incidence of respiratory illness if the first year of life compared to those without DHA and AA. Considers all these factors provide evidence the role of LCPUFAs goes beyond that of simply growth. Is not aware of studies on growth and development associated with addition of AA without DHA to infant formula. However, notes two other studies that show positive outcome with AA supplementation without DHA: • AA supplementation improved brain function of healthy elderly men. • Improved neurodevelopment in the offspring of diabetic rats with maternal supplementation of AA. Refers to studies not included in the IAR that provide further evidence of the importance of both AA and DHA including studies on speech, memory, problem solving, social skills, and language in infants fed formula containing DHA without AA. Notes infants also had decreased respiratory illness in the first year of life when fed formulas with both DHA and AA. Notes insufficient dietary AA in infants reduces organ tissue levels such as in heart and lung tissue.

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		Infant formulas for special dietary use Concerned the ratio requirement does not apply to infant formula for special dietary use, particularly due to the effect it could have on low birth weight infants. Notes most infants fed low birth weight formulas are born prematurely and are in particular need of the balanced addition of LCPUFAs to reach the same level of LCPUFA accretion as they would in utero. Evidence supporting LCPUFA supplementation in pre-term infants is more abundant than for full-term infants. Also concerned the exclusion of special dietary formulas from the LCPUFA ratio requirement may create an unintended opportunity for manufacturers to promote a specialty formula to the general public with no AA. ***Impact on consumers*** Consumers choosing formula with or without DHA and AA should be able to expect that the types and levels of LCPUFAs will be modelled on breast milk. If the requirement to add AA to formulas containing DHA is removed the formula will move away from the breastfed model which is potentially misleading to consumers as they are unlikely to be aware of this. It could also compromise optimal infant development. ***Impact on Industry*** Considers it unlikely manufacturers would add AA alone to formula due to the costs. However it is likely manufacturers would add DHA alone. Considers there would be no impact on consumers or industry (i.e. Wyeth) if the status quo is maintained but that FSANZ might find its policy differs to international consensus. Therefore supports an amendment to the standard to a ratio of 1:1. Industry could produce an internationally inferior product for less money yet market it as a LCPUFA fortified product. Removal of the ratio would reduce manufacturing costs. Considers it unclear whether this would be passed down to the consumer. ***Trade*** Considers trade issues and barriers would not change with removal of the requirement to add AA to infant formula when DHA is added.
	Omega 3 Centre W Morgan	**Supports Option 2** ***International*** Notes the EU Directive 96/4/EU has no requirement for specific ratios of omega 6: omega 3, reconfirmed by the EU Scientific Committee on Food in 2003.

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		Notes the recent draft EU Commission Working Document which continues to state upper limits but no specific ratio for LCPUFAs – but states that DHA should not exceed AA. Also notes the CODEX developments stating if DHA is added to infant formula then AA content should reach the same concentration. Recommends FSANZ support the approach taken by CODEX for consistency of international regulations.
	Nestlé Australia Stephanie Rajcyk	**Supports a Combined Option: modified Option 1 for 0-6 months and Option 2 for follow-on formula** Considers Option 1 does not reflect latest scientific evidence or promote consistency with international and domestic food standards. Supports: • the latest Codex draft revised standard for Infant Formula 0-6 months (at Step 6) which includes if DHA is added to infant formula the AA content should reach at least the same concentration as DHA, with a maximum DHA level of 0.5% of fatty acids. • the DHA:AA ratio requirement of 2:1 be replaced with a 1:1 ratio requirement in infant formula, but not in follow-on formula. • Option 2 in relation to follow-on formula. Notes CODEX recognises follow-on formula as a separate standard. Notes as there is no evidence of the benefits of addition of AA in follow-on formula, Nestle Australia would consider the addition of DHA alone in follow-on formula as is the practice in other countries. ***Science, health and safety*** Notes since the Application was made, there have been advances in the scientific knowledge base. Notes the ESPGHAN International Expert Group (IEG) concluded a large number of studies with LCPUFA added to infant formulae have not raised safety concerns, and a recent meta analysis found no indication of adverse effects on growth with the addition of both DHA and AA, or with addition of only n-3 LCPUFA (acknowledging the limited number of studies). Notes the IEG also concluded there is not sufficient documentation of the benefits and safety of the addition of DHA to infant formula at levels > 0.5% of total fat content, or of DHA without concomitant addition of AA Notes Makrides et al 1999 showed that an AA:DHA ratio of 1:1 did not influence growth in term infants. Refers to unpublished research (B Gibson and M Makrides) that has demonstrated the safety of an AA: DHA ratio of 1:1.

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		Recommends until benefits are adequately demonstrated, DHA addition should not exceed 0.5% and AA content should be at least the same concentration as DHA. Is not aware of any studies assessing the effect of AA without DHA in infant formula. Believes all studies on the addition of DHA without AA to infant formula and its affects on growth and development have been reported in the three critical reviews analysed in the FSANZ IAR. However also notes studies on the immunological effects in infants of DHA supplementation without AA. Notes a study showing an increased AA: DHA ratio was correlated with increased risk of asthma bronchial prevalence. Considers there is increasing interest in supplementing infant formula with a balanced AA:DHA ratio of 1:1. This ratio exists in many parts of the world where there is lower incidence of asthma. Considers this emerging information on the immunological effects of LCPUFAs further substantiates the case for removing the restriction of a ratio of 2:1 . Notes recent study by Birch et al (after the IAR) investigating the effects of AA:DHA supplementation in a ratio of 2:1 found no effect of LCPUFA on growth. There was higher visual function and higher red blood cell DHA and AA concentrations in the supplemented group compared to the unsupplemented group. Another study following up infants at 39 months after an initial study at 14 months, found no differences for language, IQ, visual motor function and visual acuity between formula groups or breastfed infants. Concludes adding both DHA and AA supports both visual and cognitive development through to 39 months. Concludes the scientific evidence on safety and efficacy together with information on human milk does not support a unique AA:DHA ratio of 2:1. Would support a prohibition clause in Option 2 to regulate for a 1:1 DHA:AA ratio in infant formula but not follow-on formula. Would consider addition of DHA alone in follow on formula. Believes AA should not be added alone to infant formula as no studies have demonstrated safety or benefits.

