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

EXPLANATORY STATEMENT

APPLICATION A594

ADDITION OF LUTEIN AS A NUTRITIVE SUBSTANCE TO INFANT FORMULA

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 an Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006 seeking to amend the *Australia New Zealand Food Standards Code* (the Code), to permit the voluntary addition of lutein as a nutritive substance to infant formula products[1].

Specifically, the Applicant has requested permission to add lutein from marigold (*Tagetes erecta L.*) to infant formula[2,3] at a maximum concentration of 250 µg/L. The Applicant requests permission to add lutein to infant formula in amounts that would provide 'comparable levels' to breastfed infants.

Lutein is a plant pigment; it is a non-vitamin A carotenoid that cannot be synthesised by humans. Plant foods rich in lutein include dark green leafy vegetables, peas, carrots, corn, citrus fruits, avocado and broccoli. Lutein is also present in egg yolks, the fat of animals whose diets include lutein-rich plants and in human breast milk.

This Final Assessment Report discusses issues such as safety and nutritional equivalence with breast milk, including those issues raised in submissions, regarding this Application to permit the voluntary addition of lutein to infant formula. The approved draft variation to Standard 2.9.1 – Infant Formula Products is provided at Attachment 1.

Regulatory Approach

In the absence of Ministerial policy guidance FSANZ has adopted, in accordance with the section 18 objectives of the *Food Standards Australia New Zealand Act 1991,* the following approach to the assessment of this Application.

This assessment of whether lutein should be permitted as a voluntary nutritive substance in infant formula has considered:

- if lutein is present in breast milk;
- whether the requested level of lutein in infant formula (250 µg/L) is similar to the levels found in breast milk (accounting for bioavailability);
- if the proposed fortification achieves a similar physiological effect for formula-fed infants compared to breastfed infants (e.g. serum lutein levels); and
- the safety of lutein.

This approach recognises that the health effect of many substances in breast milk is not well understood.

[1] 'Infant formula product', as defined in Standard 2.9.1 – Infant Formula Products, 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.

[2] For the purposes of this Report, use of the term 'infant formula' refers to both 'infant formula' and 'follow-on formula', which are defined in subclause 1(2) of Standard 2.9.1.

[3] A permission to add lutein would relate to all infant formula products. Infant formula and follow-on formula are a subset of this formulae product.

The above approach does not require a benefit of lutein in the target population to be demonstrated. This is consistent with the approach historically taken with existing permissions for voluntary nutritive substances in Standard 2.9.1, for example nucleotides. Accordingly, the potential health benefit of lutein to the formula-fed infant has not been assessed in this Report.

Risk Assessment

At Final Assessment, the key risk assessment findings include:

- lutein is present in breast milk, with mean values ranging from 15-57 µg/L depending on maternal lutein intake;
- the ratio of lutein to zeaxanthin found in *Tagetes erecta L.* is within the range of ratios of lutein to zeaxanthin found in breast milk; noting considerable variability among individuals;
- lutein added to infant formula is unlikely to pose any safety concerns for formula-fed infants at the requested maximum concentration of 250 µg/L;
- lutein in breast milk is considerably more bioavailable than lutein added to infant formula, with evidence indicating a four-fold difference;
- the requested concentration of lutein to be added to infant formula would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found in breast milk; and
- some losses of lutein from both liquid 'ready-to-feed' and powdered infant formula products occur during storage.

The key risk assessment issues are discussed in section 8 of this Report. Full details of the risk assessment are found at Attachment 2 – Nutrition Assessment, Attachment 3 – Hazard Assessment, Attachment 4 – Dietary Intake Assessment and Attachment 5 – Food Technology Assessment.

Risk Management

This Final Assessment Report considers, in the context of the findings from the Risk Assessment, a number of issues relevant to permitting the addition of lutein to infant formula including:

- the appropriateness of the requested maximum concentration to be added to infant formula (250 µg/L), in relation to the concentration of lutein in breast milk and serum lutein concentrations, and safety;
- the minimum amount required for labelling declaration of lutein in infant formula; and
- the immediate and potential impacts of each regulatory option on affected parties.

Decision

To amend Standard 2.9.1 to permit the voluntary addition of lutein as a nutritive substance in infant formula products at a maximum concentration of 9 µg/100 kJ (250 µg/L) with a minimum declaration of 2 µg/100 kJ required for labelling purposes.

In addition, to make a minor consequential amendment to wording in the heading of column 3 in the Table to clause 7 of Standard 2.9.1 for clarification regarding labelling for nutrition declaration purposes.

Reasons for Decision

FSANZ has undertaken an assessment, using the best available evidence, of permitting the addition of lutein to infant formula, and recommends the draft variation to the Code as at Attachment 1 be approved for the following reasons:

- Lutein added to infant formula at a maximum concentration of 250 µg/L is unlikely to pose any safety concerns for formula-fed infants and would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found naturally in breast milk.

- The minimum level for declaration of lutein of 2 µg/100 kJ (57 µg/L) exceeds the innate amounts of lutein found in unfortified formula and equates to the lower mean level present in breast milk (accounting for bioavailability).

- The amendment to the Table to clause 7 would clarify that the minimum amount relates to the minimum amount required for labelling declaration purposes only.

- Overall, permitting the addition of lutein to infant formula will provide a net-benefit. Specifically, the decision will provide formula-fed infants with a source of lutein (a substance naturally present in breast milk), and potentially provide increased opportunities for international trade.

Consultation

During the assessment of this Application, two rounds of public consultation have been undertaken, as well as targeted consultation with representatives from the Australian State and Territories and New Zealand Governments.

FSANZ received 14 submissions in response to the Draft Assessment Report. Industry submitters, in general supported the Applicant's request to add lutein to infant formula, however, no Government submitters expressly supported this option.

A summary of submissions to the Draft Assessment Report is at Attachment 6. Key issues raised by submitters at Draft Assessment are addressed in this Report, either in the main report and/or in Attachment 7 – Response to Issues raised by Submitters at Draft Assessment.

At Final Assessment, FSANZ undertook additional targeted consultation with jurisdictions. This was to discuss and explain the rationale to the approach taken for the assessment of this Application, and our consideration of and response to issues they have raised.

Implementation and Review

Following consideration and approval of the draft variation to the Code by the FSANZ Board, notification of the Board's decision will be made to the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council). Subject to any request from the Ministerial Council for a review, the amendments to the Code with respect to Standard 2.9.1 will come into effect upon gazettal.

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INTRODUCTION

Food Standards Australia New Zealand (FSANZ) received an Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006 seeking to amend the *Australia New Zealand Food Standards Code* (the Code), to permit the voluntary addition of lutein as a nutritive substance to infant formula products.

This Final Assessment Report discusses issues such as the safety of lutein and equivalence with breast milk, including those issues raised in submissions, regarding the addition of lutein to infant formula[4]. The approved draft variation to Standard 2.9.1 – Infant Formula Products is provided at Attachment 1.

1. Nature of the Application

1.1 Basis of the Application

The Applicant has requested lutein from marigold (*Tagetes erecta L.*) be permitted as a nutritive substance in infant formula, for inclusion in the Table to clause 7 of Standard 2.9.1, at a maximum concentration of 250 µg/L. The Applicant proposes that lutein should be permitted to be voluntarily added to infant formula for the following reasons:

- lutein is naturally present in breast milk and food;
- lutein is not currently added to infant formula;
- breastfed infants have more lutein in their serum and eyes compared with formula-fed infants; and
- the requested level will provide formula-fed infants the opportunity to achieve plasma lutein concentrations comparable to those of breastfed infants whose mothers regularly consume foods rich in lutein.

The Applicant requests permission to add lutein to infant formula in amounts that would provide 'comparable levels' to breastfed infants, taking account of bioavailability and product stability factors. Current formulations of infant formula contain little or no lutein. The Applicant has provided data on the amounts in infant formula necessary to raise serum levels of lutein to those of similarly-aged breastfed infants.

1.2 Scope of Application

This Application relates to the voluntary addition of lutein to infant formula products, principally infant formula and follow-on formula. However, clauses 25 and 27 of Standard 2.9.1 allow manufacturers to specifically formulate and modify the composition of infant formula products for special dietary use. Therefore, the Applicant's request will not impact on the current requirements and manufacturing practices for infant formula products for special dietary use.

[4] For the purposes of this Report, use of the term 'infant formula' refers to both 'infant formula' and 'follow-on formula', which are defined in subclause 1(2) of Standard 2.9.1.

This Application principally relates to infant formula and follow-on formula. Infant formula and follow-on formula are defined in subclause 1(2) of 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.*

Infant formula and follow-on formula are a subset of infant formula products. Infant formula product is defined in subclause 1(2) of Standard 2.9.1 as:

> *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.*

This Application excludes 'formulated supplementary foods for young children'[5]. A separate application, Application A597 – Addition of Lutein to Formulated Supplementary Foods for Young Children, has been made seeking to permit the voluntary addition of lutein to these products.

1.3 Amendment to the original Application since Draft Assessment

The original Application requested permission to add lutein to follow-on formula at a maximum concentration of 500 µg/L. Since Draft Assessment, the Applicant has amended their Application by reducing the requested maximum concentration in follow-on formula to 250 µg/L; the same concentration as requested in infant formula. Although the higher level of 500 µg/L was assessed as safe, it was not comparable to the level of lutein found in breast milk.

The Applicant's request to reduce the maximum concentration in follow-on formula from 500 µg/L to 250 µg/L was received after the risk assessment for this Application was undertaken. The risk assessment components presented in this Report have been modified, where possible, to reflect the revised level. However, the Dietary Intake Assessment has not been revised, and estimates for follow-on formula have been based on a concentration of 500 µg/L. Therefore, any outcomes presented relating to follow-on formula are conservative, as they are an overestimate of the results.

1.4 Additional information since Draft Assessment

In response to issues raised by submitters at Draft Assessment, the Applicant has provided further information to support this assessment of their Application. Additional data provided by the Applicant on the following was used at Final Assessment:

[5] a formulated supplementary food for children aged one to three years e.g. toddler formula.

- stability of lutein in liquid 'ready-to-feed' and powdered infant formula products across the shelf-life of the product; and

- data that directly compared the bioavailability of lutein in breast milk to the bioavailability of lutein in infant formula.

1.5 Identity of source

Lutein and zeaxanthin are xanthophyll carotenoids obtained from the petals of marigold flowers (*Tagetes erecta L.*). An oleoresin rich in these carotenoids is extracted from and subsequently purified and crystallized using a patented process. Xanthophyll ester bonds are broken to release free lutein and zeaxanthin which are then suspended in edible oil. The material contains lutein and zeaxanthin in a ratio of approximately 10:1.

The material proposed for addition to the Applicant's infant formula is FloraGLO® Lutein 20% Liquid in Safflower Oil obtained from Kemin Health, L.C (Des Moines, Iowa).

1.6 Lutein as a nutritive substance

The Applicant has requested permission for addition of lutein to infant formula as a nutritive substance. Nutritive substance is defined in clause 2 of Standard 1.1.1 – Preliminary Provisions as:

> *a substance not normally consumed as a food in itself and not normally used as an ingredient of food, but which, after extraction and/or refinement, or synthesis, is intentionally added to a food to achieve a nutritional purpose, and includes vitamins, minerals, amino acids, electrolytes and nucleotides.*

Clause 6 of Standard 2.9.1 states that a vitamin, mineral, food additive or nutritive substance must not be added to infant formula product unless expressly permitted in the Code or it is naturally present in an ingredient of the infant formula product.

Lutein is considered a nutritive substance on the following grounds:

Definitional elements	**Rationale**
A substance not normally consumed as a food in itself	Lutein is not available for retail sale as a food in Australia and New Zealand.
A substance not normally used as an ingredient in food	Lutein is permitted as a food additive (colour) in some food categories (not infant formula products) but it is not normally used as an ingredient.
A substance that is extracted, refined or synthesised	Lutein is extracted and highly refined from marigold flowers.
A substance intended to achieve a nutritional purpose	Consistent with other carotenoids, lutein has specific antioxidant properties and is proposed to function in the eye as an antioxidant and blue light filter. It is not synthesised in the human body.

1.7 Novel Foods and the Status of Lutein

As this Application seeks to permit the addition of lutein to infant formula as a nutritive substance, the issue of whether or not lutein is a novel food has not been specifically addressed. However, if consideration was given to whether lutein meets the definition of 'novel food' in Standard 1.5.1 – Novel Foods, consideration would firstly need to be given to whether or not lutein is a 'non-traditional food' for the purposes of that Standard. As lutein is present in breast milk and some common foods eaten by infants, it may not meet the definition of 'non-traditional food', however, this would depend on whether it was proposed for use in similar quantities to that found naturally and in similar foods. If it was considered not to meet the definition of non-traditional food, it would therefore also not meet the definition of 'novel food'. If lutein were to be proposed for use in foods that are not natural sources and/or at concentrations significantly higher than that found naturally, it may be considered non-traditional for the purposes of Standard 1.5.1, however this consideration would need to be made on a case-by-case basis.

Standard 1.5.1 requires that novel foods must be expressly permitted in that Standard before they may be sold in Australia or New Zealand. In order to ensure the safety of novel foods prior to approval, FSANZ undertakes a pre-market safety assessment. A pre-market safety assessment has been undertaken for lutein and is presented in this Report, achieving the same level of assurance of safety as would be required for novel foods.

2. Background

Carotenoids are red and yellow pigments contained in animal fat and some plants. Although several hundred carotenoids have been identified, the most prevalent dietary carotenoids are α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin. Three of these, α-carotene, β-carotene and β-cryptoxanthin, are precursors of vitamin A, whereas lutein, zeaxanthin and lycopene cannot be converted to vitamin A. Humans cannot synthesise these carotenoids and must obtain lutein from dietary sources. Lutein is not regarded as a vitamin and is not covered by the *Nutrient Reference Values for Australia and New Zealand*[6] or other dietary recommendations. Lutein and zeaxanthin contain oxygen and are referred to as xanthophyll carotenoids.

Good sources of lutein include eggs, carrots, corn, citrus fruits, avocado, broccoli, peas and dark green leafy vegetables such as spinach. Lutein is also a food colouring agent (INS 161b) although it is not permitted to be added to infant formula products in Australia and New Zealand. Carotenoids are present in blood and adipose tissue, and concentrated in the ovaries, testes, liver, skin, breast milk, and eyes.

The chemical formula of lutein and zeaxanthin is $C_{40}H_{56}O_2$ and the structures are shown in Figure 1. In light of the structural similarities of these two xanthophylls, most analyses of food and breast milk group them together as a single result and the Acceptable Daily Intake (ADI) has been established as a group ADI for 'lutein and zeaxanthin'.

[6] This document is available online at http://www.nhmrc.gov.au/publications/synopses/n35syn.htm.

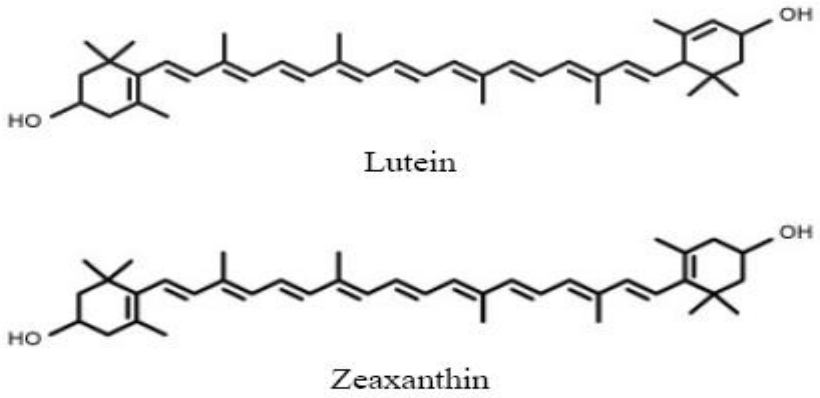

Figure 1: Chemical structures of lutein and zeaxanthin

Lutein is proposed to function in the eye as an antioxidant and a blue light filter. Dietary lutein and zeaxanthin are absorbed and subsequently accumulate in the retina, a layer of light-sensitive cells at the back of the eyeball. In particular, lutein and zeaxanthin are concentrated in an area centred on the fovea, referred to as the macular lutea (macula) or 'yellow spot'. The pigmentation of the macula is due to the abundance of lutein, zeaxanthin and *meso*-zeaxanthin. *Meso*-zeaxanthin is a non-dietary carotenoid thought to derive from lutein. Collectively, lutein, zeaxanthin and *meso*-zeaxanthin are referred to as 'macular pigment'. A major cause of irreversible vision loss is an age-related degenerative disease of the macula (Taylor et al., 2005). The presence of lutein and zeaxanthin in the macula has led to hypotheses and research into possible protective and palliative roles of these pigments against age-related macular degeneration.

3. Current Situation

3.1 Domestic Regulations

3.1.1 Australia New Zealand Food Standards Code

The Standards in the Code most relevant to this Application are:

- Standard 2.9.1 – Infant Formula Products regulates the compositional and labelling requirements for infant formula products. The Table to clause 7 lists the permitted nutritive substances that may be voluntarily added to infant formula product, the permitted form(s) in which they may be added, the minimum amount per 100 kJ for a declaration to be allowed, and the maximum amount permitted per 100 kJ when the substance is added. The maximum permitted amount applies to the sum of the naturally occurring and added nutritive substance; and

- Standard 1.3.1 – Food Additives, clause 3, permits the addition of lutein as a food colour under Schedule 3 in processed foods specified in Schedule 1. Under Schedule 1 lutein is not permitted to be added as a colour to infant formula products.

3.1.2 Therapeutic Goods Administration, Australia

Lutein is eligible for use in listed medicines on the Australian Register of Therapeutic Goods for supply in Australia, with no substance specific restrictions noted[7].

Preparations of *Tagetes erecta* L. that meet the definition of a herbal substance in Regulation 2 of the *Therapeutic Goods Regulations 1991* are approved for use in listed medicines[8].

3.1.3 Medicines and Medical Devices Safety Authority (Medsafe), New Zealand

Lutein is not a scheduled medicine in New Zealand and is not contained in any medicines currently registered in New Zealand[9].

3.1.4 Dietary Supplement Regulations, New Zealand

The New Zealand *Dietary Supplements Regulations 1985* (Dietary Supplement Regulations) currently regulate food-type and therapeutic-type dietary supplements in New Zealand. Dietary supplements are intended to supplement the intake of those substances normally derived from food. As a substance normally derived from food, lutein products are permitted to be sold as dietary supplements under the current Dietary Supplements Regulations, with products currently available on the market (e.g. lutein in capsules). While not explicitly excluded, FSANZ has been advised that infant formula product with added substances are not intended to be regulated under the Dietary Supplement Regulations, rather under the Food Standards Code.

The New Zealand Food Safety Authority (NZFSA) is currently reviewing the Dietary Supplement Regulations. A discussion document released in February 2007 outlined a proposal to separate regulation of food-type dietary supplements and therapeutic-type supplements. The intention of the proposed changes is to align food-type dietary supplements more closely with the Code where possible. This will include an explicit exclusion for infant formula from food-type dietary supplements.