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		International legislation Notes CODEX provides the global standard and does not specify any provision for the AA:DHA ratio. Refers to CODEX draft revised standard above. Notes the current and proposed Codex infant formula standards are in conflict with current FSANZ requirements. CODEX recommends AA and DHA additions should take into account levels in human milk. Notes the substantial variation in ratios in human milk around the globe and considers there is no reason to fix the AA:DHA ratio at 2:1. Notes US FDA permits the addition of LCPUFA to infant formula, but no provision is given for the ratio or levels of LCPUFA addition. ***Impact on consumers*** The nutritional products recommended by the international expert group are not available for NZ and Australian infants. Provides less choice, and manufacturers may need to remove supplemented formula as they become cost prohibitive. With less competition higher price is passed onto consumers. ***Impact on industry*** Nestlé manufactures infant formula in Europe and meets the draft CODEX recommendation (ratio 1:1). Nestle Australia is unable to obtain products harmonised with Europe and imports small volumes of infant formula made especially for Australia. This adds cost and complexity. The status quo results in barriers to trade as infant formulas will not align with international products, increased costs, increased chance of items being out of stock due to smaller runs done for Australia and NZ as lower priority than harmonised products. Ensuring consistency with global standards will allow NZ / Australia to import from a wider source. Overall considers removal of the ratio would: • allow industry to trade competitively internationally and encourage innovation; • result in economy of scale savings for production of Nestle infant formula as it would align with European products; and • reduce problems of supply. A Modified Option would: • allow manufacturers to make available to consumers products available in Europe; • remove trade barriers; • enable harmonisation with other countries; and

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		• open up choice for consumers. Consumers would have access to the best available formulas based on international expert group advice.
	Martek Biosciences Corporation, Australia Laura Colavizza	**Supports Option 1** Encourages FSANZ NOT to remove the requirement for the addition of AA. ***Science, health and safety*** Considers there is currently no scientific evidence to establish the safety of removal of AA from formulas that contain DHA. Considers there is scientific evidence to establish the growth and developmental benefits of having both DHA and AA, and some risks having omega 3 without AA. Notes Makrides and Gibson (2005a) study was not designed to consider the difference between DHA and AA supplemented formula, and formula supplemented with DHA alone. Notes human milk contains both DHA and AA on average in a ratio of approximately 2:1. Provides comments on the scientific research cited in the IAR: • considers the Makrides et al (2000 and 2005) review does not establish there is no difference in outcome between the addition of DHA and AA together, compared to the addition of DHA alone in infant formula; • notes the inherent problems with interpretation of meta-analysis reports such as Makrides et al (2005). Subgroup data from the individual studies in the meta analysis demonstrates significant differences in infant length and weight between infants fed LCPUFA supplemented formulas with both DHA and AA, compared to AA alone. Considers the individual studies need greater consideration. • considers reviews by Makrides et al (2000 and 2005) do not consider the effects of LCPUFAS on preterm infants. Notes other studies clearly provide evidence of adverse growth effects on preterm infants where AA and DHA are not included in combination in supplemented infant formula. Considers supplementation with both DHA and AA in an appropriate ratio could have benefits for all infants; • considers growth should not be the only criterion to assess nutritional health and well being of infants. Notes there is clear evidence the addition of LCPUFAs have developmental effects on the immune system and visual, cognitive and motor functions; • notes the Makrides et al review suggests infants fed formula supplemented with only omega 3 supported adequate growth despite a reduction in AA status, suggesting formula with DHA alone is adequate.

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		Notes other authors (Kuratko et al 2005, Harbige, 2003) expressed concern that an unsupported conclusion may be drawn that the omission of AA from formula may be acceptable. Also notes that reduced AA levels might present an earlier indication of deficiency, namely in development of the infant, including possible immune function; • considers it is simply incorrect to refer to routine use of growth data by health professionals as evidence that development is not affected by nutrition in a different manner; • considers the review by Kleith and Clandinin (2005) provides a comprehensive analysis. The conclusion of this review favours the addition of a combination of DHA and AA for both term and preterm infants. Considers virtually all studies showing long-term benefit of LCPUFA supplementation during infancy on cognitive function have used a combination of AA and DHA in a ratio of at least 1:1; • Refers to a review of recommendations for LCPUFA supplementation in infancy the (Akabas and Deckelbaum, 2006) which concluded current levels of DHA:AA are beneficial for visual and cognitive development of low birth weight infants and likely for normal weight infants also. • Notes several studies have shown suboptimal growth in infants fed formula with DHA but not AA. Concludes the science around interactions of LCPUFA including importance of AA on factors other than growth, demonstrates the importance of supplementing with a combination of DHA and AA. ***International*** Considers there is no international body that recommends the addition of DHA without AA. Also considers the proposal would create inconsistencies between domestic and international food standards and practices. Considers the summary of the international position in the IAR is neither complete nor correct and has overlooked approval requirements which reflect different methods of food standards administration. Refers to standards in USA, Canada, Europe and CODEX that require a minimum ratio of 1:1 AA to DHA in supplemented formula. Considers the AA:DHA ratio of approximately 2:1 in Australia is therefore more consistent with the position of these countries, while the alternative of having no AA is not. To remove the requirement for the presence of AA where DHA is added is counter to the draft CODEX policy, and to the naturally occurring ratio of AA to DHA in human milk. ***Trade*** Considers the removal of the requirement for the 2:1 ratio AA:DHA will have a negative impact on consumers and on the promotion of fair trade.

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		Impact on consumers and industry Agrees maintaining the status quo is unlikely to impact on consumers. Considers if the ratio is removed and manufacturers no longer add such a ratio, infants will be denied the benefits of LCPUFAs. Suggests deletion of clause 23(d) would foster trade barriers between domestic and international markets.
	DSM Food Specialities, The Netherlands B Schulze	**Supports Option 1** ***Science, health and safety*** Notes the DHA content of human milk is variable, however for populations consuming a typical western diet an average ratio of approximately 2 can be expected – provides data on LCPUFA content of human milk for Australia, North America and Spain. Notes AA and DHA are always present in human milk. Considers most studies cited by the applicant have not used supplementation with the respective ratio of AA:DHA. Also considers the results summarized in the table in the Application do not reflect in all cases the outcomes and conclusions drawn by the authors. Considers studies cited by the applicant that did use LCPUFA supplementation with a ratio of 'approximately 2' did mainly show a positive effect. Notes the Birch studies and Wilatts study on LCPUFA enriched formula used a ratio of 2:1 and 1:8 respectively and observed the benefit on cognitive function with no significant differences in growth. Refers to more recent studies mainly carried out with a ratio of two – provides a table of summary of studies. Notes a sound, sufficiently powered dose response study is lacking. However, considers a striking amount of studies using a 2:1 ratio have shown improvement in visual acuity and cognitive function and more recently, decreased respiratory illness. Notes the singular suppletion with DHA reduces AA levels in red blood cells. AA levels have been found to be 8-10% lower compared to non fortified control formula, and 15-40% lower compared to breast fed children. No differences were observed in growth or visual function. Is not aware of data on singular AA supplementation. Other than the beneficial effect on mental development, notes a recent study has shown imbalances among n-6 and n-3 LCPUFA by term gestation are associated with lower bone mass. ***International regulation*** Concludes the current scientific consensus is clearly that if LCPUFAs are added to infant formula DHA should be combined with AA.

Ref	Submitter	A532 Submission Comments
		Notes that although international regulations do not precisely require a ratio, the expert opinion states that the optional addition of DHA should not exceed 0.5% of total fat intake, and the AA content should be at least the same concentration as DHA. Notes the ESPGHAN Medical Position paper concludes this. Considers the reason for the current manufacturing practice to sell products only in Australia and NZ cannot be the ratio requirement of approximately 2. Believes the ratio requirement reflects the current market standards in most countries where LCPUFAs are added to infant formula – provides a table of LCPUFA content and ratios with a ratio AA:DHA range of 1.6 to 2.0. Considers the ratio requirement does not pose a barrier to international trade as consistency is not jeopardised by the ratio. ***Impact on industry*** Considers it highly likely manufacturers will add DHA alone (as in follow on formula in other countries) but still be able to claim LCPUFA on the label. Removal of the ratio in Australia and NZ could lead to an imbalance of DHA:AA. As this ratio is the market standard in many other countries in Asia / Pacific and beyond this could lead to loss of competitiveness in the market. ***Impact on consumers*** If the status quo remains consumers will be able to trust that formula resembles human milk and is backed by scientific evidence. Option 2 is likely to result in commercialisation of infant formula with varying LCPUFA contents, some not resembling human milk. Consumers could be easily misled wrongly assuming the product resembles human milk.
	Mead Johnson Deborah Diersen-Schade	**Supports Modified Option 1** Requests Option 2 be rejected and replaced with a less restrictive requirement. **Recommends a Modified Option** that AA be included when omega 3 LCPUFAs are added to infant formula, but without the requirement of a ratio of approx 2. Suggests a range of ratios should be determined from human milk and clinical studies. Notes Option 2 would remove the requirement to include omega 6 LCPUFA in formulas containing omega 3 LCPUFA. Acknowledges that ratios of AA: DHA other than 2:1 are safe and of potential benefit in the infant diet.

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		Science, health and safety Concerned the addition of omega 3 (DHA) without the balanced addition of omega 6 (AA) is a deviation from human milk. Also concerned about the complex and poorly understood interactions between these PUFA with wide ranging effects on growth, development and health. Considers there is no body of data from clinical trials that adequately supports the safety of infant formulas that contain DHA with no compensatory AA. Recommendation that <u>both</u> omega 3 and omega 6 are needed in infant formula is based on two factors: • that breastfed infants have always received both omega 3 and omega 6; and • that the two PUFAs have wide ranging, complex and intertwined metabolism and physiological effects. Is not aware of any clinical trials that have evaluated the addition of AA in the absence of DHA. Does not believe there is evidence that AA is required in itself in infants' diets. However experts have suggested (Innes 2003) that AA may be essential when omega 3 are added to the infant diet. Notes studies showing the addition of only DHA to formula actively suppresses AA levels in blood. Although the clinical significance of reduced blood AA levels below that of breastfed infants is unclear, it may have wider relevance if it is indicative of lower infant AA status in general. *Neural Development* Notes Birch et al found a significant increase in mental development in infants fed formula with both DHA and AA compared to non supplemented formula, while those fed formula with DHA only had an intermediate mental development score and not significantly different from the DHA+AA group. The mental development index of those fed DHA+AA was also not different from the breast milk reference group.
		Notes studies by Scott et al (1998) that found infants fed formula with DHA only had significantly lower vocabulary scores at 14 months. Follow up of these infants at 39 months (Auestad et al 2003)demonstrated no difference among the groups, concluding the observations at 14 months may have been a transient effect of DHA (without AA) supplementation on vocabulary, or may have occurred by chance. Agrees data does not indicate growth of term infants is negatively impacted by the addition of a combination of DHA and AA, or with DHA alone, although notes there are significantly fewer studies of DHA alone. Considers an imbalance of omega 3 to omega 6 could be a potential concern. The balance of omega 3 and omega 6 is also plays a critical role in immune response.

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		Notes Field et al (2000) who found adding DHA and AA to formula resulted in immune outcomes more similar to and consistent with human milk. Refers to studies showing other areas where LCPUFA balance has significant effects including haemostasis, thrombosis, insulin sensitivity, oxidant stress, hepatic lipid and lipoprotein metabolism. Notes human milk always contains both omega 3 and omega 6, and typically in a ratio of 1:1. Agrees the 2:1 ratio requirement is overly restrictive and a broader range if ratios can be supported both on human milk and clinical data. ***International*** Notes all marketed LCPUFA supplemented formulas in US include both AA and DHA in a ratio of 1.6 – 2.7.1. Recommends FSANZ adopt Clause 5.5 in the revised directive from EC including that DHA (omega 3) shall not exceed omega 6 (AA). Notes the proposed Codex standard for Infant Formula includes a similar requirement: if DHA is added to infant formula the AA content should reach at least the same content as DHA. Notes these specifications are in line with numerous expert recommendations e.g. FAO/WHO Joint Expert Consultation; ESPGHAN-coordinated International Expert Group. ***Impact on industry*** There is no question that removing the requirement to include AA in formula containing DHA would reduce manufacturing costs. However with limited clinical data available on formula with added DHA without AA, considers many questions remain.
	Government	
	Dept Human Services, Victorian Government Victor Di Paola	**Support for either option not specified : Recommends an Alternative Option** **Alternative option recommended:** The total DHA content should not exceed the AA total content, in line with the proposed international directive. ***Science, health and safety*** Considers there are no other regulations requiring the addition of omega 6 if omega 3 is added; this application implicitly requests permissions to add singular omega 6 or omega 3. Considers current data shows the addition of DHA without AA has no effect on linear growth in term infants.