3.2 Overseas and international regulations

3.2.1 Codex Alimentarius

The revised Codex Standard for Infant Formula[10] allows the addition of *optional ingredients*. Other ingredients, in addition to the essential compositional requirements, may be added *in order to provide substances ordinarily found in human milk and to ensure that the formulation is suitable as the sole source of nutrition for the infant or to provide other benefits that are similar to outcomes of populations of breastfed babies*.

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[7] Substances that may be used in listed medicines in Australia www.tga.gov.au/cm/listsubs.htm. Accessed 26 February 2007.
[8] Personal communication, Therapeutic Goods Administration, Australia, 14 March 2007
[9] Personal communication, Medsafe, Ministry of Health, New Zealand, 15 March 2007.
[10] Codex Alimentarius Commission. Alinorm 07/30/26 – Report of the 28th Session of the Codex Committee on Nutrition and Foods for Special Dietary Uses. Appendix II – revised standard for infant formula and formulas for special medical purposes intended for infants.

The revised Standard also states that *the suitability for the particular nutritional uses of infants and the safety of these substances shall be scientifically demonstrated* and that *the formula shall contain sufficient amounts of these substances to achieve the intended effect, taking into account levels in human milk.*

3.2.2 United States of America (USA)

Two generally recognised as safe (GRAS) notifications on lutein have been submitted to the United States Food and Drug Administration (FDA).

Although not directly relevant to this Application, the first relates to the use of crystalline lutein in a range of foods including infant and toddler foods. The FDA's response to this notice was issued on 14 June 2004, when it accepted that crystalline lutein is safe to use as a food ingredient in specified categories of foods and beverages including infant foods (for infants aged four to six months up to 12 months, excluding infant formula) and toddler foods (for children over 12 months of age), at levels up to 1 mg per serve[11]. The crystalline lutein preparation is the same as that used in FloraGLO® Lutein 20% Liquid in Safflower Oil.

The second notification was submitted to the FDA for GRAS status for crystalline lutein suspended in safflower oil (FloraGLO® Lutein 20% Liquid in Safflower Oil) in infant formula (intended from birth up to 12 months of age) to a maximum level of 250 µg/L[12]. The FDA responded on 23 October 2007 that it had no questions about this notification.

3.2.3 European Union

Lutein is not currently permitted to be added to infant formula products in the European Union. However, the European Food Safety Authority (EFSA), at the request of the European Commission, is currently evaluating the suitability of lutein for the particular nutritional use by infants and young children (Question number EFSA Q-2007-095). The EFSA is due to provide their Scientific Opinion on this matter by 31 July 2008.

3.2.4 Other countries

In China, lutein is permitted to be added as a 'nutrition fortifier' to infant formula and follow-on formula, as well as formula for young children and preschoolers. The maximum permitted levels of lutein in infant formula and follow-on formula are 2000 µg/kg and 4230 µg/kg of powdered product respectively (equates to approximately 260 µg/L in infant formula and 570 µg/L in follow-on formula[13]).

Wyeth has gained product registration approvals for lutein-containing infant formula products in Taiwan, Philippines, Indonesia, Peru, Ecuador, Colombia, Costa Rica, El Salvador, Honduras, Nicaragua, Panama, Thailand, Kuwait, Oman and Syria.

[11] FDA decision for GRAS Notice: GRN No. 140. Available at: http://www.cfsan.fda.gov/~rdb/opa-g140.html
[12] FDA decision for GRAS Notice: GRN No. 221. Available at: http://www.cfsan.fda.gov/~rdb/opa-g221.html
[13] Based on average dilution per litre for standard and 'gold' infant formula products available in Australia, using data from *The Feeding Guide, The Children's Hospital at Westmead, 2005*.

In addition, infant formula products containing added lutein are also marketed in Mexico, United Arab Emirates and Hong Kong. These countries are non-registration markets that adhere to the Codex Alimentarius requirements for the addition of optional ingredients to infant formula.

3.2.5 Permitted use as a food colour

FSANZ is aware that lutein is permitted for use as a food colour in several international regulations, for example as stated in the European Council Directives[14], but not for addition to infant formula.

3.3 Ministerial Policy Guidelines

FSANZ must have regard to any written policy guidelines formulated by the Australia and New Zealand Food Regulation Ministerial Council (the Ministerial Council) when developing and varying food standards.

The Ministerial Council recently endorsed a Policy Guideline on the *Addition to Food of Substances other than Vitamins and Minerals* (the Policy Guideline). However, the Policy Guideline does not apply to special purpose foods such as infant formula products. At the time of endorsing the Policy Guideline, the Ministerial Council agreed to commence work on development of a policy guideline on infant formula. The timing of this work is not known, but as this work has not yet commenced, the policy guidance will not be available before the statutory timelines for this Application are reached.

In the absence of policy guidance, FSANZ has considered the safety and nutritional equivalence with breast milk aspects of the addition of lutein to infant formula products; potential health benefits are not assessed in this Report. This regulatory approach is discussed further in section 6 – Regulatory Approach.

3.4 Current Market

3.4.1 Domestic Market

Four major brands of infant formula are available on the market in Australia and New Zealand. Two of these brands are manufactured in New Zealand using locally produced milk powder, and subsequently sold in both Australia and New Zealand. The remaining two brands are manufactured overseas, likely from milk powders of mixed origin, and imported into Australia and New Zealand. However, as lutein is not a permitted nutritive substance in the Code, there are no infant formula products with added lutein available on the domestic market.

3.4.2 International Market

Given the global nature of infant formula manufacture, there is a cost advantage for companies to manufacture one formulation for worldwide distribution. Also, the composition of infant formula is more likely to reflect international standards to reduce any potential barriers to trade.

[14] European Parliament and Council Directive 94/36/EC (1994). *Official Journal of the European Communities.* http://ec.europa.eu/food/fs/sfp/addit_flavor/flav08_en.pdf. Accessed on 17 August 2007.

Since FSANZ received this Application, there has been an increase in availability of infant formula containing lutein on the international market, namely in those countries noted in section 3.2.4.

Some infant formula products commonly used in hospitals in the United Kingdom as nourishment for premature babies contain egg yolk, a good source of lutein. These formulas contain lutein at levels similar to that proposed in this Application[15].

4. The Issue

The Applicant is seeking permission for the voluntary addition of lutein as a nutritive substance to infant formula. Lutein is naturally present in food and breast milk. The Applicant is requesting permission to add lutein to infant formula in amounts that would provide 'comparable levels' to breastfed infants.

Nutritive substances must not be added to food unless expressly permitted in the Code. Lutein is not permitted to be added to infant formula products because it is not listed in Standard 2.9.1 as a permitted nutritive substance.

The issue is whether the addition of lutein to infant formula, at the requested maximum level, is safe and provides lutein to formula-fed infants at levels similar to breastfed infants.

5. Objectives

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives which are set out in section 18 of the *Food Standards Australia New Zealand Act 1991*. 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

[15] Jewell VC, Mayes CBD, Tubman TRJ, Northrop-Clewes CA, Thurnham DI. A comparison of lutein and zeaxanthin concentrations in formula and human milk samples from Northern Ireland mothers. *Eur J Clin Nutr.* 2004;58:90-97.

- any written policy guidelines formulated by the Ministerial Council.

6. Regulatory Approach

In the absence of Ministerial policy guidance FSANZ has adopted, in accordance with the section 18 objectives of the FSANZ Act, the following approach to the assessment of this Application.

This assessment of whether lutein should be permitted as a voluntary nutritive substance in infant formula has considered:

- if lutein is present in breast milk;

- whether the requested level of lutein in infant formula (250 µg/L) is similar to the levels found in breast milk (accounting for bioavailability);

- if the proposed fortification achieves a similar physiological effect for formula-fed infants compared to breastfed infants (e.g. serum lutein levels); and

- the safety of lutein.

This approach recognises that the health effect of many substances in breast milk is not well understood.

The above approach does not require a benefit of lutein in the target population to be demonstrated. This is consistent with the approach historically taken with existing permissions for voluntary nutritive substances in Standard 2.9.1, for example nucleotides. Accordingly, the potential health benefit of lutein to the formula-fed infant has not been assessed in this Report.

RISK ASSESSMENT

7. Risk Assessment Questions

In assessing scientific risk the following questions have been considered at Final Assessment:

1. Is lutein found in breast milk and if so, how do the concentrations in breast milk compare with that requested for infant formula?

2. Is lutein found in the body and if so, how do the concentrations in breastfed infants compare with formula-fed infants consuming:

   (a) unfortified formula?
   (b) formula fortified at the requested concentration?

3. Are there any risks to infants from consuming infant formula containing lutein derived from marigold flowers (*Tagetes erecta L.*) at the requested concentration?

8. Risk Assessment Issues

The following section summarises the nutrition and hazard assessment; dietary intake; and conclusions. The full details of the risk assessment can be found at Attachment 2 – Nutrition Assessment, Attachment 3 – Hazard Assessment and Attachment 4 – Dietary Intake Assessment.

The Applicant's request to reduce the maximum concentration in follow-on formula from 500 µg/L to 250 µg/L was received after the risk assessment for this Application was undertaken. The risk assessment components presented below have been modified, where possible, to reflect the revised level. However, the Dietary Intake Assessment has not been revised, and estimates for follow-on formula have been based on the higher concentration of 500 µg/L. Therefore, any outcomes presented relating to follow-on formula are an overestimate of the results.

8.1 Nutritional equivalence with breast milk

8.1.1 Is lutein found in breast milk and if so, how do the concentrations in breast milk compare with that proposed for infant formula?

Yes, lutein is found in breast milk at variable concentrations.

Lutein is a carotenoid that is a normal constituent of the diet[16] and is naturally present in colostrum and mature human milk. Breastfed infants receive a continual supply of lutein and its isomer zeaxanthin from breast milk[17]. During the first few days post-partum, the breastfed infant receives a high dose of lutein which is present in colostrum at concentrations several-fold greater than the concentrations found in mature breast milk.

There are currently no published population representative data that characterise the breast milk concentration of lutein in Australian and New Zealand women. However, mean values ranging between 15-57 µg/L of lutein have been reported in the studies reviewed (Canfield *et al*., 2003; Wyeth Nutrition, 2006). This variability is most likely due to variations in maternal intake of lutein; with higher intakes of lutein-rich foods resulting in higher breast milk concentrations of lutein.

While these breast milk concentrations are lower than the maximum amount requested by the Applicant for addition to infant formula, the lower bioavailability of lutein when added to infant formula partially accounts for this request (see Section 8.1.2.1).

8.1.1.1 Ratio of Lutein to Zeaxanthin

The ratio of lutein to zeaxanthin in breast milk reflects the mother's dietary intake of carotenoids. In most foods there is a predominance of lutein over zeaxanthin, although corn has a relatively high proportion of zeaxanthin. The ratio can vary over a wide range reflective of the diet but there is very limited evidence to confirm this in human milk samples.

[16] See Section 2 for good sources of lutein in the diet.
[17] In some reports the data are reported for lutein and zeaxanthin together but as lutein predominates in breast milk (see Section 8.1.1.1), this is the substance most commonly reported.

Mean ratios of lutein to zeaxanthin in breast milk across studies have varied between approximately 2.5:1 and 8:1 (Lietz *et al*., 2006; Schweigert *et al*., 2004; Wyeth, 2006), and within individuals between 1:1 and 33:1 (Jewel *et al*., 2004). No appreciable change in the ratio of lutein to zeaxanthin in breast milk has been observed over time (Schweigert *et al*., 2004; Lietz *et al*., 2006).

As these findings show, in breast milk, lutein usually predominates over zeaxanthin, but with considerable variation in the specific ratio across and within study groups. Therefore, the ratio of lutein to zeaxanthin of approximately 10:1 found in *Tagetes erecta L.* is consistent with the predominance of lutein in breast milk and is slightly higher than the mean range of ratios but within the broad individual range of ratios found in breast milk.

8.1.2 How do the plasma concentrations in breastfed infants compare with formula-fed infants?

Breast milk appears to concentrate lutein over other carotenoids (Schweigert *et al*., 2004; Gossage *et al*., 2002), particularly one to three months post partum. The proportion of lutein and zeaxanthin in breast milk is higher than in plasma of the infant or the mother, whereas the proportion of carotenoids, such as beta-carotene is higher in plasma than in breast milk. This suggests the existence of selective mechanisms to provide lutein and zeaxanthin in the first few months of life. In one small study, the average concentration of lutein and zeaxanthin in the plasma of breastfed infants (n=10) was observed to be almost three fold higher at one month, than at birth. In contrast, plasma levels in infants fed formula without lutein and zeaxanthin (n=8) was almost three fold lower at one month, despite similarities in levels of carotenoids in cord blood of each groups (Wyeth Nutrition, 2007).

8.1.2.1 Bioavailability

The maximum concentration requested by the Applicant (250 µg/L) is greater than the amounts contained in human milk because the bioavailability of added lutein is poor.

The Applicant has provided FSANZ with additional data since Draft Assessment that directly compares the bioavailability of lutein in breast milk to the bioavailability of lutein in infant formula. Results of the study showed that the serum lutein concentration increased from baseline in each of the formula groups except in the unfortified group. A positive dose-dependent relationship was observed between lutein in fortified formula and lutein in serum after 12 weeks feeding. However, the effect was greater for lutein in breast milk than lutein in infant formula. Serum lutein concentrations increased approximately 3.7 µg/L for every 1 µg/L increase in human milk concentrations, whereas among formula-fed infants, serum concentrations increased only 0.9 µg/L for every 1 µg/L increase in lutein concentrations in formula. This study further supports the higher bioavailability of lutein from breast milk than from infant formula (approximately four-fold difference).

There is also an indication from adult human and animal studies of carotenoid interactions affecting absorption. The data are equivocal with regard to an effect of lutein on β-carotene absorption with neutral, positive or negative effects found. The interaction of lutein and zeaxanthin with other carotenoids is discussed in Section 6 of Attachment 2.

8.2 Safety of lutein in infant formula

8.2.1 Are there any risks to infants from consuming infant formula containing lutein derived from Tagetes erecta L. at the requested concentration?

FSANZ has completed a Hazard Assessment of lutein and zeaxanthin and concludes that there is negligible risk to infants when these substances are added to infant formula at the maximum level requested by the Applicant.

FSANZ advises that lutein and zeaxanthin are well tolerated, and cause no adverse effects in either animal or human studies at doses ranging up to 1000 mg/kg body weight per day (bw/day). An Acceptable Daily Intake (ADI) has been set for lutein at 2 mg/kg bw/day based on the same toxicity study and safety factor as used by the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) (discussed in further detail in Attachment 3). FSANZ considered the ADI was suitable for infants less than 12 weeks of age because investigation of the data indicated no evidence of toxicity.

The primary target group for this assessment was identified as infants aged up to 1 year. Dietary intake estimates were conducted for 3-month olds who were fully infant formula fed and 9-month olds who were fed a combination of follow-on formula and solid foods (see Attachment 4).

As the ADI is based on combined lutein and zeaxanthin at a 10:1 ratio, all dietary intakes refer to combined lutein and zeaxanthin. The Dietary Intake Assessment indicated that the intake of lutein and zeaxanthin from infant formula is well below the ADI. At the extrapolated 95th percentile intake of lutein and zeaxanthin, 3-month olds had an intake of 0.09 mg/kg bw/day (or 4% of the ADI) and 9-month olds had an intake[18] of 0.2 mg/kg bw/day (or 8% of the ADI).

These data support the safety of lutein at the level of intake that would be achieved by addition of a *combination* of lutein and zeaxanthin (at approximately a 10:1 ratio) to infant formula at a maximum concentration of 280 µg/L[19].

9. Risk Assessment Summary

Lutein is found in breast milk. There are limited data on the levels, but the available data indicate considerable variability among lactating women (mean values ranging from 15-57 µg/L), depending on maternal lutein intake. Although these data are not derived from studies of Australian and New Zealand women, the concentrations are likely to be in this range based on comparable diets.

The ratio of lutein to zeaxanthin in breast milk reflects maternal intake of carotenoids. While the ratio can vary over a wide range depending on diet, the evidence indicates that lutein predominates over zeaxanthin on average 2.5-8 fold, and up to 33 fold in some individuals. Therefore, the ratio of approximately 10:1 found in *Tagetes erecta L.* is within this range; noting considerable variability among individuals.

[18] Based on a maximum lutein concentration of 500 µg/L in follow-on formula, as per the original Application.
[19] This level equates to a maximum concentration of lutein of 250 µg/L in infant formula.

Lutein in breast milk is considerably more bioavailable than lutein added to infant formula; with recent evidence indicating a four-fold difference.

Lutein added to infant formula is unlikely to represent a risk to infants at the requested maximum level. For both 3-month old infants and 9-month old infants, the estimated mean and 95th percentile intakes of lutein and zeaxanthin following fortification of infant formula were all well below the ADI.

Therefore, FSANZ concludes that based on the available evidence, the requested concentration of lutein to be added to infant formula is unlikely to pose any safety concerns for formula-fed infants and would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found naturally in breast milk.

10. Food Technology

The food technology aspects of lutein used as a nutritive substance to be added to infant formula have been assessed.

Lutein is a natural carotenoid with the commercial lutein extract prepared from marigold (*Tagetes erecta* L.) flowers. A hexane extract of the marigold flowers is saponified with potassium hydroxide and purified by crystallisation to yield yellow prisms of lutein. The specification of the lutein extract is consistent with the recent specification prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004. The JECFA specifications are a primary source of specifications in Standard 1.3.4 – Identity and Purity, so a new specification is not required to be written for the Code. This specification is for the free lutein, not a lutein ester.

The commercial lutein preparation that is subsequently added to food is produced in vegetable oil with approved food additives being antioxidants and emulsifiers. Stability results provided by the Applicant for both liquid (ready-to-feed) infant formula products and powdered products (infant and follow-on formula), indicated some losses of lutein occurred during storage. Stability results indicated that most of the losses occurred early during storage. The summary of the worst losses of lutein from commercial infant formula products are indicated below.

For liquid products: Losses after 12 months (which is the end of shelf life of these products) at ambient temperature (27°C and 70% relative humidity (RH)) were determined to be up to a maximum of 41%.

For powdered products: Losses after 12 months at ambient temperature (27°C and 70% relative humidity (RH)) were determined to be up to a maximum of 55%. Stability results under accelerated ageing conditions (37°C and 75% RH) indicated the worst losses to be 58% after 6 months storage.

Manufacturers will need to be aware of losses of lutein that occur for their products with storage conditions and could apply a suitable over dosing to account for such losses (commonly referred to as overages). The Applicant has requested an overage of 250%, so to achieve a level of 100 µg/L in infant formula, they have asked for a maximum level of 250 µg/L. For their commercial operations they are aiming for an overage of 180% to account for losses during storage to the end of the products shelf life.

The extra allowance up to an overage of 250% is to ensure their product would always meet the requirements of the Code. The request is comparable to that commonly used for dosing sensitive vitamins to food.

Lutein is not being considered for an extension of use as a food additive in infant formula, where it can act as a food colour, since its proposed use is not for this purpose.

The full Food Technology Assessment is at Attachment 5.