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		Studies looking at the effect of DHA supplementation on cognitive development are equivocal with studies showing both no effect (Austed 2001, Makjrides 2000) or a negative effect (Birch 1998 and 2000, Scott 1998). Notes the lack of consistency in study findings. However DHA supplementation consistently shows a modest reduction in serum AA levels compared to unsupplemented formula fed babies. Considers no studies have evaluated the biochemical and immunological effect of this reduction. Notes there are no studies to date examining the effects of singular addition of AA to infant formula. Considers one issue not reviewed in the IAR is the total amount of AA and DHA permitted in infant and follow-on formula. By removing sub clause 23(d) the permissible limit of added AA and DHA would be up to 1%. The majority of studies looking at safety of added DHA use a DHA intake of O.12 to 0.45% with only one study using a maximum of 1% (Makrides 1995). Considers the safety of DHA above 0.45% and AA at any level has not been adequately assessed. Recommends before Option 2 is further considered the following issues need to be addressed: • assessment of the safety of the singular addition of omega 6 • assessment of safety of singular addition of omega 3 at levels greater than 0.45% • whether a replacement ratio or minimum amount of a second PUFA should be mandated in a standard.
	Food NZ Standards Authority Carole Inkster	**Supports Option 1** Considers it premature to adopt Option 2. ***Science, health and safety*** Considers a full risk assessment and independent peer review is needed. Considers it important that the permitted ratio approximates breast milk and allows some flexibility e.g. approximately 2:1. Notes the Draft European Directive on Infant Formula proposes the DHA content shall not exceed AA content. Removing the ratio, while maintaining the maximum **%** of LCPUFAs in Clause 23 of Standard 2.9.1 does not. Notes the application considers no potential infant formula ingredient provides a natural ratio of 2:1. Considers this is not a valid reason to remove the ratio. Suggests the advice of independent experts be sought for independent review prior to finalisation and consultation on the DAR.

Ref	Submitter	A532 Submission Comments
	NSW Food Authority, Australia Bill Porter	**Supports Option 2** Has no concerns with this application at the IAR stage, and does not object to further consideration.
	Health Professional / Academic	
	Women and Children's Hospital, Australia Dr Maria Makrides, Director Child Nutrition Research Centre, and Robert Gibson, Prof Nutritional and Functional Food Science, Adelaide University	**Supports Option 2** ***Science, health and safety*** Considers data from randomised controlled trials and breast milk composition shows: • levels of breast milk AA rarely exceed 0.5% total fatty acids so any recommendation above this as a maximum is difficult to justify; • DHA levels can vary in human milk from 0.1 to 1% total fats and this range has been tested in recipient breastfed infants and formula fed infants with no demonstrated adverse effects; and • cannot find evidence to support any fixed ratio of AA to DHA in formulas for term infants. Has undertaken a review and meta analysis to evaluate the effect of supplementing infant formula with LCPUFA on the growth of term infants. Growth was the primary focus as it is used by health professionals to assess well being. Reviewed 14 randomised controlled trials of formula feeding, and demonstrated: • no significant effect of LCPUFA supplementation on infant weight, length or head circumference at any age regardless of whether omega 3 only or omega 3 plus AA are added, or the source of supplementation. The review concluded even when formulas were supplemented with omega 3 only there was no clinical effect on growth. Six of the studies reviewed included supplementation with DHA only with DHA levels at 0.3% total fatty acids. This indicates a safe level in terms of growth without adding AA. Concludes a fixed ratio of AA to DHA could not be supported from the clinical trials to date. • term infants fed formula with added omega 3 alone have lower AA status, however the review clearly showed that growth was not compromised. Considers there are few studies to understand whether lower plasma AA, caused by addition of omega 3, has negative health impacts. Considers no negative clinical effects of dietary omega 3 have been reported to date in term infants. Is not aware of trials assessing the addition of AA without DHA to infant formulas. Notes 3 trails comparing DHA+AA with DHA alone and control.

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		Two of the three trials find no difference between visual or neurological outcomes to two years of age. One study showed a benefit of DHA+AA at a single assessment age, and data may have been skewed by statistical outlier. Considers definite statements about AA can only be made after sufficient evidence is aggregated. In the absence of strong evidence from clinical trails, the levels of the two LCPUFAs in human milk provide guidance. The ratio of DHA: AA in human milk varies according to the diet of the mother. The ratio of AA to DHA in breast milk around the world varies from 4:1 to 0.3:1. The AA content is similar (generally does not exceed 0.5% total fatty acids) while DHA levels varies by 10 fold. The variation is not due to race.
	Institute Food Nutrition and Human Health, Massey University Suzi Penny	**Option supported not stated.** ***Science, health and safety*** Notes a large body of research has shown that: • DHA is specifically critical for development and function of the retina and aspects of brain function; • variations in maternal diet affect levels of DHA and AA in breast milk; • conversion of AA to DHA is relatively inefficient; and • DHA and AA are not interconvertable. Considers overall research is consistent with a benefit from the addition of DHA to infant formula. Considers it imperative that biological rationales and the core neuro science be considered along side supplementation intervention trials. Considers there is a large rapidly expanding body of research that emphasises the key role of DHA in neuronal function, neuroprotection, photoreceptors and synaptic plasticity. Considers current consensus is that western populations average diets provide insufficient omega 3 compared to omega 6. Notes there is potential that DHA administration not balanced appropriately with AA might increase the risk for infants with haemorrhagic disease. Notes excessive bleeding has been identified as a potential risk with relative excess of omega 3 in adults and a slight increase in haemorrhagic stroke in adults in omega 3 supplementation intervention trails. Notes also a significant amount of research has highlighted concerns about the presence of contaminants in DHA of marine origins, and its impact on the developing brain.

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	Gerard Hornstra Prof Emeritus of Experimental Nutrition, Maastricht University, Netherlands.	**Supports Option 1** ***Science, health and safety*** • *Interactions between omega 6 and omega 3* Notes supplementation with omega 3 usually lowers omega 6 in the blood which may imply lower AA status in the brain. Since the importance of lower AA levels in the brain is not known, considers it prudent not to create conditions which could result in reduced concentrations. Considers if supplementation with omega 3 is thought desirable, co-supplementation with omega 6 seems prudent to maintain balance. • *Functional comparisons between formulae containing AA+DHA or DHA only.* Considers the studies are difficult to compare. Notes one study (in IAR) where the AA+DHA formula caused a significant developmental advantage over the DHA only formula. Considers additional studies are required and need to be evaluated – strongly advises FSANZ to maintain the Status Quo until this occurs. Notes the LCPUFA sources used in studies analysed for the IAR differ considerably. This needs to be taken into account. Notes human milk contains a number of other omega 6 and omega 3 that can all play a role so should be considered. Notes the maternal diet affects the omega 6 to omega 3 ratio in breast milk. A recent study (manuscript in preparation) clearly demonstrates this holds for DHA but also for AA, though to a lesser extent. Due to large variation in LCPUFA in the diet considerable variations in breast milk can be expected. Literature reviews demonstrate the AA/DHA ratio in human milk varies considerably with the average ratio of almost 2 (33 samples). Considers this also supports maintaining the status quo.
	Ludwig-Maximilians University of Munich, Germany Berthold Koletzko, Prof Paediatrics.	**Supports Modified option 1** **Recommends FSANZ should maintain a requirement for the inclusion of arachidonic acid in infant formula if DHA is added, requiring an AA content reaching at least the content of DHA.** Considers it reasonable to remove the requirement for a ratio of approximately 2. However, notes the application does not propose an alternative to this ratio, or of an AA content. Notes if the proposal is adopted there would be no requirement to add AA with the addition of DHA. Considers this is unreasonable as has not been adequately demonstrated to be suitable and safe for infants, and is not in line with current scientific knowledge.

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		Also notes it contrasts with regulations to be adopted in the EU and Codex Alimentarius. ***Science, health and safety*** Considers IAR point 6 needs to be corrected. Believes there is limited evidence on clinical trials comparing formula with different omega 3 to omega 6 ratios. Considers independent experts agree there is no conclusive evidence on the suitability and safety of including DHA alone without simultaneous addition of AA. Considers the review cited in the IAR by Makrides et al 2000(a) is an internal paper not peer reviewed. The meta-analysis by Makrides et al 2005(a) evaluated growth as the only an endpoint. While there was no difference in growth between the small numbers of studies using only DHA compared with those using both AA and DHA, these studies were not designed to test this question. Concludes no evidence is available in the accountable literature showing the addition of DHA alone would be suitable and safe for infant formulae. Considers the possible consequences of adding DHA alone and the effect on lowering blood AA levels have not been adequately evaluated in infants. Suggests the statement under Point 6.3 IAR that 'the European Scientific Committee on Food's recommendation was developed from two publications' is not correct and should be deleted (as a member on this committee at the time). Considers a regulation on the minimum content of AA is necessary to protect infant safety unless conclusive evidence becomes available on the suitability and safety of the addition of DHA alone. Notes human breast milk always contains both DHA and AA. Human milk providing only DHA has never been reported. Breast milk content of AA is metabolically regulated, whereas DHA contents are much more variable depending on maternal diet. Notes studies on the addition of DHA only are very limited, however tend to find reduced blood levels of AA and in some studies adverse effects on weight gain and longitudinal growth. Notes there are very few studies undertaken to compare formula with and without added AA, but limited data points to a potential need to add both AA and DHA. Refers to data raising concern about adding DHA alone (Scott et al 1998), and pointing to the potential advantage of providing both DHA and AA for mental development (Birch et al 2000). Concludes the limited data available raises serious concerns about the adequacy and safety of adding only omega 3 LCPUFA without omega 6 LCPUFA, and indicates the need for more research.

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		International Notes proposed international regulations require the inclusion of AA, along with the inclusion of DHA providing at least the same levels of AA as the chosen level of DHA. Refers to: • the draft Directive of the European Commission, which includes 'the DHA content shall not exceed that of AA'; • the Codex draft revised standard for infant formula which includes 'if DHA is added to infant formula, AA concentration should reach at least the same concentration as DHA'. Notes this has been adopted by consensus; • USA: only LCPUFA enriched formulae with a ratio of AA to DHA of about 2 have been accepted; and • EU: the expert report of the Scientific Committee on Food (2003) concluded the concentration of AA should not be lower than DHA in infant formulae to avoid relative deficiency of AA.
	Prof. M.T Clandinin Director, Alberta Institute for Human Nutrition, University of Alberta, Canada.	**Supports Modified Option 1.** Considers formula containing DHA should always contain AA in a ratio of approx 1:1 to 2:1. ***Science, health and safety*** Notes: • recent clinical studies indicate feeding both AA and DHA improve infant growth and development scores, and there is not evidence this improvement will occur in the absence of AA in the formula. • tissue analysis has for several decades indicated AA is quantitatively as important a fatty acid constituent of brain as 22:6n-3. Considers all studies indicate that when DHA is fed in the absence of AA levels of AA decline in tissues and plasma. There is no reason to expect this decline is desirable and it does not mimic breast milk. Notes AA is a normal consistent component of human milk.
	Eric Lien Dept Food Science and Human Nutrition, University of Illinois	**Supports Modified Option 1** Suggests an alternative option to require formula AA levels to at least equal DHA levels. Considers the ratio of 2:1 is restrictive and not supported by the range in human milk. Disagrees with the proposal for the following reasons: Notes numerous studies have evaluated the addition of both DHA and AA, while fewer have studied the addition of DHA alone.

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		Refers to studies with positive results for vocabulary production and cognitive development with formula with the combined addition of AA and DHA, compared to unsupplemented formulas. The addition of DHA only did not show the same positive results. Studies comparing formulas with AA and DHA to unsupplemented formula for immune function, blood pressure and incidence of respiratory infection showed infants taking supplemented formulas responded more closely to breast fed infants than those using the control formulas. Studies have not been reported for DHA alone. Refers to a paper (Yuhas et al 2000 and Yuhas et al 2006) analysing 50 samples of human milk from nine countries demonstrating AA concentrations in human milk are relatively constant across countries, but DHA levels are highly variable. Considers AA to be a protected nutrient with breast milk production actively maintaining relatively constant levels. Variations in the ratio are primarily due to variations in DHA not AA. Considers growth is not the only measure to be considered, cognitive development is of central importance. Notes formulas containing only DHA are the exception - formulas containing both AA and DHA are currently available in numerous countries. Considers a requirement for balanced addition of both AA and DHA would not harm most infant formula manufacturers. Concludes observations argue for the importance of AA in the developing infant. Until additional outcome data with DHA alone is published it would be unwise to permit the addition of DHA alone. The facts strongly support the combined addition of AA and DHA to formula. ***International*** Notes several regulatory and authoritative bodies are currently reviewing the status of LCPUFAs. Refers to draft documents for Codex and the European Commission which require the addition of AA when DHA is added to formula.
	J Thomas Brenna Prof Human Nutrition Cornell University New York, USA	**Supports Option 1** Interprets the application as permitting the use of DHA without AA in infant formula and is opposed to this proposal. ***Science, health and safety*** Considers the use of DHA without AA has not been studied in detail. Previous studies including those cited in the Application, assess both AA and DHA. Considers the use of DHA-only formulae constitutes an uncontrolled experiment.