RISK MANAGEMENT

11. Risk Management Issues

On the basis of FSANZ's risk assessment the following sections discuss approaches to managing any identified public health and safety risks, other broader issues relevant to the regulation of lutein in infant formula, and responds to issues raised in submissions.

11.1 Protection of public health and safety

The protection of the public health and safety of formula-fed infants is the primary objective in consideration of this Application.

FSANZ's risk assessment has examined substantial evidence from the Applicant and other sources. The findings of the risk assessment are consistent with the approach taken to the assessment of this Application in the absence of Ministerial policy guidance, as described in the regulatory approach in section 6.

Firstly, the regulatory approach requires that the substance be present in human milk. As reported in the risk assessment, lutein is present in breast milk at variable levels depending on maternal lutein intake. It is also noted that the ratio of lutein to zeaxanthin found in *Tagetes erecta L.* is within the range found in breast milk.

The substance must also be found at levels similar to breast milk, accounting for bioavailability, and achieve similar health or physiological outcomes to breastfed babies. The requested concentration of 250 µg/L in infant formula is greater than the mean concentration of lutein found in mature breast milk (15-57 µg/L). However, as shown in the risk assessment, lutein from breast milk is more bioavailable than lutein from infant formula – approximately four-fold difference. In addition, the risk assessment found that the requested concentration of lutein to be added to infant formula would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found naturally in breast milk.

The regulatory approach also requires that the substance be assessed as safe. The risk assessment concluded that lutein added to infant formula at the requested maximum level of 250 µg/L is unlikely to represent a risk to formula-fed infants. Specifically, it showed that intakes for formula-fed infants of lutein and zeaxanthin following fortification of infant formula, accounting for additional lutein from complementary foods consumed by infants aged six months and above, were all well below the ADI.

As demonstrated above, the request to permit the addition of lutein to infant formula is consistent with the approach to the assessment of this Application.

Furthermore, the addition of lutein to infant formula allows formula-fed infants the opportunity to achieve serum lutein concentrations comparable to those of breastfed infants.

11.2 Levels of addition

The Applicant has requested to add lutein to infant formula at a maximum concentration of 250 µg/L to provide 'comparable levels' to breastfed infants, taking into account bioavailability and stability factors.

11.2.1 Infant formula

Some submitters to the Draft Assessment Report expressed concern that the requested levels in infant formula and follow-on formula (250 µg/L and 500 µg/L respectively[20]) were greater than the lutein concentration in breast milk.

There is considerable variation in breast milk concentrations of lutein between women, depending on maternal diet. The requested maximum level of lutein for addition to infant formula (250 µg/L) is greater than the level of lutein found in mature breast milk (mean range of 15-57 µg/L). However, as discussed in section 11.1, when bioavailability is taken into account (approximately four-fold difference) the requested level is comparable to the mean upper level of lutein found in mature breast milk.

In addition, the requested maximum concentration of 250 µg/L in infant formula accounts for losses of lutein during storage (as discussed in section 10). Losses after 12 months, the end of shelf life of these products, for liquid products and powered products were determined to be up to a maximum of 41% and 55% respectively. Therefore, manufacturers will need to apply a suitable overage to account for such losses, while ensuring the level of lutein in the product does not exceed the maximum permitted level prescribed in the Code. For example, the Applicant has requested a maximum concentration of lutein in infant formula that allows an overage of up to 250% – up to 250 µg lutein/L is added to achieve 100 µg lutein/L in the product on average over 12 months shelf life.

Overall, the requested maximum concentration of 250 µg/L in infant formula is comparable to the upper mean level of lutein found in mature breast milk, accounting for bioavailability, and would achieve a nutritionally equivalent effect in relation to serum lutein concentrations compared to breastfed infants. In addition, as losses of lutein occur during storage, it is not practical for manufacturers to achieve an average level of 250 µg/L lutein over the shelf life of their product. Therefore, lutein will most likely be present in infant formula at levels less than the maximum limit of 250 µg/L.

11.2.2 Unit for lutein concentration in draft Standard

In the draft Standard, the minimum and maximum concentrations of lutein are expressed per 100 kJ (of reconstituted or 'ready to drink' formula), consistent with permissions for other voluntary nutritive substances in Standard 2.9.1. Specifically, 250 µg/L equates to 9 µg/100 kJ.

[20] As previously discussed, since Draft Assessment the original Application had been amended to a maximum concentration in follow-on formula of 250 µg/L, rather than 500 µg/L. This is the same as in infant formula.

11.3 Labelling and claims

Specific labelling requirements for infant formula products are prescribed in Standard 2.9.1. In addition, the general labelling requirements under Part 1.2 of the Code, including Standard 1.2.4 – Labelling of Ingredients, also apply to these products, subject to any specified exemptions. If lutein is permitted to be added to infant formula products, the current labelling requirements for infant formula products would remain unchanged.

11.3.1 Minimum levels for labelling purposes

Nutritive substances permitted for addition to infant formula products are specified in Standard 2.9.1. Minimum levels for declaration of permitted voluntary nutritive substances are specified in column 3 of the Table to clause 7. As prescribed in subclause 7(2), the label on a package of infant formula product must not include any words indicating, or any other indication, that the product contains a permitted nutritive substance unless the total amount of the nutritive substance is no less than the amount specified in column 3 of the Table.

At Final Assessment, FSANZ recommends a minimum level for declaration of lutein of 2 µg/100 kJ of infant formula. The basis for this minimum level is that 2 µg/100 kJ (57 µg/L) exceeds the innate amounts of lutein found in unfortified formula and therefore ensures that the declaration of lutein occurs only when lutein is added to infant formula. In addition, it is within the range of lutein found in breast milk, taking account of bio-availability.

Some submitters considered that the minimum level for declaration should reflect purpose; the minimum effective level. Setting the minimum level for labelling declaration based on purpose would be inconsistent with the approach taken for other permitted voluntary nutritive substances in infant formula products (e.g. nucleotides). However, when the proposed minimum level is compared to breast milk, it corresponds with the lower mean level present in breast milk – 2 µg/100 kJ (57 µg/L) equates to approximately 14 µg/L accounting for bioavailability, where the lower mean level in breast milk is 15 µg/L.

11.3.2 Nutrition, health and related claims

Subclause 20(f) of Standard 2.9.1 prohibits a reference to any nutrient or nutritive substance on the label of an infant formula product, except where the reference to a nutrient or nutritive substance is in the statement of ingredients or a nutrition information statement (exceptions apply also to information relating to lactose (clause 30) and infant formula products for specific conditions (clause 28)).

FSANZ has considered new regulations for nutrition, health and related claims under Proposal P293, which will be contained within draft Standard 1.2.7. At Draft Assessment, it was reported that current claim prohibitions in relation to infant formula products would be maintained, with these products specifically noted as ineligible for claims under the draft Standard 1.2.7.

Many government submitters commented on the issue of claims on infant formula products. It was noted that some infant formula products marketed in Australia carry nutrition content claims about nucleotides and omega-3 fatty acids, and some overseas infant formula products carry lutein nutrition content claims. The Government submitters expressed concern that:

- the wording of clauses 7, 16 and 20 of Standard 2.9.1 is ambiguous in relation to the requirements for labelling and could be interpreted as permitting nutrition content claims; and

- existing requirements in the Code (in the Transitional Standard 1.1A.2 – Health Claims) and proposed provisions (in the draft Standard 1.2.7 – Nutrition, Health and Related Claims) would not prohibit a lutein nutrition content claim on the label of an infant formula product.

The intent of Standard 2.9.1 is to prohibit nutrition claims on infant formula products (with the exception of claims permitted under clauses 28 and 30). The rationale for this approach was provided in Proposal P93 – Review of Infant Formula, which resulted in Standard 2.9.1. In the Supplementary Final Assessment Report for Proposal P93, FSANZ (formerly ANZFA) considered that:

> *The only reason for manufacturers to want to include any of these representations or declarations of nutrients in the label of an infant formula product is as a marketing tool. ANZFA does not consider it appropriate to use such information to market infant formula.*
>
> *The prohibition of representations of infant formula products is consistent with the requirements of the WHO International Code of Marketing of Breast Milk Substitutes and with the requirements of the MAIF agreement*[21]*. Inclusion of these provisions in the Food Standards Code makes them mandatory requirements and enforceable by law.*

In addition, Transitional Standard 1.1A.2 specifically prohibits health claims from being made on infant formula products.

Similar comments about infant formula products carrying claims were raised in submissions to Proposal P306 – Addition of Inulin/FOS & GOS to Food. Given the overlap between this Application and Proposal P306, FSANZ has proposed amendments to Standard 2.9.1 within Proposal P306 to address submitters concerns. Specifically, Standard 2.9.1 will be amended to clearly reflect that nutrition claims are not permitted on infant formula products (with the exception of claims regulated in clauses 28 and 30).

In addition to amendments within Proposal P306, FSANZ recommends a minor amendment within this Application. The words 'for claim' in the title to column 3 of the Table to clause 7 have been misinterpreted by some stakeholders as referring to nutrition content claims. To aid clarity, FSANZ recommends the words 'for claim' be deleted from the title.

Furthermore, the revised approach under draft Standard 1.2.7 is that the provisions for claims will not apply to Standard 2.9.1. Unless already permitted under Part 2.9 of the Code, the draft Standard expressly prohibits nutrition content claims, general level and high level health claims, endorsements, dietary information and cause-related marketing statements for food on a label or in an advertisement for food. This means that the labelling provisions contained within Standard 2.9.1 will stand alone.

[21] The MAIF agreement is the Marketing in Australia of Infant Formulas: Manufacturers and Importers Agreement (May, 1992). Adopted as its Code of Conduct, the MAIF Agreement sets out the obligations of infant formula manufacturers and importers and it gives effect to the principles of the WHO Code.

12. Options

At Final Assessment, FSANZ is considering two options for addressing this Application:

- Option 1 – rejecting the Application, thus maintaining the *status quo* by not amending the Code to permit the voluntary addition of lutein as a nutritive substance in infant formula; and

- Option 2 – amend Standard 2.9.1 to permit the voluntary addition of lutein as a nutritive substance in infant formula at a maximum concentration of 9 µg/100 kJ (250 µg/L) with a minimum declaration of 2 µg/100 kJ required for labelling purposes.

13. Impact Analysis

13.1 Affected Parties

The parties affected by this Application are: **consumers** being formula-fed infants and their **caregivers**; **industry** being Australian and New Zealand manufacturers and importers of infant formula and follow-on formula; and the **Governments** of Australia and New Zealand.

13.2 Benefit Cost Analysis

The Benefit Cost Analysis assesses the immediate and potential impacts of each regulatory option on the affected parties.

13.2.1 Option 1 – Rejecting the Application and maintaining the status quo

13.2.1.1 Consumers

It is likely that maintaining the *status quo* will have little impact on formula-fed infants, as safe and suitable products will continue to be available for caregivers to purchase. However, infant formula currently available in Australia or New Zealand contains little or no lutein. This does not provide an opportunity for formula-fed infants, particularly those reliant on infant formula as their sole source of nutrition, to access a source of lutein, a substance normally present in breast milk.

13.2.1.2 Industry

There are no additional benefits for industry in maintaining the *status quo.* The recent approvals and potential increase in availability of infant formula on the international market could result in an increased demand for formula with added lutein. Maintaining the *status quo* would prohibit the importation of infant formula containing added lutein and also limit the ability to manufacture one formulation for both domestic and export markets.

13.2.1.3 Government

Maintaining the *status quo* is not expected to have any impact for government.

13.2.2 Option 2 – Amend Standard 2.9.1 to permit the voluntary addition of lutein to infant formula

13.2.2.1 Consumers

Permitting the voluntary addition of lutein to infant formula product, a breast milk substitute, would provide formula-fed infants with a source of lutein in their diet. In addition, caregivers would be provided with a choice to purchase either a product with or without added lutein. The addition of lutein at the level proposed would provide a safe amount of lutein for formula-fed infants.

It is unknown whether caregivers will bear extra costs or pay a premium for lutein-fortified infant formula and follow-on formula.

13.2.2.2 Industry

Option 2 would allow industry to produce a new product, consistent with international developments, for the Australian and New Zealand markets, and potentially for international markets.

As the addition of lutein to infant formula would be a voluntary permission, there would not be additional barriers to trade. Rather, Option 2 could provide an opportunity to expand the export of infant formula products to the countries where the addition of lutein is now approved, further enabling manufacturers to compete on the international market. It could also allow for the importation of formula with added lutein, and be a cost advantage for companies to manufacture one formulation for worldwide distribution.

While there would be a cost to manufacturers to add lutein to infant formula, this is a voluntary permission. Market forces will determine to what extent manufacturers will pass on these additional costs to caregivers of formula-fed infants.

13.2.2.3 Government

It is expected that Option 2 would have minimal impact on government. The respective enforcement agencies have existing procedures to enforce the composition and labelling of infant formula products.

13.3 Comparison of Options

A comparison of the Options presented at Final Assessment indicates that both maintaining the *status quo* and Option 2 would continue to protect the health and safety of formula-fed infants. Evidence indicates that the addition of lutein in the form and at the level proposed in Option 2 is safe and suitable for infants.

Although breast milk is the ‘gold standard’ for meeting the nutritional needs of infants, Option 2 provides a source of lutein, a substance present in breast milk, for formula-fed infants. Option 2 also provides choice to caregivers to provide a product with added lutein to their infant. Added lutein is currently not available in infant formula in Australia or New Zealand.

Option 2 also potentially increases opportunities for increased international trade through potential importation and export of infant formula with added lutein.

Therefore, at Final Assessment in comparing the proposed options, Option 2 is considered to provide net benefits to the affected parties.

COMMUNICATION AND CONSULTATION STRATEGY

14. Communication

FSANZ has reviewed the nature of the feedback received from submitters at Initial and Draft Assessment and does not intend to undertake specific communication strategies in relation to this Application.

15. Consultation

15.1 Public consultation

15.1.1 Initial Assessment

A joint Initial Assessment Report for both this Application and Application A597 was released for public comment from 4 April to 16 May 2007. FSANZ received ten submissions in response to the Initial Assessment Report.

Overall, five of the ten submitters (including four of the five government submitters) did not specify a preferred option, with several recommending that further assessment of safety and efficacy was required. Of those who did indicate a preferred option, the majority of industry submitters supported permitting the addition of lutein to infant formula. However, one submitter's support was contingent on the safety and efficacy of lutein being scientifically demonstrated. Two submitters supported the *status quo*, citing insufficient evidence and a need for evidence of health benefit to the target group.

15.1.2 Draft Assessment

The Draft Assessment Report for this Application was released for public comment from 3 October to 14 November 2007. In response, FSANZ received 14 submissions, with eight submissions from government, five from industry and one from a public health association. A summary of these submissions is at Attachment 6.

The majority of industry submitters supported Option 2 to permit the addition of lutein to infant formula and follow-on formula at the requested levels[22]. However, no Government submitters supported Option 2.

Key issues raised by submitters that opposed permitting the addition of lutein to infant formula included:

- inadequate evidence for benefit/efficacy;

[22] In the Draft Assessment Report, Option 2 provided maximum lutein concentrations of 250 µg/L in infant formula and 500 µg/L in follow-on formula.

- inadequate evidence for equivalence with human milk (level and ratio);
- inadequate evidence of equivalence with measured physiological parameters such as blood levels between formula-fed and breastfed infants;
- inadequate data on bioavailability;
- use of Applicant funded non-peer-reviewed data;
- lack of justification for proposed minimum declaration amount;
- unjustified doubling of the level of lutein in follow-on formula;
- potential nutrient interactions between lutein and other carotenoids; and
- concern that the Code would not prohibit nutrient content claims for lutein.

Responses to key issues raised in submissions to the Draft Assessment Report can be found at Attachment 7.

15.2 Targeted consultation

At Final Assessment, FSANZ undertook additional targeted consultation with representatives from the Australian State and Territories and New Zealand Governments. This was to discuss and explain the rationale to the approach taken for the assessment of this Application, and our consideration of and response to issues they have raised.

15.3 World Trade Organization

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.

There are relevant international standards that permit the addition of lutein to infant formula products (e.g. the US FDA), and other overseas regulatory agencies are currently considering the approval of lutein in these products (e.g. the European Commission).

It is expected that the proposed changes will harmonise Australian and New Zealand regulations with current and future international practices.

Therefore, amending the Code to permit the voluntary addition of lutein to infant formula is unlikely to have a significant effect on trade. As such, WTO member nations were not notified of the proposed amendment to Standard 2.9.1 under either the Technical Barriers to Trade or Sanitary and Phytosanitary Agreements.

CONCLUSION

16. Conclusion and Decision

Decision

To amend Standard 2.9.1 to permit the voluntary addition of lutein as a nutritive substance to infant formula products at a maximum concentration of 9 µg/100 kJ (250 µg/L) with a minimum declaration of 2 µg/100 kJ required for labelling purposes.

In addition, to make a minor consequential amendment to wording in the heading of column 3 in the Table to clause 7 of Standard 2.9.1 for clarification regarding labelling for nutrition declaration purposes.

16.1 Reasons for Decision

FSANZ has undertaken an assessment, using the best available evidence, of permitting the addition of lutein to infant formula, and recommends the draft variation to the Code as at Attachment 1 be approved for the following reasons:

- Lutein added to infant formula at a maximum concentration of 250 µg/L is unlikely to pose any safety concerns for formula-fed infants and would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found naturally in breast milk.

- The minimum level for declaration of lutein of 2 µg/100 kJ (57 µg/L) exceeds the innate amounts of lutein found in unfortified formula and equates to the lower mean level present in breast milk (accounting for bioavailability).

- The amendment to the Table to clause 7 would clarify that the minimum amount relates to the minimum amount required for labelling declaration purposes only.

- Overall, permitting the addition of lutein to infant formula will provide a net-benefit. Specifically, the decision will provide formula-fed infants with a source of lutein (a substance naturally present in breast milk), and potentially provide increased opportunities for international trade.

17. Implementation and Review

Following consideration and approval of the draft variation to the Code by the FSANZ Board, notification of the Board's decision will be made to the Ministerial Council. Subject to any request from the Ministerial Council for a review, the amendments to the Code with respect to Standard 2.9.1 would come into effect upon gazettal.

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ATTACHMENTS

1. Draft variation to the *Australia New Zealand Food Standards Code*
2. Nutrition Assessment
3. Hazard Assessment
4. Dietary Intake Assessment
5. Food Technology Assessment
6. Summary of Submissions to the Draft Assessment Report
7. Response to Issues Raised by Submitters at Draft Assessment

Attachment 1

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

Standards or variations to standards are considered to be legislative instruments for the purposes of the Legislative Instruments Act (2003) and are not subject to disallowance or sunsetting.