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		Breast milk worldwide contains both DHA and AA; AA varies less than DHA. With the best information available at the time, considers both DHA and AA are needed when LCPUFAs are added. Notes all formulas in the USA contain both AA and DHA if LCPUFAs are added. Refers to an analysis of breast milk AA and DHA concentrations (2004 - updated 2006) at final stages for publication. Notes AA is much less variable than DHA. Considers data provides a best estimate for the ratio of DHA to AA of 1.6. As this varies widely amongst breast milk considers the 'approximately 2' target is appropriate. DHA alone in formula without AA is inconsistent with the philosophy that formula model breast milk.
	Students	
	Amy Barnes, Food Science student, New Zealand	**Supports Option 1** ***Science, health and safety*** Considers there is insufficient evidence to ensure safety of infants if the standard is amended as proposed. Considers no studies have been identified that assess the risk of using formula with the addition of AA only. Notes without the ratio requirement DHA could be added without AA – reviews have identified this decreased serum AA levels although growth was not affected. Notes it has been suggested that decreased AA levels may be an early indication of deficiency and that DHA should be added in the presence of AA to avoid this decrease. Considers the long-term effects of formulae with DHA but not AA have not been investigated. Considers the ratio should be the same range as found in human milk. Notes human milk always contains AA and studies show the ratio of LCPUFAs in human milk vary. Notes the importance of the combination of both DHA and AA on infants' mental development. ***International*** Notes the European Scientific Committee on Food recommends DHA should not be higher than the omega 6 content. Notes this recommendation had been included in a draft revision of the European Directive on infant formula.

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	Xiaolu Long Food Science student, University of Auckland, New Zealand	**Supports Option 1** ***Science, health and safety*** Notes DHA and AA are required for brain development and both are present in human milk. Notes the serum level of AA is negatively affected by DHA supplementation alone. Considers that although there is no significant evidence that the decreased serum level of AA directly affects growth the potential risk cannot be ignored. Considers studies have not looked at long-term effects. Believes formula should align with human milk. Considers further research is needed before making the decision to change to current standard. ***International*** Notes other countries do not have the ratio requirement as in Standard 2.9.1, however considers reduction of trade barriers is insufficient justification to lower standards of food regulation. ***Impact on industry*** Considers it likely manufacturers will add DHA or AA alone to infant formula and may add DHA only to reduce costs, as DHA is less expensive than AA. Considers maintenance of public health is more important than any cost benefit of not adding DHA or AA.
	Jenny Wong Food science student, University of Auckland, New Zealand	**Supports Option 1** ***Science, health and safety*** Considers the ratio should mimic that in breast milk. Notes the range of ratios in breast milk varies and considers this has no significant effects on normal growth outcomes. Refers to studies on visual acuity showing infants fed on a 2:1 ratio of AA: DHA showed benefits in mental development, psychomotor development and cognitive, language and motor subscales compared to standard formulas with no DHA or AA. Notes single addition of DHA has reported a decline in serum AA. Notes the effect of this on normal growth and the nervous system are poorly understood (Innis et al 1996) but that its importance to infant nutrition should not be omitted (Kurato et al, 2005). Considers, as there is no clinical evidence supporting the irrelevance of AA this should not be neglected in infant formula as the positive impact is yet to be elucidated. Considers the long term effects of AA suppression are not fully understood.

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		International / trade Considers although there is no new evidence to further support the benefits of maintaining this ratio, it should not be amended for the expansion of trade within the international market.
	Selina Chan Student, Auckland, New Zealand	**Supports Option 2** Considers there is insufficient evidence to warrant the requirement for a 2:1 ratio between omega 3: omega 6 LCPUFAs. . Recommends FSANZ consider replacing this requirement with one similar to that recommended by the European Scientific Committee on Food (ESCF) with monitoring over time. ***Impact on industry / trade*** As no other country requires a specific ratio considers it places an unreasonable demand on Australia and NZ manufacturers and considers standardisation of food products is important for overseas trade. ***International*** Suggests it may be pragmatic to adopt the ESCF requirement in which the omega 6 content of infant formulae is required to be 'not lower than the DHA content', in addition to stated maximum levels. Considers this may safeguard any potential harmful effects caused by the depletion of AA due to insufficient omega 6. This would also support export to Europe as other regulations are similar to the ESCF.
	Krishna Jones	**Supports Option 2** ***Science, health and safety*** Considers recent scientific literature does not support the current ratio in the CODE of 2:1. Considers the application provides evidence that changing the ratio of LCPUFAs added to infant formula will not affect the health and safety of infants as long as maximum values are not exceeded. Considers the current ratio was based on the assumption that the ratio in breast milk remains constant, but recent studies show this varies. Considers there is evidence that a wider range of ratios seen in breast milk are suitable for growth of infants. ***International / trade / industry / consumers*** Notes no other international legislation supports this ratio. Notes the ESCF recommends the omega 6 content should not be lower than the DHA content to prevent deficiency of AA and to ensure a balance. Considers improved trade opportunities will result from removal of the ratio requirement.

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		Impact on industry / consumers Considers costs to manufacturers and the consumers will be reduced with Option 2.
	Prithika Ram Food science student Auckland, New Zealand	**Supports Option 1** ***Science, health and safety*** Considers the current ratio required in Standard 2.9.1 has not caused any health issues and there are no studies proving this ratio has any detrimental effects on infants. Considers DHA should be considered an essential nutrient for normal eye and brain development in infants. Considers that as fatty acids are essential determinants of growth, visual and neural development in an early infant's life the Application should be rejected. Considers the appropriate ratio of fatty acids is required to have beneficial effects. ***International / industry*** Considers the request for an amendment is to meet international marketing needs, and removing the requirement would influence manufacturers to add differing concentrations of fatty acids. Considers the cost of adding DHA and AA may attract manufacturers to exclude fatty acids in infant formulas, or include them in concentrations that may not provide benefits. Notes there is no international requirement regarding the ratio of omega 6 and omega 3. However considers international markets may soon consider adding these. ***Impact on consumers*** Notes the current standard does not affect the complete range of infant formulas and consumers currently have a choice of infant formula without added LCPUFAs.
	Danae Larsen Auckland, New Zealand	**Supports Option 2** Considers current evidence has not demonstrated the current ratio of 2 is the ideal ratio or is significantly better than other ratios. ***Science, health and safety*** Notes the 2:1 ratio in formula was aligned to breast milk, but breast milk is known to vary. Considers the evidence around LCPUFA supplementation of infant formulas is still inconclusive; refers to a review by Wright et al 2006 in which six of 10 randomised controlled trials did not show any significant benefits to infants consuming the LCPUFA enriched formulas.

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		Refers to the studies noting generally that infants fed formula with DHA alone had reduced serum AA levels. However notes **Auestad** et al 2003 found infants at 39 months of age had similar levels of DHA and AA regardless of which dietary group they were in over their first year of life. Considers this significant in showing the current ratio is not necessary as DHA and AA levels appear to 'even out' over time. Also refers to four trials which tested DHA alone and found no negative results regarding growth, despite depleting infants' AA supply. Considers adding DHA alone or with AA to term infant formula still supports normal growth. Considers studies show a range of ratios demonstrate differing results. Advantages seen in younger infants fed supplemented formulas, such as visual development, have not been present at older ages. Suggests follow-up research is needed in children to see if effects are long term. Considers is difficult to assess the effect of formulae without AA added as there is little scientific study trialling formula with AA alone. ***International / impact on trade and consumers*** Considers removal of the requirement could have positive benefits for consumers through reduced production costs for formula, potentially increase trade options, and promote consistency with international standards.
	Pei San Lum Food Science student	**Supports Option 2** Considers three types of formula should be available – non supplemented, supplementation at a 2:1 ratio for omega 6 and omega 3, and formula with DHA and AA, or DHA alone without a ratio requirement. Notes this would require additional labelling. ***Science, health and safety*** Considers it useful to include maximum and minimum ratios for all formula adding DHA and AA to avoid a significant imbalance. Notes the current ratio is based on breast milk, but that this varies. Refers to the reviews done by Makrides (2002 and 2005); notes this was based on research before 1998. Considers a review of more current results is necessary. Considers differences in growth or development reported in the literature reviews are not due to differences in the ratio of DHA to AA. Refers to a review undertaken in 2006 (Wright et al 2006). Three out of 10 studies investigated differences in growth and development of infants fed formula supplemented with DHA, formula supplemented with DHA and AA, and standard formula. No significant difference was found.

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		The reduction of AA due to competition with DHA was noted in association with reduced infant growth. It was suggested that AA should not be added together with DHA. Considers there is no evidence of a health risk to infants fed supplemented formula outside the DHA:AA ratio 2:1. Considers it too early to reach a conclusion on potential risks due to reduced serum AA level. ***International*** Notes there are currently no international regulations that impose a ratio rule in infant formula. Notes the draft CODEX standard does not require a ratio of 2:1, and that the European Commission revised directive fixes the total % of LCPUFAs added to infant formula, and that DHA should not exceed AA.. Also notes Canada and the United States have placed limits on total fat content, not on the ratio required. ***Impact on industry and consumers*** Considers removing the ratio requirement will enable industry to become more competitive, to produce products for export, to reduce costs, and supplemented infant formulae will be less expensive for the consumer.
	Kusum Edirisinghe Food science student, University of Auckland, New Zealand.	**Supports Option 2** ***Science, health and safety*** Notes the 2:1 ratio is based on the assumption that breast milk remains relatively constant, however more recent published data does not support this. Notes FSANZ has not identified any scientific literature that assesses the singular addition of AA. Notes studies concluding there is no effect on normal growth patterns with different omega 6 to omega 3 ratios. Notes the ESCAN recommendation that the omega 6 content of infant formula should not be lower than the DHA content as a means of preventing relative deficiency of AA, and to ensure balance. Also notes the concern of Kuratko et al that a reduction in serum AA levels may be an early sign of poor nutrition. ***International*** Notes no overseas international regulations specify a ratio between omega 6 and omega 3 content of infant formula. ***Impact on industry*** Considers removing Clause 23(d) would eliminate compliance costs for industry with savings passed onto consumers, would widen trade opportunities through harmonisation with international standards and enable industry to manufacture one formulation world wide.

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	Cheryll Chuah Auckland, New Zealand	**Supports Option 2** ***Science, health and safety*** Considers there is uncertainty about the benefits of supplementing infant formula with LCPUFAs, predominantly DHA and AA, and their respective ratio. Notes the literature agrees that infants fed supplemented formula will have raised levels of DHA and AA compared to an infant fed non-supplemented formula. Considers the ratio 21:1 is based on unsound statistics. Refers to a paper by Remko et al 2005 noting the ratio in breast milk is dependant on maternal diet and a 2:1 ratio is based on mothers living on a western diet so is not representative of the world. Notes it is difficult to find studies looking at the affect on growth and development associated with the addition of AA without DHA to infant formula. ***International, trade*** Considers removing the 2:1 ratio would enable Australasia to be internationally competitive, the retail cost of infant formula will reduce due to lower manufacturing costs, and trade opportunities will widen.
	Aditee Naik Auckland University, New Zealand	**Preferred Option not stated** Provides general information related to infant feeding. No conclusion or supporting information regarding the proposed options for the addition of LCPUFAs to infant formula is provided.
	Jasmine Zhou Food Science student, New Zealand	**Supports Option 2** ***Science*** Believes science does not support the ratio 2:1. Considers more research is necessary to determine the best ratio. Considers the ratio should align with human milk, but notes there is a wide range of ratios in breast milk. ***International and trade*** Notes there is no international legislation requiring such a ratio. Therefore considers Clause 23(d) could present a barrier to trade. Considers an amendment to the Code would eliminate compliance costs incurred by industry and therefore the consumer, and promote fair trading. ***Impact on industry and consumers*** Notes the cost of infant formula with added LCPUFAs is higher than those without and that this is passed onto the consumer.