To commence: on gazettal

[1] ***Standard 2.9.1*** *of the Australia New Zealand Food Standards Code is varied by –*

[1.1] *omitting the column headings from the* Table to clause 7, *substituting –*

Column 1	**Column 2**	**Column 3**	**Column 4**
Nutritive substance	**Permitted forms**	**Minimum amount per 100 kJ**	**Maximum amount per 100 kJ**

[1.2] *inserting in the* Table to clause 7 –

Lutein	Lutein from *Tagetes erecta L.*	2 µg	9 µg

Attachment 2

Nutrition Assessment

Summary

Lutein is present in colostrum and mature human milk. During the first few days postpartum, the breastfed infant receives a relatively high dose of lutein from colostrum at concentrations several-fold greater than the concentrations found in mature breast milk. The concentration of lutein in mature breast milk is variable, reflecting maternal dietary intake. Previously most studies of carotenoids in breast milk have been of healthy women consuming diets high in fruits and vegetables with concentrations of lutein in breast milk differing substantially. There are currently no population representative data that characterise the breast milk concentration of lutein and zeaxanthin in Australian and New Zealand women.

The concentration of lutein requested in infant formula is greater than that contained in breast milk. The justification for requesting a greater amount in formula is the poorer bioavailability of lutein contained in formula compared with breast milk. There are no published studies in which the serum lutein concentrations of breastfed and lutein-fortified formula-fed infants have been directly compared to show a difference in bioavailability. However, recent unpublished data from a Wyeth study (not included in the Draft Assessment Report) support the addition of lutein to formula in higher amounts than in breast milk in order to approximate the serum concentrations observed in breastfed infants. This is due to a difference in lutein bioavailability between breast milk and lutein-fortified formula. There are currently no representative data available on the serum lutein concentrations of Australian or New Zealand breastfed infants.

There is an indication from animal and human adult studies of carotenoid interactions affecting absorption. The data are equivocal with regard to an effect of lutein and zeaxanthin on β-carotene absorption with a neutral, positive or negative effects found. The nutritional implication to formula-fed infants of a lutein and zeaxanthin interaction with β-carotene is unclear because, although carotenes provide a source of vitamin A precursors, there is a requirement for infant formula to contain pre-formed vitamin A.

There is emerging evidence that lutein and zeaxanthin may play a role in eye health but further research is needed to confirm the potential role.

1. Background

Xanthophyll carotenoids are typically present in plant chloroplasts as long chain fatty acid esters. Lutein in FloraGlo (the lutein-containing substance proposed to be added by the Applicant) is in a free form (unesterified), purified from marigold flowers using a patented process (Ausich & Sanders, 1997). No carotenoid esters have been detected in peripheral tissue (Perez-Galvez and Minguez-Mosqura, 2005) and based on a study by Schweigert *et al.*, (2000) the Applicant contends that the predominant form of lutein in human milk is also unesterified.

This is suggestive that lutein contained in human milk and that proposed for addition to formula is in the same form.

2. Aim of nutrition assessment

The aim of this nutrition assessment is to compare the concentrations and physiological response of lutein in breast milk with lutein added to infant formula and to consider any potential nutrient interactions and potential nutritional effects.

3. Concentration of lutein and zeaxanthin in colostrum and mature human milk

3.1 Colostrum

The mean lutein and zeaxanthin concentration in the breast milk of 21 North American women sampled four days postpartum was approximately 140 µg/L (Gossage *et al*., 2002). The concentration declined over the following two weeks to approximately 60 µg/L. In the breast milk of 21 German women, mean lutein and zeaxanthin concentrations at 4 and 19 days postpartum were 93 µg/L (164.0 ± 84.9 nmol/L) and 50 µg/L (88.1 ± 37.8 nmol/L), respectively (Schweigert *et al*., 2004). Jewell *et al*., (2004) obtained samples of breast milk from five Irish mothers from day one postpartum. Milk obtained early in lactation ranged in lutein and zeaxanthin concentration among women from 27 to 193 µg/L, falling approximately five-fold over the following 2 to 3 weeks.

These data show that early milk contains relatively high concentrations of lutein and zeaxanthin compared with mature milk.

3.2 Mature milk

Most studies have reported a combined lutein and zeaxanthin concentration in human milk. However, from techniques whereby the isomers can be measured separately, the mean (SD) concentrations of lutein and zeaxanthin in the breast milk of 43 North American women were 41.1 µg/L (16.7) and 16.2 µg/L (8.2), respectively, corresponding to a lutein:zeaxanthin ratio of approximately 3:1 (Wyeth, 2006a). Combined lutein and zeaxanthin concentrations have been determined in a multinational cross-sectional study (Canfield *et al*., 2003). Convenience samples of around 50 lactating mothers of healthy full-term infants 1 to 12 months postpartum were enrolled from each of nine countries. The mothers consumed at least 3 servings of fruits and vegetables (combined) per day. A single mid-afternoon complete breast expression of milk was obtained by electric pump except in Japan where women used a hand-held pump. The HPLC method of analysis could not separate lutein from zeaxanthin so a combined concentration of these carotenoids was measured. The results are shown in Table 1.

Table 1: Mean lutein and zeaxanthin concentrations in human milk (Canfield *et al*., 2003)

Country[1]	N	Lutein and Zeaxanthin µmol/L ± SEM	Lutein and Zeaxanthin[2] µg/L
Australia	53	0.027 ± 0.002	15.4
Canada	55	0.030 ± 0.001	17.1
Chile	51	0.057 ± 0.005	32.4
China	52	0.076 ± 0.008	43.2
Japan	51	0.077 ± 0.004	43.8
Mexico	50	0.044 ± 0.003	25.0
Philippines	60	0.035 ± 0.003	19.9
United Kingdom	50	0.027 ± 0.002	15.4
United States	49	0.026 ± 0.001	14.8

[1] Convenience sample only

2 Conversion to µg/L by multiplying µmol/L x 568.87 (the molecular weight of lutein)

Because convenience samples were used, the data are not necessarily representative of the lutein breast milk concentrations within each country. Another group of women in the U.S., two-thirds of whom were selected based on a high intake of dark green leafy vegetables, had a combined lutein and zeaxanthin mean concentration in their breast milk of 57 µg/L (Wyeth Nutrition, 2006a). This value of 57 µg/L is markedly different to the concentration of 14.8 µg/L reported by Canfield *et al*. (2003) in U.S. women. The rank order of five major carotenoids, β-carotene, α-carotene, lycopene, lutein and b-cryptoxanthin varied, generally reflective of the carotenoids in the maternal diets (Canfield *et al*., 2003).

These data indicate that human milk lutein and zeaxanthin combined concentrations vary among countries, and within countries, and probably directly reflect maternal dietary intakes of foods containing these xanthophyll carotenoids. Data from one group of Australian women cannot be regarded as being representative of lutein and zeaxanthin concentrations in the breast milk of women across Australia.

4. Ratios of lutein and zeaxanthin in breast milk

The ratio of lutein to zeaxanthin in breast milk reflects the mother's dietary intake of carotenoids. In most foods there is a predominance of lutein over zeaxanthin, although corn has a relatively high proportion of zeaxanthin. The ratio can vary over a wide range reflective of the diet but there is very limited evidence to confirm this in human milk samples.

The majority of studies have measured breast milk lutein and zeaxanthin in combination. However, a few studies have reported concentrations for lutein and zeaxanthin separately. Mean ratios of lutein to zeaxanthin across studies have varied between approximately 2.5:1 and 8:1 (Lietz *et al*., 2006; Schweigert *et al*., 2004; Wyeth, 2006a). The only study reviewed that reported the ratio of lutein and zeaxanthin in breast milk for each individual study participant indicated the ratio ranges from approximately 1:1 to 33:1 (Jewel *et al*., 2004).

The ratio derived from the median lutein and zeaxanthin concentrations in this study was approximately 9:1.

These studies did not conduct statistical analyses of the change in ratio over time. Comparison of the ratio of mean lutein and zeaxanthin concentrations at four and 19 days postpartum (Schweigert *et al*., 2004), and at one month and three months postpartum (Lietz *et al*., 2006), did not suggest any appreciable change in breast milk lutein and zeaxanthin ratio over time.

It is clear from these findings that lutein usually predominates over zeaxanthin in breast milk, but with considerable variation in the specific ratio across and within study groups. The approximate 10:1 ratio of lutein to zeaxanthin found in *Tagetes erecta L.* is consistent with the predominance of lutein in breast milk and falls within the broad range of ratios reported in the available literature.

5. Comparisons between breastfed and formula-fed infants

5.1 Serum lutein and zeaxanthin concentration in breastfed infants

A range of serum lutein and zeaxanthin combined concentrations shown in Table 2 have been found in groups of breastfed infants. Relatively low concentrations of around 50-60 µg/L were found in 7-month old Honduran infants whose mothers' diets were generally low in fruits and vegetables (Canfield *et al*., 2001). A mean plasma lutein and zeaxanthin concentration of 46 µg/L was found in a large group (n = 192) of Nigerian neonates (Adelekan *et al*., 2003). The mothers' diets were not recorded but the plasma β-carotene concentration of the neonates was also low leading the authors to suggest that the mother's vegetable intake was low. In contrast, a higher infant plasma lutein and zeaxanthin concentration of 143 µg/L was found in a small group of U.S. infants aged 1 month, although no mention of maternal diets was made (Johnson *et al*., 1994). A mean plasma lutein and zeaxanthin concentration of 168 µg/L was found in a group of 173 Malawian infants aged 12 months (Dancheck *et al*., 2005).

Many of the infants were eating lutein and zeaxanthin-rich foods including eggs (76% of the infants) and corn porridge (91% of the infants). In a study involving 41 U.S. infants, a mean plasma lutein and zeaxanthin concentration of 126 µg/L was found (Wyeth Nutrition, 2006a). As a group, the women tended to eat a lot of dark green leafy vegetables, with 68% reporting a consumption of six or more one-half cup servings per week.

Table 2: Combined lutein and zeaxanthin serum concentrations in breastfed infants

Reference	Country	n	Age	Concentration	Conc. µg/L
Johnson *et al.*, 1994	U.S.	10	1 mo	14.3 (SEM) 1.9 µg/dL	143
Canfield *et al*., 2001	Honduras	28 28 10	7 mo	0.090 (SEM) 0.04 µmol/L 0.084 (SEM) 0.04 0.098 (SEM) 0.04	51 48 56
Adelekan *et al*., 2003	Nigeria	192	0-20 d	0.080 geometric mean (SE) 0.060	46
Dancheck *et al*., 2005	Malawi	173	12 mo	Lutein 0.252 (SD) 0.118 µmol/L Zeaxanthin 0.044 (SD) 0.019 Combined L+Z	 ~168
Wyeth Nutrition, 2006a	U.S. multi centre	41	58 d	Lutein 9.24 (SD) 4.70 µg/dL Zeaxanthin 3.35 (SD) 1.44 Combined L+Z	 ~126

These data suggest that a low maternal intake of lutein-rich foods would predict a low infant serum lutein concentration. There are no serum lutein data for Australian or New Zealand breastfed infants by which to assess where in the range Australian and New Zealand infants might lie.

5.2 Serum lutein and zeaxanthin concentrations in formula-fed infants

Data from a β-carotene supplementation trial was used to assess serum lutein and zeaxanthin combined concentrations in cord blood and in infants at 1 month of age (Wyeth Nutrition, 1994). The mean (SEM) serum lutein and zeaxanthin cord blood concentration was 48.9 (3.8) µg/L. At 1 month of age, mean (SEM) serum lutein and zeaxanthin concentration of infants receiving lutein-unfortified infant formula was 17.9 (2.9) µg/L. In contrast, the serum lutein and zeaxanthin concentrations in breastfed infants increased over the same time period to 143 (18.6) µg/L. In another study, 63 healthy Philippino infants aged 0–14 days were randomised to receive formula (Wyeth, S-26 Gold) containing an 'innate' amount of lutein and zeaxanthin, or the same formula fortified with lutein and zeaxanthin at combined concentrations of 47 or 289 µg/L (Wyeth Nutrition, 2006b). After 35–40 days, the mean serum lutein and zeaxanthin concentrations of the infants were 17.3 µg/L (unfortified), 30.2 µg/L (fortified with 47 µg/L), and 143.2 µg/L (fortified with 289 µg/L).

5.3 Relative bioavailability of lutein in human milk and in infant formula

FSANZ is not aware of any published studies in which the relative bioavailability of lutein from human milk or formula has been directly tested. However, since Draft Assessment Wyeth has provided FSANZ with additional data on the bioavailability of lutein in human milk. Wyeth conducted a prospective, double-blinded study that included 34 healthy term infants who were exclusively breastfed or formula-fed for 12 weeks. The lutein fortification levels for this study were 22, 45, 119 and 224 µg lutein per litre of infant formula. The results showed an approximate four-fold difference in the blood lutein response in the breastfed infants compared with formula-fed infants (Wyeth Nutrition, 2007).

Data on human milk and infant serum lutein and zeaxanthin combined concentrations are available from cross-sectional analyses. The data suggest that the lutein and zeaxanthin concentration in formula needs to be higher than the concentration in breast milk to achieve comparable lutein concentrations in infant serum (refer to Table 3). Supplemental lutein has also been found to have lower bioavailability than an equivalent amount of lutein contained in egg yolks (Chung *et al*., 2004).

Table 3: Lutein and zeaxanthin combined concentrations (µg/L) in breast milk, infant formula and infant serum.

Reference	Breast milk	Formula	Infant serum	Approximate response
Canfield *et al*., 2001	9		~50	x6
Wyeth Nutrition, 2006a	57		126	x2
Wyeth Nutrition, 2006b		20	17.3	x0.9
Wyeth Nutrition, 2006b		47	30.2	x0.6
Wyeth Nutrition, 2006b		289	143.2	x0.5
Wyeth Nutrition, 2007	24		91	x4
		22	11	x0.5
		45	36	x0.8
		119	110	x0.9
		224	197	x0.9

6. Interaction of lutein and zeaxanthin with other carotenoids

Data from a study in which people consumed various amounts of carotenoids from vegetables and supplements indicated that there may be an interaction among carotenoids whereby consumption of one carotenoid affects the absorption of another (Micozzi *et al*., 1992).

The authors suggested that a large dose of purified β-carotene may impair the intestinal absorption of lutein and zeaxanthin. A possible interaction between lutein and β-carotene has also been examined by taking serial blood samples following single oral doses of lutein and zeaxanthin, β-carotene, or both (Kostic *et al*., 1995). Following ingestion of a test supplement, lutein and zeaxanthin enhanced or diminished the mean serum concentration of β-carotene dependent on the individual's response to β-carotene alone. The authors discussed whether the apparent 'enhancement' of β-carotene absorption by lutein and zeaxanthin might be due to β-carotene not being converted to vitamin A in the presence of the xanthophyll carotenoids. Data from the Micozzi *et al*. (1992) study were indicative of lutein and zeaxanthin interfering with the absorption of β-carotene.

Although interactions between β-carotene and the xanthophyll carotenoids have been found in animals and humans, the evidence among studies is equivocal, both in magnitude and direction of effect, and the underlying mechanisms are not understood (van den Berg, 1999). The Applicant has conducted a supplementation trial in which 63 infants were randomised to receive formula containing lutein and zeaxanthin at concentrations of 20, 47, and 289 µg/L for 5 weeks (Wyeth Nutrition, 2006b). There was a difference in post-supplementation plasma *cis* β-carotene between groups receiving the lowest and highest amounts of lutein and zeaxanthin but no difference in the plasma concentrations of all *trans* β-carotene between groups.

These data show that under some circumstances there may be interactions between carotenoids when co-ingested such that the presence of one carotenoid may interfere or enhance the absorption of another. However, the nature of these interactions is not understood and more research is needed in this area.

The nutritional implication to formula-fed infants of a lutein and zeaxanthin interaction with β-carotene is unclear because, although carotenes provide a source of vitamin A precursors, there is a requirement for infant formula to contain pre-formed vitamin A.

7. Potential antioxidant activity

Oxidative stress in the retina appears to promote the formation of degradation products that accumulate with age (Katz and Robison, 2002). Lipofuscins, also known as age-pigments, accumulate in the retinal pigment epithelial (RPE) cells. A compound found in RPE lipofuscin, *N*-retinylidene-*N*-retinylethanolamine (A2E), can be generated *in-vitro* from retinoids (Eldred and Lasky, 1993). The immediate precursor of A2E is *N*-retinylidene-*N*-phosphatidylethanolamine (A2-PE) which is formed in photoreceptor outer segments and deposited in RPE cells. An antioxidant function for lutein and zeaxanthin in the eye is indicated *in-vitro* by the findings that lutein and zeaxanthin are protective against the photo-oxidation of A2-PE (Kim, 2006).

These data indicate that lutein and zeaxanthin may play a role in eye health but further research is needed to confirm the potential role.

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Attachment 3

Hazard Assessment

Summary

Lutein is a naturally occurring xanthophyll carotenoid. Lutein is a normal constituent of the diet, is well tolerated and unlikely to have any adverse effect when consumed in the range of normal consumption from fruit and vegetables.

The product under evaluation in this Application is an extract of marigold (*Tagetes erecta L.*) flowers containing predominately lutein (~90%) with a small amount of zeaxanthin (~10%). The extract is present at approximately 20% in safflower or other edible oil.

FSANZ has assessed the submitted evidence on the safety of lutein including a ninety-day repeat-dose toxicity study and a developmental toxicity study, in rats, and a 52-week study in non-human primates. In particular, ocular toxicity was evaluated in the non-human primate study, and no adverse effects seen. Two additional studies on the bioavailability of lutein from infant formula in pigs and non-human primates, and two studies on the effect of lutein-supplemented infant formula on the growth and occurrence of adverse events in human infants were also considered. No adverse effects, including effects on eye health, have been observed in any of the studies on lutein and zeaxanthin. Carotenodermia (skin yellowing) is observed at high doses; however this is considered harmless and is readily reversible upon discontinuation of high intakes of lutein.

JECFA evaluated this lutein and zeaxanthin preparation at its 63rd meeting (in 2004) and established an Acceptable Daily Intake (ADI) of 2 mg/kg bw per day. This was based on the highest dose tested in a ninety day repeat dose toxicity study in rats and includes a safety factor of 100. The ADI set by JECFA was not specifically set for infants aged 12 weeks or below.

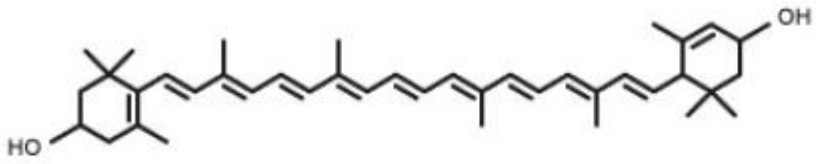
FSANZ has established an ADI for lutein of 2 mg/kg bw per day based on the same study and safety factor as used by JECFA. The ADI relates only to lutein preparations meeting the specification developed by JECFA at its 63rd meeting. The ADI was considered to be suitable for infants under 12 weeks of age because a consideration of the data (including a clinical trial in young infants aged 0 – 16 weeks), indicated no evidence of toxicity.

FSANZ considers that lutein in infant formula at the level proposed in this Application represents negligible risk to young infants.