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	Shou Lin	**Supports Option 2** ***Science, health and safety*** Considers LCPUFAs are an important additive to infant formula but that the ratio is not necessary. Notes the importance of LCPUFAs for growth, brain development and visual acuity. ***International*** Notes the US and Canada do not require a specific ratio of omega 6 to omega 3 but do have a requirement for total fat content. Notes also the European Commission is in the process of revising their infant formula directive and define a range of omega 6 and omega 3 LCPUFAs.
	Jing Zhou	**Supports Option 2** ***Science, health and safety*** Considers there is no reliable evidence that the omega 6: omega 3 ratio should be approximately 2. Notes there is no effect on normal growth patterns with different omega 6: omega 3 ratios. Considers more work needs to be undertaken on the balance of these fatty acids. ***International and trade*** Notes infant formula regulations around the world do not require a 2:1 ratio of omega 6: omega 3 in infant formula. Notes the US and Canada set a requirement for the total fat content of infant formula, and the European Commission sets a limit on omega 3 and omega 6 as a percentage of total fat content. Also notes the recently drafted CODEX standard does not specify a ratio of omega 6:omega 3. Notes world trade of infant formula may be impacted with the status quo due to differing regulations. ***Impact on industry and consumers*** Considers adding omega 6 and omega 3 may increase costs of production which will be passed onto consumers.
	Gloria Lam	**Supports Option 2** ***Science, health and safety*** Notes DHA has an important role in visual development and brain functioning and infants fed formula with DHA added have higher IQ than those fed standard formula.

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		Notes conditions that can result with formulas that do not contain DHA including foetal alcohol syndrome, ADHD, cystic fibrosis, PKU, unipolar depression, aggressive hostility, and adrenoleukodystrophy (no references provided). Also notes DHA has an important role in maintenance of normal neural function, which AA does not have. Notes the addition of DHA alone can reduce serum AA. Refers to six of 30 trails that reported lower weight, length, and / or head circumference, and / or lower weight for length ratio in infants fed formula with DHA added compared to those fed control formula. Considers if AA is not added to formula it is likely infants will experience AA deficiency. Notes size and rate of growth is significantly correlated with serum AA level, therefore low AA levels can affect infants' growth rate. Notes a study (Innes et al 2002) showing infants fed formula with the ratio DHA : AA of 1.8:1 gained weight faster than infants fed formula supplemented with DHA only. However, notes a UK study contradicting this (Fewtrell et al 2002) where after 30 days infants fed a supplemented formula with a ratio omega 6: omega 3 of 1.8:1 weighed less than the control group. Refers to studies showing AA levels decrease in the first year if life if infants are fed formula without AA. ***Impact on industry / consumers*** Notes if the ratio was removed from the Code industry could introduce a range of formulae into NZ giving greater consumer choice, and could increase competition amongst manufacturers. Considers that if the price of formula decreases this could discourage breast feeding. However, if the cost of formula increases through the addition of DHA and AA this may encourage breastfeeding, or the use of formulas without LCPUFA supplementation.
	Chen Hao Qiu Food Science student, Auckland University.	**Supports Option 2** ***Science, health, safety*** Considers no research has been identified that assesses the addition of AA alone. However studies on DHA alone demonstrate the benefits of DHA on visual acuity. Notes the ratio of omega 6: omega 3 LCPUFA of about 2 was based on the findings of the US Life Science Research Office who considered inappropriate addition of LCPUFAs could have clinical safety risks especially in relation to growth.

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		Notes the review of LCPUFAs by Makrides showed there were no significant effects on normal growth of infants fed formula with variations in the omega 6: omega 3 ratios. Notes studies show the addition of DHA alone decreases serum AA levels but that this did not affect normal growth in term infants. This was also identified in literature reviews by the European Scientific Committee on Food (ESCF). ***International*** Notes there is no international requirement to have a specific ratio of omega 6: omega 3 in infant formula. Notes US and Canada require a specific total fat intake and the CODEX draft standard on infant formula does not include a specific ratio between omega 6 and omega 3. Notes the ESCF recommends the omega 6 content should not be lower than the DHA content. ***Impact on consumers*** Considers there will be little impact on consumers if the status quo remains. The cost of supplemented formulas will likely remain higher than infant formula without LCPUFAs. Option 2 is unlikely to affect growth and development of infants, and there could be cost savings for consumers. ***Impact on Industry*** Maintaining the requirement for a ratio of 2 will affect trade due to the differing international legislation. Option 2 may widen trade opportunities as Australia and NZ standards will be in line with international standards. Cost savings would result if only one formulation is manufactured for worldwide distribution.
	Jiayan Shen Food Science student, New Zealand.	**Supports Option 2** Considers there seems to be little or no risk in removing the requirement for a ratio of omega 6:omega 3 in infant formula with added LCPUFAs. ***Science, health and safety*** Considers the literature indicates infant physical measurements do not seem to be affected by the ratio of omega 6:omega 3 in their formula diet. Notes visual evoked potential and cognitive function was either no different or significantly benefited by formulas with a LCPUFA2:1 ratio. However this benefit was also obtained by the addition of omega 3 but not omega 6 to standard infant formula. Considers no risks or negative effects were reported for infants fed formula with omega 6: omega 3 at ratios other than 2:1.

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		Considers it crucial to establish whether a ratio of 2:1 naturally occurs in breast milk. The wide range of AA: DHA ratios in human milk does not support the notion of a restrictive 2:1 ratio. Considers the variable AA: DHA ratio in human milk supports Option 2. Considers the source of LCPUFAs is more important than the ratio (Gil, Ramirez, & Gil, 2003). ***International*** Recommends consideration of the European Commission Directive that states the DHA content should not exceed the omega 6 LCPUFA content. ***Impact on Consumers*** Amending Standard 2.9.1 may allow more choice for consumers as a greater range of formula may be imported into Australia and NZ. ***Impact on Industry*** Notes the benefits to industry have been highlighted by the Applicant. There would be fewer barriers to trade and lower production costs.
	Vandana Patel Food Science student, New Zealand.	**Supports Option 2** Considers Option 2 appropriate for the following reasons: • Human milk does not maintain a ratio of 2:1 omega 6: omega 3. • Believes there are no differences in growth and development of infants fed with varying ratios of omega 6: omega 3 LCPUFA.