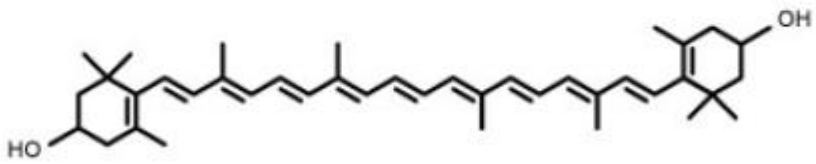
1. Background

Lutein is a xanthophyll carotenoid, which is found in many yellow and dark green vegetables including corn, spinach and green peas. It has no pro-vitamin A activity, but is used in food as a yellow food colour. Under IUPAC nomenclature rules, lutein has the chemical name 4-[18-(4-hydroxy-2,6,6-trimethyl-1-cyclohex-2-enyl)-3,7,12,16-tetramethyl-octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-3-en-1-ol.

It has the molecular formula $C_{40}H_{56}O_2$. The chemical structures of lutein and its isomer zeaxanthin are shown in Figure 1. Lutein is insoluble in water, soluble in hexane.



Lutein



Zeaxanthin

Figure 1: Chemical structures of lutein and zeaxanthin

This Application relates to the purified extract from marigold (*Tagetes erecta L.*) oleoresin. This extract meets the specifications developed for lutein by JECFA (JECFA, 2004). The purified extract is combined with vegetable oil (e.g. safflower oil) to give a preparation containing approximately 20% lutein and is sold as FloraGLO® Lutein 20% Liquid in Safflower Oil.

2. Risk Assessment

The Applicant has provided statements that their product, FloraGLO® Lutein 20% Liquid in Safflower Oil, is tested for a range of contaminants including polycyclic aromatic hydrocarbons, dioxins, aflatoxins and pesticides.

To date, all recognised food allergens are proteins. Therefore it is very unlikely that lutein has any potential to be allergenic. Although anecdotally, allergic reaction has been reported to be associated with high carotene exposure, this has not been confirmed in clinical trials (Institute of Medicine, 2000). In addition, the lutein preparation is not sourced from, nor contains any of the foods considered by FSANZ to be common allergens. This includes crustaceans, eggs, fish, milk, peanuts, soybeans, tree nuts, sesame seeds and cereals containing gluten. The preparation does not contain added sulphites at concentrations of 10 mg/kg or more.

2.1 Previous considerations of lutein by the Joint Expert Committee on Food Additives

The Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) first considered xanthophylls obtained from *Tagetes erecta* L. petals at its 31st meeting, in 1987.

At that time, no toxicological data was available, however, tentative quality specifications were prepared. *Tagetes* extract containing low concentrations of lutein was considered by JECFA at its 55th and 57th meetings, in 2001 and 2002 respectively, at which time the tentative specifications were superseded by full specifications.

These specifications relate to the low concentration lutein preparations only, not the high lutein concentration preparation under consideration in this Application.

2.1.1 Sixty third meeting of JECFA, 2004

Toxicological data on *Tagetes* preparations with high lutein content (>80%) was submitted to JECFA and evaluated at its 63rd meeting, in 2004 (JECFA, 2006). The studies examined included: pharmacokinetic studies in mice, rats, cows and humans; an acute toxicity study in rats; short term toxicity studies in mice (28 days), rats (28 days and 13 weeks) and monkeys (52 weeks); *in vitro* and *in vivo* genotoxicity studies; and a developmental toxicity study in rats. Special studies on cardiovascular effects (mice), immune responses (mice, and cats and dogs), ocular toxicity (monkeys), and dermal and ocular irritation (rabbits) were also examined, as were clinical and epidemiological studies in humans. The following is a summary of the evaluation conducted by JECFA.

No adverse effects were observed in the toxicity studies conducted in a number of species. As lutein was not genotoxic, has no chemical structural alert or tumour promoting activity, and is a natural component of retinal pigment in the eye, JECFA did not consider it necessary for a carcinogenicity study to be conducted.

Lutein and β-carotene have several chemical structural similarities. As β-carotene supplements have been reported to enhance the development of lung cancer when given to heavy smokers, JECFA considered whether lutein might be expected to have a similar effect. The available data suggest that lutein from food is not be expected to enhance the development of lung cancer. However, JECFA was unable to assess whether lutein in supplement form might have this effect in heavy smokers.

A 52-week study in monkeys, designed to evaluate ocular effects, was not used to set the ADI as although no adverse effects were reported at the highest dose tested (20 mg/kg bw per day), much higher doses had been used in other studies with no adverse effects reported. A comparison of toxicokinetic studies in rats and humans indicated that repeat dose toxicity studies in rats were suitable to derive an ADI. An ADI of 2 mg/kg bw per day was established based on the NOEL of 200 mg/kg bw per day (the highest dose tested) in a 90-day rat study and a safety factor of 100. The safety factor incorporates a factor of 100 for inter- and intra-species differences. The application of an additional safety factor for the absence of a long term study was considered unnecessary because no effects were observed in the toxicity studies involving a number of species and at higher doses, including the developmental toxicity study (a NOEL of 1000 mg/kg bw per day, the highest dose tested).

The ADI was established as a group ADI for both lutein and zeaxanthin, in light of their structural and physiological similarities. At this same meeting JECFA established a new set of full specifications for 'lutein from *Tagetes erecta*'. JECFA noted that this ADI only applies to products complying with the specifications. In addition, JECFA ADIs do not generally apply to infants below 12 weeks of age.

2.2 Aims of the current assessment

FSANZ has not previously assessed the safety of lutein. Therefore, the aims of the current assessment were to:

- review supplementary data on the absorption and toxicology of lutein in laboratory animals and humans to determine its safety as a nutritive substance in infant formula; and

- determine whether the ADI is suitable for infants less than 12 weeks of age as well as older infants.

A short term toxicity study in rats and a developmental toxicity study in rats, both of which have been evaluated by JECFA, were submitted as part of this Application and are summarised at Attachment 1.

3. Summary of Supplementary Data

3.1 Animal studies

3.1.1 Unpublished Wyeth Research Report RPT-64673 (2006) Lutein absorption from S-26 Gold Liquid Infant Formula in neonatal pigs

This study investigated the absorption of lutein from S-26 Gold infant formula fed to female neonatal pigs (2 days old). The piglets had been removed from their mothers at 12 hours and fed standard carotenoid-free infant formula. At 48 hours of age, pigs were fasted for 11 hours and divided into two groups of four pigs. Each was given a single dose of either 332 µg or 1660 µg lutein per kg body weight in infant formula by oro-gastric gavage. Blood was collected from each animal at 0, 15, 30 and 60 minutes and 2, 4, 8, 12, 24, and 36 hours post-dosing and analysed by HPLC for lutein and zeaxanthin. The LOQ was not stated. For lutein, the mean C_{max}, mean T_{max}, and mean AUC were calculated and are shown in the table below.

Parameter	**332µg lutein/kg bw**	**1660µg lutein/kg bw**
Baseline serum lutein (µg/mL range)	Nd[1] – 0.0001	Nd – 0.00008
C_{max} (µg/mL) ± SD[2]	0.0055 ± 0.0024	0.0179 ± 0.089
T_{max} (hours) ± SD	4 ± 3	2±0
AUC[3] µg/mL · h ± SD	0.0823 ± 0.0289	0.3834 ± 0.1884

[1] not detected
[2] Standard deviation
[3] Time period over which this was calculated was not given

The background serum lutein concentration range was large, making the interpretation of this study difficult. There was a five fold difference between doses, which was reflected in the observed AUC. Serum lutein concentrations were shown to increase in response to feeding lutein-fortified infant formula to neonatal pigs, indicating that the lutein in infant formula is bioavailable.

This study was conducted according to Good Laboratory Practice.

3.1.2 Unpublished Wyeth Report RPT-64484. (2006) Lutein absorption from S-26 Gold Liquid Infant Formula by Infant Rhesus Monkeys

This study aimed to determine the absorption of lutein by two groups of three 13-week old infant rhesus monkeys (*Rhesus macaques*) when administered in infant formula. On the day of dosing, infants were separated from their mothers and fasted for six hours. Monkeys were given a single dose of either 166 µg lutein/kg bw or 1660 µg lutein/kg bw in S-26 Gold infant formula via gavage.

Blood was drawn at 0, 1, 2, 4 and 6 hours after formula administration and serum prepared. Serum lutein, cholesterol and triglycerides were measured. For lutein, measured by HPLC, the mean C_{max}, mean T_{max}, and mean AUC were calculated and are shown in the table below.

Parameter	**166µg lutein/kg bw ± SD***	**1660µg lutein/kg bw ± SD**
Baseline serum lutein,T=0 (µg/mL)	0.188 ± 0.084	0.322 ± 0.162
C_{max} (µg/mL)	0.196 ± 0.154	0.399 ± 0.219
T_{max} (hours)	4 ± 2	4 ± 0
AUC[#] µg/mL · h	1.13 ± 0.48	2.16 ± 1.14

* Standard deviation
[#] Time course was not given

This study indicated that a single dose of 1660 µg lutein/kg in infant formula led to a small increase in mean serum lutein in infant rhesus monkeys. However, the mean baseline serum lutein level in the higher dose group was almost twice that of the low dose group. The differences in baseline lutein may be due to differences in the lutein status of the mothers. The monkeys' lutein levels were much higher than those in neonatal pigs in the previous study, possibly due to the monkeys' exposure to breast milk for 13-weeks. Very little change was seen in the serum lutein levels of monkeys given the low dose (166 µg/kg bw). The 10-fold difference in lutein dose between test groups was not reflected in the only 2-fold increase in AUC observed between the two groups, however, the high background lutein levels and the difference between low and high dose background levels make this study difficult to interpret.

This study was conducted according to Good Laboratory Practice.

3.2 Human studies

3.2.1 Unpublished Wyeth study. (2006) Effect of Lutein in S-26 Gold on Infant Plasma Lutein Concentration. Protocol n. 9041A1-903; and

Unpublished Wyeth study. (2006) Effect of Lutein in S-26 Gold on Infant Plasma Lutein Concentration. Protocol Number 9041A1-903-AMENDMENT II Dated 9 June 2006

The objective of this study was to compare infant plasma lutein concentrations among infant groups receiving S-26 Gold alone and S-26 Gold with either 25 or 200 µg lutein/L for 36-37 days.

The lutein source used for fortification contained lutein and zeaxanthin in a ratio of approximately 13:1. The S-26 Gold formula naturally contains 19.8 μg lutein/L, so the two test formulas contained 47.4 and 288.5 μg/L respectively (added to 150% of the label claim to account for manufacturing and storage shelf life losses).

It was calculated that plasma lutein concentrations would have reached a steady state within this time period. In addition to lutein, other carotenoids (alpha- and beta-cryptoxanthin, cis- and trans-beta carotene, lycopene, zeaxanthin and cis-lutein and zeaxanthin) in the plasma were measured. The growth of the infants and any adverse effects were measured. In total, 63 infants participated in the study (21 in each study group).

At the end of the study, the mean levels of lutein in the plasma of the control, low dose and high dose groups were 17.34 μg/L, 30.24 μg/L and 143.15 μg/L respectively.

Only the high dose group was statistically significantly higher than the control group. Statistically significant increases in plasma zeaxanthin, cis-lutein and zeaxanthin and cis-beta carotene were observed in the high lutein group. The lower level of fortification did not result in statistically significant increases in the tested carotenoids.

Mean head circumference was comparable between the three groups. Infants on all study formulas demonstrated appropriate growth and there were no differences between the groups. All adverse events were mild or moderate and resolved in a timely manner. None of these were considered formula-related in any of the groups.

The authors concluded that this study provides new information on the plasma lutein levels of formula fed infants compared with those fed lutein fortified formula. In addition, the highest level of lutein intake had no adverse effects on the infants in the study.

This study was conducted according to Good Clinical Practice.

3.2.2 Unpublished Wyeth Report (2006) Effect of lutein in S-26 gold on growth and safety. Protocol Number 9041A1-902

A prospective, randomised, controlled, double-blind study was conducted in healthy <14 day old Philippine infants. The addition of lutein to infant formula at a level of 200 μg/L was evaluated with regard to growth, incidence of adverse events, blood chemistry, general eye health and visual acuity. 230 infants (118 females and 112 males) were randomised into one of two formula groups: control formula (S-26 Gold) and experimental formula (S-26 Gold with 200 μg/L lutein). Formula was provided for four months. Subjects were weighed and measured at weeks 0, 4, 8, 12 and 16. Formula intake over three days was recorded during weeks 4, 8 and 12. Temperament scales were completed by the parent/caregiver in weeks 8 and 12. Infant health history and physical examination, including fundoscopic exam was conducted at week 0 and 16. Visual acuity measurements were conducted at week 16, followed by the collection of infant blood samples. Any adverse events that occurred throughout the study were recorded.

One hundred and ten (110) infants in each group completed the study, five from each group did not complete it. Of the ten withdrawals, four from the control group and three from the treatment group withdrew due to adverse events. Three were removed from the trial at the request of their parent/guardian.

The mean intake of formula for all infants at weeks 4, 8 and 12 was 964 mL, 1192 mL and 1255 mL respectively. The maximum intake of formula over the course of the study was reported to be 3401 mL/day. This is equivalent to 680 µg of lutein/day, well below the JECFA ADI of 2 mg/kg bw per day.

There were no differences between the two treatment groups for the rate of weight gain, rate of length increase or rate of head circumference increase for either male or female infants or when both sexes were considered together. When compared to the US CDC growth data, weight-for-age, length-for-age, weight-for-length and head-circumference-for-age, the Philippine infants in the both groups were below the mean values for the US reference data. The infants in the study demonstrated growth over the study that was comparable to the mean US values for three of the four measurements. For head-circumference-for-age, the Philippine infants in neither group demonstrated the same rate of increase as observed in the US population.

However, when compared to data from a Philippine reference population of almost 27,000 children, the data of the study population followed the growth curve established from the Philippine data.

The frequency and severity of adverse events in the study were similar between groups, with all symptoms resolving over the study. The authors stated that clinical chemistry of the blood samples obtained at the study termination demonstrated that the mean values for all parameters fell within the normal ranges for infants and there was no difference between the values for the two groups, however this data was not provided to FSANZ. Data on the blood levels of lutein were not presented.

The study authors concluded that fortification of S-26 Gold formula with lutein at levels of 200 µg/L results in growth equivalent to that of infants fed non-fortified S-26 Gold formula.

This study was conducted according to Good Clinical Practice.

4. Discussion

Lutein is a naturally occurring carotenoid present in many foods which have a history of consumption by human populations. Lutein is also found in human milk, however the levels vary significantly and are dependent on the amount of lutein in the mother's diet (IOM, 2000).

The supplementary data submitted by the Applicant included two studies on the bioavailability of lutein from formula in pigs and monkeys, and two studies on lutein absorption and effects on growth in human infants. The results of these studies are consistent with the results of the studies considered by JECFA (JECFA, 2006). In particular, no differences in growth and occurrence of adverse events were seen in a study of human infants given formula containing lutein compared to infants given non-fortified formula.

Lutein is proposed to have beneficial effects on eye health. This has not been considered in the Hazard Assessment, however potential adverse effects on eye health have been considered in the evaluated studies. In the 52-week study in monkeys, comprehensive ophthalmic examinations were conducted and no evidence of adverse effects observed.

Relatively large doses of lutein (6000 µg/d) have been used safely in humans over periods of several months as an exploratory treatment for age-related macular disease (Bartlett & Eperjesi, 2007). Other primates (Rhesus Macaque monkeys) have received even larger doses of either lutein or zeaxanthin equivalent to 28,000 to 44,000 µg of the carotenoids per day, dependent upon the weight of the monkey, over a period of several months without ocular toxicity (Khachik et al., 2006). There is no evidence that lutein supplementation has adverse effects on eye health.

4.1 Application of the ADI to infants up to 12 weeks

The principles that direct the safety of new ingredients in infant formula are essentially the same as those applied to food safety for older children and adults. However, infancy is considered a uniquely vulnerable period of life and so some additional considerations may also apply. Infant formula is the only source of nutrition for some infants, thus the presence of a chemical in infant formula is likely to have greater implications for the infant, than it would for an older child with mixed sources of nutrition.

In 1971, an FAO/WHO meeting on Additives in Baby Foods recommended that a distinction should be made between children up to 12 weeks of age and children over 12 weeks. This distinction was made on the basis that the organs and tissues of very young children are functionally immature and as a result may be more sensitive to the toxic effects of exposure to chemicals (JECFA, 1987).

Therefore, in general it was considered prudent that any toxicological investigations of substances proposed to be added to infant formula should include evidence of safety in young animals. In general ADIs developed by JECFA do not apply to infants up to 12 weeks of age.

With regard to the safety of lutein in infant formula, several issues have been taken into consideration and are discussed below.

Lutein is present in breast milk; the level at which is it present is variable and dependent on the diet. Although the range of levels detected in mature breast milk (mean concentrations at a range of locations worldwide of 15-44 µg/L (Canfield et al., 2003) is much below the level anticipated to be used in infant formula (250 µg/L), lutein is a substance to which breastfed infants are generally exposed. In addition, colostrum generally contains higher levels of lutein than mature milk. Lutein is also present in some infant formula products intended for premature babies and used internationally, at levels similar to those proposed in this Application (0 – 243 µg/L) (Jewel et al, 2004).

A 16-week study in human infants indicated that formula containing lutein (200 µg/L) sustained normal physical growth, and that no adverse events (e.g. diarrhoea, vomiting etc) due to lutein where observed in these infants. In total, there is no evidence of toxicity due to lutein.

The only observed effect from the supplementary intake of high levels of lutein is carotenodermia, a yellowish discolouration of the skin that is also observed with a high intake of β-carotene. Carotenodermia is harmless and readily reversible when carotene ingestion is discontinued (Institute of Medicine, 2000).

At supplementary intakes of 15 mg/day (0.25 mg/kg body weight) for 20 weeks, carotenodermia was observed in about 40% of a cohort of Spanish volunteers, however this was not observed in cohorts from the Netherlands, Northern Ireland, or the Republic of Ireland (JECFA, 2006). Actual exposure to lutein would have been greater than 15 mg/day if dietary intakes had also been included.

The anticipated mean exposure of young infants (12 weeks) to lutein from fortified infant formula is in the vicinity of 0.035 mg/kg bw per day (see Attachment 4 – Dietary Intake Assessment for further information on expected exposure). This is more than 20,000 times below the highest doses tested in animal studies (1000 mg/kg bw per day) which were without adverse effect, and 2,000 times below the NOEL on which the ADI is based. It is also greater than seven times below the level that causes carotenodermia in sensitive individuals, recalling that in addition to the known lutein supplements taken by these individuals, dietary exposure to lutein would also have contributed to the precipitation of carotenodermia. Infant formula would be the only source of lutein for infant formula-fed infants.

Given the available information regarding lutein, and what is known about the differences between young infants and adults, there is no reason to expect that lutein would have any adverse effects in young infants. Therefore, while the JECFA ADI has not been set for infants below 12 weeks of age and as a consequence is not intended to apply to this population, FSANZ considers that lutein in infant formula does not represent a risk to young infants at the level proposed in this Application.

5. Conclusions

The toxicological database considered by JECFA at its 63rd meeting in 2004 was adequate to derive an ADI. No toxic effects were observed in a developmental toxicity study, a sub-chronic toxicity study in rats and a 52-week toxicity study in non-human primates. Two additional studies on the absorption and safety of the lutein and zeaxanthin formulation in human infants indicate that at the levels of supplementation (200 μg/L in formula), no effects on growth or occurrence of adverse events were observed.

No suitable human studies were identified that could serve as a basis to establish an ADI for lutein. However, lutein and zeaxanthin are normal constituents of the human diet, are well tolerated and unlikely to exert adverse effects within the wide range of normal consumption from their natural sources.

No adverse effects were observed in the available animal and human studies. In addition, given the available information regarding lutein and what is known about the differences between young infants and adults, there is no reason to expect that lutein would have any adverse effects in young infants due to these differences. Therefore, FSANZ has adopted the JECFA ADI of 2 mg/kg bw per day. This ADI applies only to lutein preparations which meet the JECFA specifications. While the JECFA ADI has not been set for infants below 12 weeks of age and as a consequence is not intended to apply to this population, FSANZ considers that lutein in infant formula is unlikely to represent a risk to young infants at the level proposed in this Application.

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A1. Annex 1

A1.1 13-Week Oral Toxicity (Dietary Administration) Toxicity Study in the Rat with a 4 Week Treatment-free Period. (2000) Pfannkuch, F., E. Wolz, C.P. Aebischer, J. Schierle, and C. Green. Unpublished Roche Study Report No. B-172'300.

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The toxicity of FloraGLO® (approximately 79% lutein and 5% zeaxanthin) was evaluated in a 13-week oral toxicity study conducted in Wistar rats. The study complied with GLP and met the requirements of OECD test guideline 408. Groups of 10 rats of each sex were given FloraGLO® incorporated into beadlets in the diet at levels of 0, 2, 20 or 200 mg/kg bw per day. Five additional animals of each sex were included in the control and high dose groups; these animals were included for a four week recovery phase.

There were no treatment related deaths in the study, nor were there any treatment related clinical signs or adverse effects. Analysis of blood and liver samples showed that lutein was present at dose-related levels in the plasma and liver, and it was concluded that adequate exposure to lutein and zeaxanthin had occurred in the study.

Administration of FloraGLO® to rats for 13 weeks did not produce any evidence of toxicity. The No Observed Effect Level in this study was 200 mg FloraGLO®/kg bw per day, the highest dose used in the study.

A1.2 Lutein 10% WS (Ro 15-3971/000) – Developmental toxicity study by the oral route (dietary admixture) in the rat. Edwards J.A., F. Pfannkuch, E. Wolz, E. Marsden. Unpublished Roche Study. Report No. 1008196.

A developmental toxicity study was conducted in groups of 25 mated female Sprague-Dawley rats given diets containing 0, 250, 500 and 1000 mg lutein/kg bw per day. The study was GLP compliant, but did not comply with the relevant OECD test guideline as the test article was administered in the diet rather than by gavage. The test article was contained in 'beadlets' and was comprised of 19% lutein and 5% zeaxanthin. Control, low and medium dose groups received placebo beadlets in addition to the lutein beadlets to ensure all animals received the same quantity of beadlets. Dosing occurred from day 6 to day 20 of gestation. All females were killed on day 20 of gestation for examination of the uterine contents. Foetuses were examined for external defects, and live foetuses killed by injection of sodium pentobarbitone. Approximately half of each litter examined for visceral abnormalities, then eviscerated. The eviscerated carcasses were examined for skeletal abnormalities. The remaining foetuses were preserved for fixed soft tissue examination under low power magnification.

There was no evidence of effects due to lutein in the dams, although control, low and medium dosed animals showed an inverse dose-related decrease in food consumption and maternal and foetal body weights.

This was attributed to the decreased palatability of the control beadlets as animals in the high dose group showed food intake and body weight gain similar to that of historical control animals. In addition, the control and low dose group foetuses showed reduced ossification; this was attributed to the decrease food consumption by the dams, as the degree of ossification in the highest dose group was consistent with that of historical controls.

There were no effects on pre- or post-implantation, embryo-foetal survival or sex ratio. In the high and intermediate dose groups, there was a slight dose-related increase in the rudimentary extra lumbar ribs, but this finding was not considered toxicologically relevant as this minor skeletal change is known to be reversible.

Plasma samples taken on gestation days 7 and 16 indicated that mean plasma lutein levels increased by approximately 80% over the study.

Under the conditions of this embryotoxicity/teratogenicity study, the NOEL for lutein in rats was established as 1000 mg/kg bw per day (the highest dose tested).

Attachment 4

Dietary Intake Assessment

Note: The Dietary Intake Assessment was conducted prior to the Applicant's request to reduce the maximum concentration in follow-on formula from 500 µg/L to 250 µg/L. This Dietary Intake Assessment Report has not been amended to accommodate this change. Therefore, outcomes presented in this Report relating to follow-on formula are conservative, as they are an overestimate of results.

Summary

An Application was received by FSANZ to amend the Code to allow the addition of lutein from marigold (*Tagetes erecta* L.) to infant formula and follow-on formula. The material proposed by the Applicant for addition to infant formula and follow-on formula is a purified extract of lutein from marigold oleoresin which contains both lutein and its isomer zeaxanthin. The ratio of lutein to zeaxanthin is approximately 10:1.

As the Acceptable Daily Intake (ADI) [23] is for lutein and zeaxanthin, dietary intakes of lutein and zeaxanthin were calculated for Australian and New Zealand infants aged 3 months and Australian infants aged 9 months. Infants aged 3 months were assumed to be exclusively infant formula fed. Infants aged 9 months were assumed to be consuming follow-on formula in addition to solid foods. Estimated mean and 95th percentile dietary lutein and zeaxanthin intakes were below the ADI for both 3 month old infants and 9 month old infants. The highest estimated dietary lutein and zeaxanthin intake, as a proportion of the reference health standard, was the 95th percentile intake for 9 month old infants following the lutein and zeaxanthin fortification of follow-on formula (8% ADI).

At *'Baseline'*, lutein and zeaxanthin intakes for infants aged 3 months was zero. The major contributors (≥ 5%) to lutein and zeaxanthin intakes for Australian infants aged 9 months from food were fruit and vegetables juices (20%), carrots (7%), peas (7%), sweet corn (6%), onions (6%) and broccoli and cauliflower (5%). However, fortification of follow-on formula resulted in the major contributor to lutein and zeaxanthin intakes being follow-on formula (52%) rather than food.

1. Background

An Application was received by FSANZ to amend the Code to allow the addition of lutein from marigold (*Tagetes erecta* L.) to infant formula (up to 250 µg/L) and to follow-on formula up to 500 µg/L (see Table 1).

[23] An ADI is 'an estimate of the amount of a substance in food or drinking-water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk' (Joint FAO/WHO Expert Committee on Food Additives, 2007).

Table 1: Proposed uses of lutein in foods, as provided by the Applicant

Food Name	Lutein concentration (µg/L)
Infant formula	250
Follow-on formula	500

Lutein is an oxygenated carotenoid (xanthophyll pigment) which occurs naturally with the isomer zeaxanthin in many foods such as vegetables and fruits (Joint FAO/WHO Expert Committee on Food Additives, 2005).

Carotenoids are synthesized by all plants and some micro-organisms (Ahmed *et al*., 2005). Rich sources of lutein include: kale, spinach, cress, Swiss chard, green peas, lettuce, zucchini, Brussels sprouts, broccoli and corn (maize) (U.S.Department of Agriculture, 2005b).

The material proposed by the Applicant for addition to infant formula and follow-on formula is a purified extract from marigold oleoresin which contains both lutein and its isomer zeaxanthin. The ratio of lutein to zeaxanthin is approximately 10:1.

2. Dietary Intake Assessment Provided by the Applicant

Dietary intake assessment data for lutein and zeaxanthin were provided by the Applicant (see Table 2). The Applicant estimated lutein exposure for America (U.S.A.) to be at 12% ADI for infants aged 2-6 months and 7-11 months. The Applicant stated that the contribution of fortified follow-on formula to lutein intakes would be significant and that older infants and children consuming 600 ml of lutein-fortified follow-on formula would increase lutein intakes by approximately 300 µg/day.

Table 2: Estimated mean and 90th percentile daily intake of lutein and zeaxanthin for US and Australian children aged 2 months – 8 years, as provided by the Applicant

Country	Age Group	Number	Lutein and zeaxanthin intake (µg/day)	
			Mean	90th percentile
United States of America*	2-6 months	143	199	819
	7-11 months	192	463	1,113
	1-3 years	597	636	1,194
	4-8 years	920	678	1,369
Australia#	1-3 years	38	344	776

* NHANES 2001-2 Intake Data (2004 release)
# Uses the Food Intake and Nutrition Status (FINS) study and the USDA National Nutrient Database for Standard Reference (Release 17, 2004)

A FSANZ dietary intake assessment was considered necessary in order to estimate the current and potential dietary intakes of lutein and zeaxanthin and the impact of allowing the use of the lutein and zeaxanthin in infant and follow on formulas on public health and safety. Since the ADI relates to lutein and zeaxanthin rather than lutein only, all dietary intake assessments in this report refer to lutein and zeaxanthin.

3. Dietary Modelling conducted to estimate Lutein and Zeaxanthin Intakes

3.1 What is dietary modelling?

Dietary modelling is a tool used to estimate dietary exposure to food chemicals, including nutrient intakes, from the diet as part of the FSANZ risk assessment process. To estimate dietary exposure to food chemicals, records of what foods people have eaten are needed along with reports of how much of the food chemical of interest is in each food.

The accuracy of these dietary exposure estimates depends on the quality of the data used in the dietary models. Sometimes, all of the data needed are not available or their accuracy is uncertain so assumptions have to be made, either about the foods eaten or about chemical levels, based on previous knowledge and experience. The models are generally set up according to international conventions for food chemical dietary exposure estimates. However, each modelling process requires decisions to be made about how to set the model parameters and what assumptions to make. Different decisions may result in different answers. Therefore, FSANZ documents clearly all such decisions, model assumptions and data limitations to enable the results to be understood in the context of the data available and so that FSANZ risk managers can make informed decisions.

3.2 Population groups assessed

The primary target group was identified as infants aged up to 1 year. Children aged 1 year were considered by FSANZ to not fall within the scope of the term ‘infant’. The lutein intakes of children aged 1-3 years are considered in another Application (A597 – Lutein as a nutritive substance in formulated supplementary foods for young children).

Within the population group of infants aged up to 1 year, dietary lutein and zeaxanthin intakes were investigated for:

- 3-month old infants since infants of this age are solely infant formula or breastfed; and
- 9-month old infants since infants of this age consume both solid foods and an infant formula product or breast milk.

3.3 Dietary survey data

DIAMOND contains dietary survey data for both Australia and New Zealand; the 1995 NNS from Australia that surveyed 13,858 people aged 2 years and above, and the 1997 New Zealand NNS that surveyed 4,636 people aged 15 years and above. Since the target group was children aged up to one year, the data from the NNSs could not be used directly in assessment of this Application. However, theoretical diets were constructed to estimate dietary lutein and zeaxanthin intakes for infants aged 3 months and 9 months (see below).

3.4 Dietary intake assessment approach

Lutein and zeaxanthin intakes were estimated by combining usual patterns of food consumption, as derived from the theoretical diets, with current concentrations of lutein and zeaxanthin in foods and the current proposed levels of use of lutein and zeaxanthin in infant formula and follow-on formula.

Dietary Intake = nutrient concentration x food consumption amount

3.5 Lutein and zeaxanthin concentration data

The levels of lutein and zeaxanthin in foods that were used in the dietary intake assessment were derived from the Application and from the U.S. Department of Agriculture (USDA) nutrient database (U.S.Department of Agriculture, 2005a).

Concentrations of lutein and zeaxanthin were assigned to each of the food groups in the theoretical diets. The Applicant provided proposed maximum concentrations of lutein in infant formula and follow-on formula. Since the reference health standard (ADI) is for lutein and zeaxanthin, the proposed concentrations of lutein have been converted into lutein and zeaxanthin concentrations, based on a ratio of lutein:zeaxanthin of approximately 10:1.

The lutein and zeaxanthin concentrations for infant formula and follow-on formula that were used in the dietary intake assessments are outlined in Table 3.

Table 3: Lutein and zeaxanthin concentrations in infant formula and follow-on formula, as used in the dietary intake assessments

Food Name	Lutein and zeaxanthin concentration (µg/kg)
Infant formula	280
Follow-on formula	550

3.6 Scenarios for dietary intake assessments

The scenarios that were investigated in the dietary intake assessments are outlined below.

3.6.1 Baseline *model*

This model represents current estimated lutein and zeaxanthin intakes for each population group, assessed in the current regulatory environment (i.e. before permission to add lutein and zeaxanthin to infant formula and follow-on formula is in effect in Australia and New Zealand). The model took into account naturally occurring lutein and zeaxanthin in food but not lutein and zeaxanthin intakes from the use of supplements or the small quantities of lutein from ingredients used in some brands of infant formula products. For infants aged 3 months, *Baseline* intakes were therefore assumed to be zero as no food was consumed.

3.6.2 Scenario *model*

This model represents estimated lutein and zeaxanthin intakes for each population group after permission to add lutein and zeaxanthin to infant formula and follow-on formula is given in Australia and New Zealand. As for *'Baseline'*, the model took into account naturally occurring lutein and zeaxanthin in food (other than unfortified infant formula products) but not lutein and zeaxanthin intakes from the use of supplements.

3.7 How were the estimated dietary lutein and zeaxanthin intakes calculated?

As there were no data available from the 1995 Australian NNS for children aged < 2 years, theoretical diets were constructed to estimate dietary lutein and zeaxanthin intakes for the target groups of children aged 3 months and 9 months. Similarly, as there were no data available from the 1997 New Zealand NNS or 2002 New Zealand Children's NNS for children aged < 5 years, the same theoretical diet was used for New Zealand children aged 3 months. A theoretical diet for 9 month old New Zealand children was not constructed since NNS data were not available on the food consumption patterns of 2 year old New Zealand children.

Since the theoretical diets were based on mean food consumption amounts only, individual records were not available to derive a distribution of food intakes and hence a distribution of lutein and zeaxanthin intakes. The 95th percentile dietary lutein and zeaxanthin intakes were estimated and then compared to the ADI, using the internationally accepted equation (WHO, 1985) of:

95th percentile intake = mean intake x 2.5

3.7.1 Australian and New Zealand infants aged 3 months

The recommended energy intake for a three-month-old boy (FAO, 2004) at the 50th percentile weight (WHO, 2007) was used as the basis for the theoretical diet. Boys' weights were used because boys tend to be heavier than girls at the same age and therefore have higher energy and food requirements. Dietary intakes of lutein and zeaxanthin were calculated as follows:

1. Calculate the energy requirements for 3 month old infant:

   = Estimated energy requirement (kJ/kg bw/day) x body weight (kg)
   = 343 kJ/kg bw/day x 6.4 kg
   = 2195 kJ/day

2. Calculate the amount of infant formula required to meet energy requirements:

   = Estimated energy requirement (KJ/day) ÷ energy content of infant formula (KJ/100g)
   = $\frac{\text{2195 kJ/day}}{\text{274 kJ/100 g formula}}$
   = 800 g infant formula per day

3. Calculate the estimated mean dietary intake of lutein and zeaxanthin
   = Daily amount of infant formula x concentration of (lutein and zeaxanthin) in formula
   = 0.8 kg infant formula/day x 280 µg (lutein and zeaxanthin) per kg infant formula
   = 224 µg lutein and zeaxanthin per day
   = 0.224 mg lutein and zeaxanthin per day

3.7.2 Australian infants aged 9 months

The theoretical diet for Australian children aged 9 months was based on information on recommended energy intakes, mean body weight and the proportion of milk and solid foods in the diet for a 9 month old child, and data from the 1995 NNS on foods consumed by a 2 year old child.

The recommended energy intake for a nine-month-old boy (FAO 2004) at the 50th percentile weight (WHO 2007) was used as the basis for the theoretical diet. Boys' weights were used because boys tend to be heavier than girls at the same age and therefore have higher energy and food requirements. The body weight of a 50th percentile 9 month old boy was 8.9 kg.

It was assumed that 50 per cent of energy intake was derived from follow-on formula and 50 per cent from solids (Hitchcock *et al*., 1986). The patterns of consumption of a two-year-old child from the 1995 NNS were scaled down and used to determine the solid portion of the 9-month old's diet. Certain foods such as nuts, tea, coffee and alcohol were removed from the diet since nuts can be a choking risk (National Health and Medical Research Council, 2001) and coffee and alcohol are unsuitable foods for infants (ACT Community Care, 2000).

Consumption of breakfast cereals was assumed to be in the form of either infant cereal or single grain breakfast cereals, excluding bran-based cereals. All milk consumption was assumed to be in the form of follow-on formula.

4. Assumptions Used in the Dietary Modelling

The aim of the dietary intake assessment was to make as realistic an estimate of dietary lutein and zeaxanthin intakes as possible. However, where significant uncertainties in the data existed, conservative assumptions were generally used to ensure that the dietary intake assessment did not underestimate intake.

The assumptions made in the dietary intake assessment are listed below, broken down into several categories.

4.1 Consumer behaviour

- consumers select products that, on average, contain lutein and zeaxanthin at the concentrations specified;
- consumers do not alter their food consumption habits upon lutein and zeaxanthin fortified products becoming more available on the market;
- infants aged 3 months are exclusively infant formula fed; and
- infants aged 9 months consume follow-on formula in addition to solid foods.

4.2 Concentration Data

- It was assumed that US data (USDA, 2005) on the lutein and zeaxanthin concentrations in foods were representative of Australian and New Zealand foods;
- the lutein and zeaxanthin concentration of infant formula and follow-on formula is currently assumed to be zero (i.e. at *Baseline*); and
- there is no contribution to lutein and zeaxanthin intakes through the use of complementary medicines (Australia) or dietary supplements (New Zealand).

4.3 General

- naturally occurring sources of lutein and zeaxanthin have been included in the dietary intake assessment;
- for the purpose of this assessment, it is assumed that 1 millilitre is equal to 1 gram for all liquid and semi-liquid foods (e.g. infant formula).

5. Dietary Intake Assessment Results

5.1 Risk assessment

Dietary intakes of lutein and zeaxanthin were estimated for solely formula fed infants aged 3 months and for 9 month old Australian infants who consume both solid foods and follow-on formula (see Table 4).

Table 4: Estimated dietary intake of lutein and zeaxanthin for infants aged 3 months and 9 months

Age (months)	**50th percentile body weight (kg)**	**Estimated energy requirement (KJ/kg bw/day)**	**Estimated intake of infant formula# (ml/day)**	**Estimated dietary intake of lutein and zeaxanthin (µg/day)**			
				Mean		**95th percentile**	
				Baseline	***Scenario***	***Baseline***	***Scenario***
3	6.4	343	800	0	224	0	560
9*	8.9	335	545	273	572	683	1,430

* Takes into account the intake of lutein and zeaxanthin from follow-on formula and foods (Australian infants only)
# Energy content of cow's milk based infant formula = 274 KJ/100 g

The Applicant stated that the contribution of fortified follow-on formula to lutein intakes is significant and that older infants and children consuming 600 ml of lutein-fortified follow-on formula would increase lutein intakes by approximately 300 µg/day. The FSANZ assessment estimated formula intakes for 9 month old infants at 545 ml per day, with a similar increase in mean lutein and zeaxanthin intakes to that estimated by the Applicant.

Using U.S. data (see Table 2), the Applicant estimated mean lutein and zeaxanthin intakes for 7-11 month old children as 463 µg/day. In the FSANZ assessment, estimated mean lutein and zeaxanthin intakes were 572 µg/day for 9 month old Australian children following the fortification of follow-on formula with lutein and zeaxanthin.

The major contributors from food (≥ 5%) to lutein and zeaxanthin intakes at *Baseline* for Australian infants aged 9 months were fruit and vegetables juices (20%), carrots (7%), peas (7%), sweet corn (6%), onions (6%) and broccoli and cauliflower (5%). Under the fortification *Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were follow-on formula (52%) and fruit and vegetables juices (9%).

5.2 Risk characterisation

In order to determine if the level of intake of lutein and zeaxanthin following fortification of infant and follow on formulas will be a public health and safety concern, the estimated dietary intakes were compared to the ADI for lutein and zeaxanthin of 2 mg/kg bw/day (see Attachment 3 for details).

For both 3 month old infants and 9 month old infants, the estimated mean and 95th percentile intakes of lutein and zeaxanthin were all below the ADI (see Table 5). The FSANZ assessment estimated mean lutein and zeaxanthin intakes for 3 month old infants at 2% ADI and 3% ADI for 9 month old infants following the fortification of infant formula and follow-on formula with lutein and zeaxanthin. Estimated 95th percentile intakes were 4% and 8% ADI for 3 and 9 month old infants, respectively, following the fortification of infant formula and follow-on formula with lutein and zeaxanthin.

The Applicant estimated lutein exposure to be at 12% of the ADI for American (U.S.A.) infants aged 2-6 months and 7-11 months. The results provided by the Applicant differ from those estimated by FSANZ.

This is likely to be due to (1) the different methodologies used to conduct the assessments; (2) the different sources of food consumption data; and (3) the age groups used in the assessments.

Table 5: Estimated mean and 95th percentile intakes of lutein and zeaxanthin

a. In mg/kg bw/day

Age (months)	**50th percentile body weight (kg)**	**Estimated intakes of lutein and zeaxanthin (mg/kg bw/day)**			
		Mean		**95th percentile**	
		Baseline	*Scenario*	*Baseline*	*Scenario*
3	6.4	0	0.035	0	0.088
9*	8.9	0.031	0.064	0.077	0.161

* takes into account the intake of lutein and zeaxanthin from follow-on formula and foods (Australian infants only)

b. As a percentage of the ADI

Age (months)	50th percentile body weight (kg)	Estimated intakes of lutein and zeaxanthin (%ADI)			
		Mean		95th percentile	
		Baseline	*Scenario*	*Baseline*	*Scenario*
3	6.4	0	2	0	4
9*	8.9	2	3	4	8

* takes into account the intake of lutein and zeaxanthin from follow-on formula and foods (Australian infants only)

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Attachment 5

Food Technology Assessment

Summary

The food technology aspects of lutein used as a nutritive substance to be added to infant formula have been assessed.

Lutein is a natural carotenoid with the commercial lutein extract prepared from marigold (*Tagetes erecta* L.) flowers. A hexane extract of the marigold flowers is saponified with potassium hydroxide and purified by crystallisation to yield yellow prisms of lutein. The specification of the lutein extract is consistent with the recent specification prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004. The JECFA specifications are a primary source of specifications in Standard 1.3.4 – Identity and Purity, so a new specification is not required to be written for the Code. This specification is for the free lutein, not a lutein ester.

The commercial lutein preparation that is subsequently added to food is produced in vegetable oil with approved food additives being antioxidants and emulsifiers. Stability results provided by the Applicant for both liquid (ready-to-feed) infant formula products and powdered products (infant and follow-on formula), indicated some losses of lutein occurred during storage. Stability results indicated that most of the losses occurred early during storage. The summary of the worst losses of lutein from commercial infant formula products are indicated below.

For liquid products: Losses after 12 months (which is the end of shelf life of these products) at ambient temperature (27°C and 70% relative humidity (RH)) were determined to be up to a maximum of 41%.

For powdered products: Losses after 12 months at ambient temperature (27°C and 70% relative humidity (RH)) were determined to be up to a maximum of 55%. Stability results under accelerated ageing conditions (37°C and 75% RH) indicated the worst losses to be 58% after 6 months storage.

Manufacturers will need to be aware of losses of lutein that occur for their products with storage conditions and could apply a suitable over dosing to account for such losses (commonly referred to as overages). The Applicant has requested an overage of 250%, so to achieve a level of 100 µg/L in infant formula, they have asked for a maximum level of 250 µg/L. For their commercial operations they are aiming for an overage of 180% to account for losses during storage to the end of the products shelf life. The extra allowance up to an overage of 250% is to ensure their product would always meet the requirements of the Code. The request is comparable to that commonly used for dosing sensitive vitamins to food.

Lutein is not being considered for an extension of use as a food additive in infant formula, where it can act as a food colour, since its proposed use is not for this purpose.

1. Introduction

This Food Technology Report aims to address the chemistry of lutein, how it is manufactured, and more specifically the stability of lutein in the relevant food matrices; being both liquid (ready-to-feed) and powdered infant formula products.

The Application is seeking permission for lutein as a nutritive substance not as a food additive where it has the technological function of a colour.

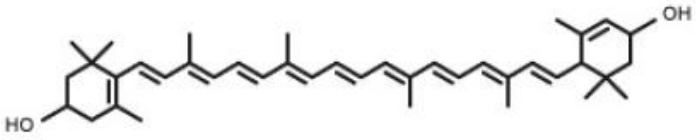
2. Background

Lutein is a xanthophyll carotenoid (of the oxygenated carotenoid family) found in many yellow and dark green vegetables including maize, spinach and green peas. More than 600 carotenoids have been isolated and characterised from natural sources and are characterised as brightly coloured plant pigments.

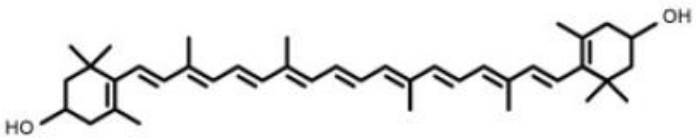
Carotenoids are synthesised by higher plants and certain fungi, algae and bacteria, but they are not synthesised by animals, including humans, though they may be biochemically modified by them. This means that humans cannot produce lutein and its presence comes from exogenous food sources. Lutein has no pro-vitamin A activity.

3. Chemistry of lutein

Food carotenoids have the general C_{40} tetraterpenoid structure where eight C_5 isoprenoid units are joined head to tail, except at the centre, where a tail-to-tail linkage reverses the order and results in a symmetrical molecule. The chemical structures of lutein and its isomer zeaxanthin are shown in Figure 1.



Lutein



Zeaxanthin

Figure 1: Chemical structures of lutein and zeaxanthin

Lutein has the molecular formula of $C_{40}H_{65}O_2$, with the molecular weight of 578.87 g/mol. Under IUPAC nomenclature rules, lutein has the chemical name 4-[18-(4-hydroxy-2,6,6-trimethyl-1-cyclohex-2-enyl)-3,7,12,16-tetramethyl-octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-3-en-1-ol. It has the Chemical Abstracts System (CAS) number 127-40-2. Lutein also has the food additive number INS No. 161b when it is used as a colouring.

Lutein is listed in Schedule 3 of Standard 1.3.1 – Food Additives as a colour that can be added to many processed foods to levels determined by Good Manufacturing Practice where permitted by Schedule 1. However, lutein is not permitted as a colour for food category 13.1 – Infant formula products or 13.2 – Foods for infants in Schedule 1 of Standard 1.3.1.

Alternative names for lutein are xanthophyll, vegetable lutein, vegetable luteol and 3R,3'R,6'R -β,ε-carotene-3,3'-diol; all-*trans*-lutein;4',5'-didehydro-5',6'-dihydro-beta,beta-carotene-3,3'-diol (Joint FAO/WHO Expert Committee on Food Additives (JECFA) Compendium of Food Additive Specifications, 2004).

Lutein consists of yellow prisms with metallic lustre when crystallised from ether and methanol. Lutein is insoluble in water but soluble in hexane, fats and other fat solvents.

Lutein is very similar in structure to another carotenoid, zeaxanthin, which can also be extracted from marigold flowers (see the above structures). When lutein is extracted from marigold flowers from the production process outlined in the next section a small concentration of the isomer, zeaxanthin is also extracted, which can not be separated. That is the final lutein extract also contains a small concentration of zeaxanthin.

The JECFA specifications of the lutein extract of this Application indicates that lutein makes up at least 70% of the extract, while the zeaxanthin component is not more than 9%. The Application contains analytical results of three batches of the extract which gave the average ratio of lutein:zeaxanthin of approximately 77:7. The other minor components include other carotenoids and waxes.

4. Manufacture of lutein extract

The lutein extract of the Application is prepared from marigold (*Tagetes erecta* L.) flowers. A lutein oleoresin is prepared from a hexane extract of marigold flowers, which is then saponified with potassium hydroxide in either methanol or propylene glycol (also called 1,2-propanediol in the Application). The lutein extract is crystallised to partially purify it, though it contains other carotenoids (mainly zeaxanthin) and waxes.

A more detailed manufacturing process for producing the lutein extract from marigold flowers is contained in the Application. The lutein manufacturing process is also covered by a number of patents, including the United States Patent 5,648,564 and European Union Patent EP 904,258. A schematic of the manufacturing process has been taken from the Application and is shown in Figure 2.

Marigold flowers are dried, ground and pelleted and then extracted with hexane. Removing the hexane leaves a marigold oleoresin. The oleoresin is mixed with 1,2-propanediol and heated to 55°C. Saponification occurs after addition of aqueous potassium hydroxide (called caustic potash in Fig 2) and heating to 70°C. This mixture is gently agitated at 70°C for 10 hours. Lutein crystals are obtained after dilution with warm deionised water and are subsequently removed using centrifugation. The lutein crystals are washed with more warm deionised water to remove further potassium hydroxide and 1,2-propanediol and then they are freeze dried. Lutein is insoluble in water.

To produce the commercial lutein preparation in vegetable oil (including but not limited to high oleic safflower and soybean oil) the crystallised lutein is agitated in the oil for 30 minutes to form the uniform lutein suspension. Other components of the lutein preparation such as approved additives (antioxidants and emulsifiers), fat soluble vitamins, long chain polyunsaturated fatty acids, proteins, minerals and carbohydrates are also added into the mixer to produce the lutein in oil product. The compounded material is further processed to produce either powdered or liquid products.

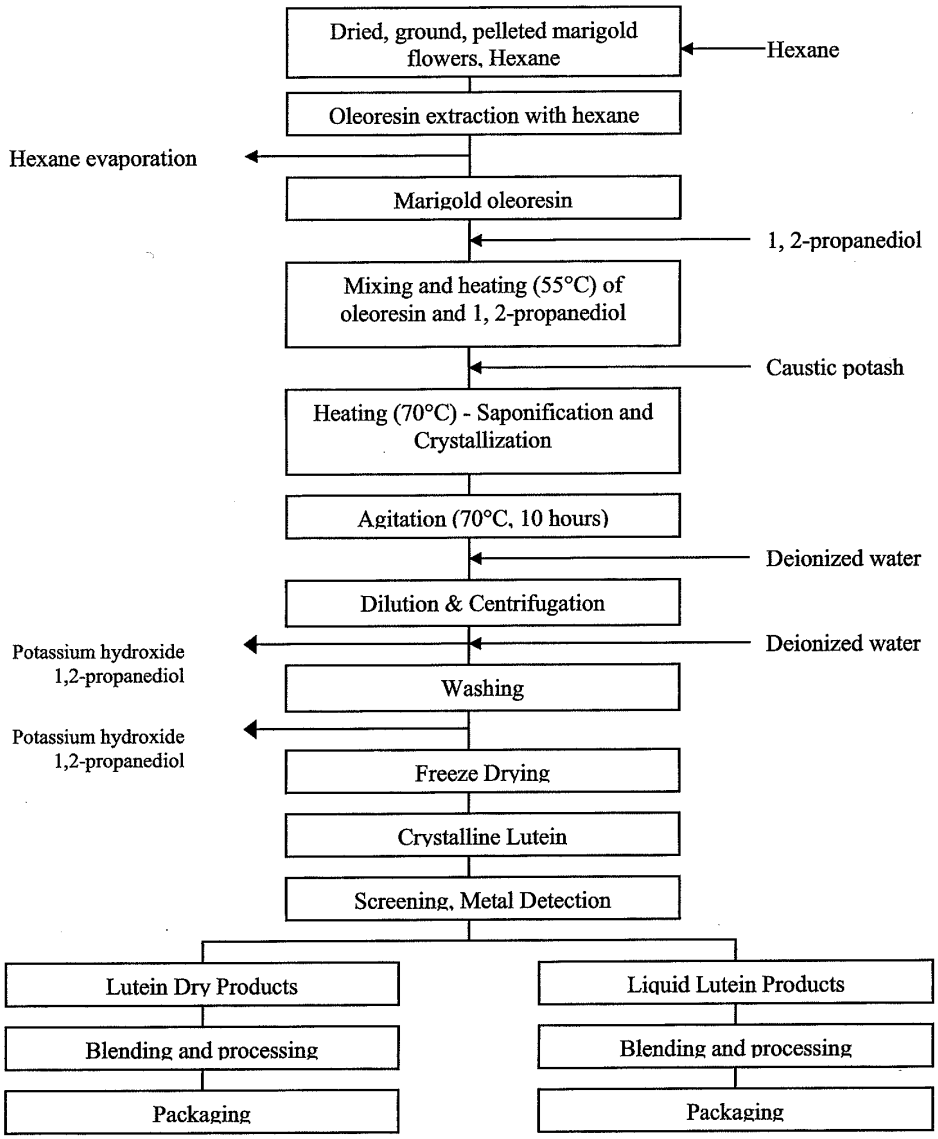


Figure 2: Schematic of the lutein preparation manufacturing process

5. Specification of lutein extract

The specification of lutein extracted from marigold (*Tagetes erecta* L.) flowers of the Application is consistent with the recent specification prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004 (JECFA Compendium of Food Additive Specifications, 2004) titled Lutein from *Tagetes Erecta*. The JECFA specifications are a primary source of specifications, being reference (a) in clause 2 of Standard 1.3.4.

This means the specification of the lutein extract is currently consistent with the Code, and a new specification is not required to be written. It is important to note that this specification is for the free lutein, not a lutein ester.

The Applicant then takes the lutein extract and makes up a 20% commercial blend of lutein in vegetable oil which it adds to infant and follow-on formula as discussed in the previous section. The specifications for the Applicant's commercial preparation of 20% lutein in a vegetable oil has been taken from the Application and formulated into Table 1 below.

It is important to note this is a commercial specification written by the Applicant for their blend of 20% lutein extract from marigold flowers in vegetable oil, while the lutein extract itself has its own specific JECFA specification as referenced above.

Table 1: Quality Specifications for Lutein 20% in vegetable oil

Lutein	Min. 20%
Zeaxanthin	Min. 0.8%
Moisture	Max 1%
Appearance	Oily suspension, free of foreign matter
Odour	Bland
Colour	Orange-red
Ash	Max. 1%
Aerobic plate count	Max. 100 cfu/g
E. coli enrichment	Negative/10 g
Listeria monocytogenes	Negative/25 g
Salmonella	Negative/10 g
Staph enrichment	Negative/10 g
Coliform enrichment	Negative/25 g
Yeast count	Max. 100 cfu/g
Mould count	Max. 100 cfu/g

6. Stability of lutein in food

The Application contains some information about the stability of lutein in the safflower oil preparation, which is the commercial lutein preparation sold. The Application also contains information about the stability of their lutein preparation (20% lutein in safflower oil), in solid (powders) and liquid (ready-to-feed) infant formula products.

The Applicant performed a large number of stability trials on lutein concentration in pilot plant, factory trials and commercially prepared products for both liquid and powdered products. The Applicant performed stability trials at ambient conditions (27°C and 70% relative humidity (RH)) at 3 month intervals till the end of shelf life at 12 months (3,6,9 and 12 months) as well as some results at 18 months. They also performed accelerated ageing trials (37°C and 75% RH) at 3 and 6 months. A point to note, which the Applicant explained, is that the ingredients of the lutein preparation also contains some lutein, meaning that the vegetable oil used to make up the preparation contains approximately 10-20 ug/L of lutein, which the Applicant factored in when dosing lutein. The results indicated that the largest losses occurred early during storage and then the losses stabilised (explained by the initial availability of oxygen in the package which diminishes as it oxidises the lutein). The important results are summarised below.

6.1 Powders

After 12 months at 27°C and 70% RH, the largest losses for powdered product was 55%. Separately, the highest losses for storage at more extreme conditions (37°C and 75% RH) was 58% after 6 months storage.

6.2 Liquids

For liquid (ready-to-feed) products the largest losses after 12 months at 27°C and 70% RH was 41%. Surprisingly the losses were only found to be 5% after 6 months storage at 37°C and 75% RH.

7. Overages

The stability results and losses found indicated to the Applicant that they needed to overdose with extra lutein to account for losses during storage. The term commonly used for overdosing to account for losses is 'overage'. A useful explanation of overage is provided in the literature (Food and Nutrition Bulletin, 1998 (b)):

Overage is the use of kinetic data on nutrient stability to calculate the amount of added nutrient so that the anticipated level of the nutrient at the end of the product's shelf life is in accordance with the level indicated on the label

Overage = (formulated level-declared label level)/declared label level x100.

Or sometimes overage can be referred to as:

Overage = (declared label level + (formulated level-declared label level))/declared label level x100

So for a formulated level of 150 µg/L compared to a label level of 100 µg/L, the overage could be referred to as an overage of 50% or 150%. The Applicant has provided results using the second form of referring to overages.

Manufacturers will need to be aware of losses of lutein that occur for their products with storage conditions and could apply a suitable overdosing to account for such losses.

8. Justification for Applicant's overage

The Applicant has sought regulatory permission for a 250% overage for lutein in infant formula in the Code. That is, for their liquid product (ready-to-feed) labelled to 100 µg/L they are requesting the maximum permission of 250 µg/L. They have justified this figure from their stability results which they conclude they need and use a 180% overage to account for losses of lutein with storage to the end of shelf life of the product. Over and above that the Applicant has wanted to ensure that there is sufficient leeway in the regulations so they can always market their product, that is no product will have a lutein concentration greater than allowed in the Code. FSANZ sought further understanding from the Applicant to explain their request for their overage level.

The Applicant claimed that for many vitamin additions the overage is in the range of 150-300% depending on the sensitivity and stability of the vitamin and the food matrix. From the literature it appears that overages can be as high as 200% for sensitive vitamins, sometimes just related to losses during processing.

The Applicant also provided summary results of the initial levels of lutein in their commercial manufactured product. The maximum level of lutein was about 180% overage of the label amount. Also the average plus three times the standard deviation (to give an upper level at 99% confidence level) of 37 samples was about 190% of the label claim.

It is not in the commercial interests of the Applicant to overdose to higher levels than is required to ensure their product is comparable to their label claim. That means the Applicant will not want to grossly over dose lutein into their product, over and above what is required to take account of losses with shelf life since lutein will have an economic cost and gross overdosing would be an added cost to their business.

9. Conclusion

This review of the food technology aspects of addition of lutein to infant formula indicates that there are no technological concerns. The Application states that the lutein preparation uses approved food additives being antioxidants and emulsifiers. The specification of lutein extracted from *Tagetes erecta L.* meets the JECFA specification. This specification is referenced in the Code so no new specification needs to be written if the Application is approved.

Stability results from trials performed by the Applicant on pilot plant, production trials and commercial liquid and powdered products indicated some losses of lutein. The largest losses being 55% after storage of 12 months at ambient temperature (27°C and 70% RH) for the powdered product. Manufacturers can take account of such losses by overdosing with lutein, provided levels of product for commercial sale meet the regulatory requirements for lutein in infant formula in the Code.

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Attachment 6

Summary of Submissions to the Draft Assessment Report

FSANZ received 14 submissions in response to the Draft Assessment Report on Application A594 – Addition of Lutein as a Nutritive Substance to Infant & Follow-on Formula, during the 6-week public consultation period of 3 October to 14 November 2007. A summary of submitter comments is provided in the table below.

Two regulatory options were presented in the Draft Assessment Report:

Option 1 – Reject the Application, thus maintaining the *status quo*; or

Option 2 – Amend Standard 2.9.1 to permit the voluntary addition of lutein as a nutritive substance at a maximum concentration of 9 µg/100 kJ (250 µg/L) in infant formula and 18 µg/100 kJ (500 µg/L) in follow-on formula with a minimum declaration of 2 µg/100 kJ required for labelling purposes.

No.	Submitter	Submission Comments
Industry		
1.	**Australian Food and Grocery Council** *Kim Leighton*	**Supports Option 2** ***Public health and safety*** Supports the FSANZ safety assessment that the Application does not pose any public health or safety concern to formula-fed infants. ***Role of lutein*** Supports that the principle role of lutein in the eye is as an antioxidant. ***Nutritive substance*** Supports that lutein meets the definition of a nutritive substance. ***International regulations / practice*** Notes that various countries permit the use of lutein and considers that Option 2 will increase consistency with international practice and trade with these countries. ***Labelling / claims*** Recognises that health claims are not permitted on infant formula products. However, considers FSANZ should provide guidance for manufacturers to differentiate advertising from advice for health professionals, as health professionals need to provide advice to carers of formula-fed infants.

No.	Submitter	Submission Comments
2.	**Chr Hansen Pty Ltd** *Ron Cracknell*	**Supports Option 2** Supports the Application and the setting of maximum amounts. ***Form of lutein*** Notes the proposed amendment appears to be restricted to free lutein, excluding lutein esters. Notes lutein is present as esters in the petals of marigold (Tagetes erecta L), similarly to other natural sources of lutein in the diet. States lutein esters are readily converted to free lutein in the body and therefore are of equivalent nutritive value (when expressed as active lutein equivalent). Recommends that Option 2 permit the voluntary addition of free lutein and/or lutein esters, and suggests this could be achieved through use of an editorial note.
3.	**International Formula Council (IFC)** *Mardi K Mountford*	**Supports Option 2** ***International regulations / practice*** Option 2 is consistent with current thinking in the US infant formula industry which supports the addition of lutein in infant formula. Includes a letter of no objection from United States Food and Drug Administration (US FDA) that grants an extension of generally recognised as safe (GRAS) status for suspended lutein to include infant formula (0-12 months). Includes comments that the IFC submitted to the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) requesting that lutein (and other substances) be added to the Advisory List of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Infants and Young Children.
4.	**The Food Technology Association of Australia** *David Gill*	**Supports Option 1** ***Quality of evidence*** Considers there was insufficient evidence presented to support the claims made in the Application.
5.	**Wyeth Australia Pty Ltd and Wyeth New Zealand Ltd** *Yvonne Bowyer*	**Supports Option 2** ***International regulations / practice*** Notes the recent US FDA decision to grant GRAS status for use of lutein as an ingredient in term infant formula at a maximum level of 250 µg/L. Notes that for the purpose of obtaining GRAS status, infant formula is defined as a breast-milk substitute suitable from birth to six months of age.

No.	Submitter	Submission Comments
		Notes that GRAS notification GRN 000141 granted GRAS status for use of lutein in infant and toddler foods (other than infant formula) when added at 1 mg per eating occasion. Requested the US delegation to the CCNFSDU propose that lutein be added to the Advisory List of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Infants and Young Children. Notes the European Food Safety Authority (EFSA) scientific review is ongoing with expected date of completion in late February 2008. Advises that infant formula, follow-on formula and toddler milks with lutein are now also marketed in the Philippines, Indonesia and China. ***Maximum / minimum amounts and ratio*** Notes that Wyeth provided rationale for adding lutein to infant formula at a maximum of 250 µg/L in their original Application. Maternal diets appear to predict infant serum concentrations. A high quality maternal diet high in green vegetables, and therefore lutein, is expected to impart the maximum potential lutein benefit to the breastfed infant. Comments on two Wyeth studies (previously provided) that demonstrate the maximum proposed level of lutein added to infant formula results in infant plasma levels of lutein comparable to those of breastfed infants whose mothers regularly consume lutein-rich vegetables.
Public Health		
6.	**Dietitians Association of Australia** *Kate Poyner*	**Supports Option 1** Overall considers that insufficient evidence has been provided to support the proposed level of lutein to be added to infant and follow-on formula. ***Public health & safety*** Supports the Codex principles for adding additional ingredients to infant formula. Considers limited evidence has been provided to: • support the role of lutein intake and pigmentation of the eye in babies; • support a maximum level for follow-on formula that is twice that for infant formula; and • set a maximum amount that achieves serum lutein levels comparable with those of breastfed infants whose mothers regularly consume lutein-rich vegetables. Raises equity concerns about voluntary addition of substances to infant formula products – questions if a substance is added to formula to make it nutritionally similar to breast-milk for optimal infant health then should this substance be added to all infant formula?

No.	Submitter	Submission Comments
		Quality of evidence Raises the following concerns about the evidence provided: • lack of data on lutein concentration and variability in breast-milk for Australian and New Zealand women; • questions the effect of maternal serum lutein variability on infant serum levels of lutein; • lack of information on the lutein content of infant and follow-on formulas available in Australia; • indicative data only on bioavailability of lutein in infant formula; • equivocal evidence about the interaction of lutein and zeaxanthin with other carotenoids; • need to consider the ratio of lutein to zeaxanthin in the marigold extracts compared to breast milk and whether this ratio changes during lactation; • limited evidence on the effects of lutein on visual development and function of infants, and requires further studies; and • insufficient evidence to establish an optimal intake or a minimum effective level for infants. Notes a recent systematic review that concluded there was insufficient evidence to support the role of dietary antioxidants, including lutein, for the primary prevention of early age related macular degeneration (Chong et al, 2007). ***Maximum / minimum amounts and ratio*** Considers it is unclear why the proposed level of lutein in follow-on formula is twice that of the level in infant formula, as older babies and toddlers are eating other foods and are not reliant on human-milk or formula to meet their full nutritional requirements. Assumes the higher level in follow-on formula is based on increased needs of older infants. However, dietary modelling shows that follow-on formula would become a dominant source of lutein in the mixed diet of older infants.
Government		
7.	**Dairy Food Safety Victoria** *Doug Eddy*	**Supports Option 1** ***Public health and safety*** Considers the Draft Assessment Report fails to provide evidence of benefit to the target group, and prefers a cautious approach for this sensitive population group.

No.	Submitter	Submission Comments
8.	**Department of Health, South Australia** *Elena Anear*	**Supports Option 1** ***Public health and safety*** Considers there does not appear to be a clear functional purpose for lutein in infant formula or benefit to formula-fed infants. Questions the reasons for adding this substance to a food intended for a vulnerable population group. Supports the concept that infant formula should be closely aligned to the composition of breast-milk where possible, however evidence for lutein does not convincingly support the application at this stage. ***Quality of evidence*** Considers there is a lack of data on: • the variability in levels of lutein in breast-milk in the Australian and New Zealand population; • baseline blood lutein levels in infants; • the relative bioavailability of lutein/zeaxanthin in infant formula; • the role of lutein in eye health in infants; • the efficacy of the proposed levels of lutein; and • the role of lutein in eye function as opposed to zeaxanthin as both are found in eye macular pigment. ***Maximum / minimum amounts and ratio*** Notes the proposed maximum level of lutein/zeaxanthin is higher than found in breast milk and is comparable to colostrum which declines in the first few weeks. Considers it is unclear why a higher level of lutein is proposed for follow-on formula, as older infants will be consuming a mixed diet that contains naturally occurring carotenoids. Considers there is no justification for the proposed ratio of lutein:zeaxanthin of 9:1, which is higher than in breast milk (3:1). ***Labelling / claims*** Believes there is some confusion over the future use of content claims on infant formula. Considers Standard 2.9.1 is ambiguous in its wording around the use of nutrient claims and therefore creates a possible loophole to enable claims to be made for these products. ***Additional information required*** Considers the following information is required for the further consideration of this Application: • the impact of the ratio of lutein to zeaxanthin;

No.	Submitter	Submission Comments
		• the bioavailability of the lutein and zeaxanthin in formula compared to breast-milk; • Australian and New Zealand data on the variation of lutein levels in breast milk (from colostrum to mature milk); • Australian and New Zealand data of blood lutein levels for breastfed infants at the different ages; and • data on the dietary intake of lutein of older infants.
9.	**Department of Health and Human Services, Tasmania** *Jennifer Savenake*	**Supports Option 1** Overall does not believe there is sufficient evidence to support the addition of lutein to infant formula and follow-on formula. ***Public health & safety*** Considers a high level of substantiation and scrutiny is appropriate when developing standards for infant formula, as infant formula may be the sole source of nutrition for formula-fed infants up to six months of age. Supports the Codex principles for adding additional ingredients to infant formula. The addition of lutein as a nutritive substance (as per the definition) implies that the addition of the substance will be able to achieve the nutritional purpose. Considers there is insufficient evidence for the nutritional use of the inclusion of lutein in infant formula. Questions the purpose of adding lutein to infant formula, as the amounts requested are higher than for breast milk, there is limited evidence to support that it will have a similar physiological function as breast-milk, and the evidence for eye health is not convincing. ***Quality of evidence*** Raises the following concerns about the evidence provided: • lack of data on lutein concentration and variability in breast-milk for Australian and New Zealand women; • lack of information on the lutein content of infant and follow-on formulas available in Australia; • lack of data on the serum concentrations of Australian and New Zealand breastfed infants to compare with similar international data; • limited data on the bioavailability of lutein in infant formula compared with breast-milk; • no evidence about the impact on older infants of the higher concentration of lutein proposed in follow-on formula; • limited evidence on the effects of lutein on visual development and function of infants, and requires further studies;

No.	Submitter	Submission Comments
		• there may be an interaction among carotenoids, whereby the consumption of one affects the absorption of another; and • the data on safety is predominantly unpublished data provided by the Applicant. Notes a recent systematic review that concluded there was insufficient evidence to support the role of dietary antioxidants, including lutein, for the primary prevention of early age related macular degeneration (Chong et al, 2007). ***Maximum / minimum amounts and ratio*** Considers it is unclear why the proposed level of lutein in follow-on formula is twice that of the level in infant formula, as these infants will be consuming a mixed diet containing naturally occurring carotenoids. Dietary modelling shows that follow-on formula would become a dominant source of lutein in the mixed diet of older infants. Questions if the proposed minimum level is based on avoidance of misleading and deceptive conduct; that the formula would contain some lutein if listed as an ingredient. Considers the minimum level, if permitted, should reflect the purpose. Notes that the proposed ratio of lutein to zeaxanthin (9:1) is different to that of breast-milk (3:1). ***Additional information required*** Considers the following information is required for the further consideration of this Application: • the impact of the ratio of lutein to zeaxanthin; • the bioavailability of the lutein and zeaxanthin in formula compared to breast-milk; • Australian and New Zealand data on the variation of lutein levels in breast milk (from colostrum to mature milk); • Australian and New Zealand data of blood lutein levels for breastfed infants at the different ages; and • data on the dietary intake of lutein of older infants.
10.	**Department of Health, Western Australia** *Stan Goodchild*	**Preferred Option Not Specified** Overall has no significant issues about the addition of lutein to infant formula. However to determine a definitive position requests further information on: • the allergenicity of lutein from marigold flowers; • the variability of levels of lutein in Australian women over the duration of breastfeeding; • whether the level of lutein added to infant formula mimics the level normally found in breast-milk and does not exceed these levels; and

No.	Submitter	Submission Comments
		• how the level of lutein in follow-on formula will ensure that Australian Dietary Intake levels for lutein are not exceeded for the specific age group, taking into account the amount of lutein obtained from other foods. Notes the potential eye health benefits of lutein for infants and young children, and that lutein is found in breast-milk and naturally in food. Notes the varying international approval for lutein, and therefore considers a conservative approach is required.
11.	**Queensland Government** *Gary Bielby*	**Supports Option 1** Overall, considers there is insufficient evidence to support the application and justify the addition of lutein as a nutritive substance. ***Public health & safety*** Supports in-principle improvements to infant formula to provide benefits for formula-fed infants equivalent to breast milk. However, takes a conservative approach for this vulnerable group given that infant formula may be the sole source of nutrition. Notes that the Acceptable Daily Intakes (ADI) set be JECFA do not apply to infants under 12 weeks. ***Quality of evidence*** Believes a robust level of substantiation is required for vulnerable population groups, including for voluntary fortification permissions. Concerns about the use of unpublished studies commissioned and undertaken by the Applicant, and the overall lack of published, independent and peer reviewed research associated with this Application. Considers more information is required to establish that the addition of lutein as requested would provide a formula suitable as a substitute for breast-milk, including data on: • the content of lutein in breast-milk; • breast-milk concentration and variability of lutein in different population groups of Australian and New Zealand women; • the relative bioavailability of lutein from human milk compared to formula; • lutein content of formulas available in Australia, its bioavailability and whether higher levels comparable to those in breast-milk could be achieved through product reformulation; and • any physiological or nutritional consequences of different ratios (i.e. 9:1 vs. 3:1) and whether it influences bioavailability. Considers there is insufficient data to support a nutritional purpose for lutein, for example there is a lack of data: • on serum concentrations of lutein in breastfed infants;

No.	Submitter	Submission Comments
		• on the relationship between lutein intake and serum levels of lutein in infants; • to establish an optimal intake or a minimum effective level for any population group (in the absence of a RDI for lutein); • to determine the extent of interactions among carotenoids; • to understand why lutein is much higher in colostrum, why levels decline and what effect these characteristics have on the function of lutein; • to understand why the bioavailability of lutein from lutein extract is so poor compared to lutein from breast-milk (raising the issue of adding extracts in isolation without considering the complex interactions between nutrients); • on the effects of lutein on visual development and function of infants; • on the roles lutein and zeaxanthin play separately or together and the importance of the ratio between them; and • on the relationship between plasma levels of lutein and macular levels of lutein. ***Policy*** Believes there is an important need to develop policy around infant formula products, infant food and supplementary food for young children. Notes that no specific policy to guide standards development in these areas is available. Considers the revised Codex Standard for Infant Formula would be a suitable basis for policy guidelines. Highlights the Codex principle that 'the suitability for the particular nutritional uses of infants and the safety of these substances shall be scientifically demonstrated'. Notes that the intent of Standard 2.9.1 is for infant formula to match the composition of breast-milk as closely as possible. ***Dietary Modelling*** Notes limitations of the dietary modelling database used (theoretical diets) due to no national survey data for children aged less than 2 years. Considers FSANZ, Commonwealth and the States and Territories need to work together in order to determine how best to monitor the dietary intake of this population group. ***Labelling / claims*** Concerns that the current wording of Standard 2.9.1 does not prohibit the Applicant from making label claims relating to lutein content. Notes that Wyeth currently make a number of prohibited health claims on its products and websites.

No.	Submitter	Submission Comments
		Maximum / minimum amounts and ratio Questions the justification for greater amounts of lutein in infant formula compared with breast-milk, noting that the data used in support is from two studies provided by the Applicant, but there is no other data available to support or disprove this. Considers the level proposed for infant formula (250 µg/L) is more consistent with that found in colostrum than mature breast-milk, and thus would expose formula-fed infants to consistently high levels of lutein, which is different to breastfed infants. Considers there is no justification for adding lutein to follow-on formula at 500 µg/L, and that this appears to exceed the recommendations of the US FDA. Also, notes that infants begin to consume lutein containing foods from around six months. Notes the ratio of lutein to zeaxanthin from marigold extracts (9:1) is different to that of breast-milk (approximately 3:1 or 5:1). Considers no justification has been provided for this higher ratio, except that it is a patented product approved for use in other foods. Considers the physiological or nutritional significance of the ratio of lutein to zeaxanthin is not known, but appears to remain stable during lactation. ***Nutritive substance*** Notes that the definition of 'nutritive substance' includes 'to achieve a nutritional purpose' Notes supporting eye health could be a physiological purpose rather than a nutritional purpose. Considers there is insufficient evidence to support a nutritional purpose or physiological purpose for lutein.
12.	**New South Wales Food Authority** **(in consultation with NSW Health)** *Craig Sahlin*	**Supports Option 1** Does not support the progression of this Application due to insufficient evidence demonstrating the public health and safety of the addition of lutein to infant formula. ***Policy*** Prefers a conservative approach in the absence of policy guidelines. Notes the guidance provided by the revised Codex Standard for Infant Formula. ***Public health & safety*** Believes that the proposed health benefits of adding lutein to infant formula must be scientifically proven. However, considers a clear benefit to the target population has not been demonstrated.

No.	Submitter	Submission Comments
		Believes that efficacy of substances like lutein need to be demonstrated. However, considers evidence that the proposed benefits will be achieved through the addition of lutein from marigold flowers at the proposed level has not been provided. Considers the need to demonstrate efficacy may be increased as infants are a vulnerable group of the population and in some cases infant formula is the sole source of nutrition. ***Quality of evidence*** Considers there is a general lack of evidence of the: • breast milk concentration of lutein in Australian and New Zealand women; • serum concentration of lutein in Australian and New Zealand breastfed infants; • bioavailability of lutein in infant formula compared with breast milk; • stability of lutein in powered infant formula over the shelf-life of the product (up to 18 months); • complex interactions between lutein and zeaxanthin and the absorption of other carotenoids; and • health benefits of lutein from marigold flowers compared with lutein in breast milk. Notes the lack of published, independent and peer reviewed research relating to lutein in infant formula. Considers that regulators should not reply on unpublished studies commissioned and undertaken by the Applicant. ***Labelling / claims*** Concerns that the current wording of Standard 2.9.1 does not prohibit the Applicant from making label claims relating to lutein content. Concerns that there is a conflict between labelling permissions granted under clause 7 and labelling permissions prohibited by clause 20 of Standard 2.9.1. Requests that the Final Assessment Report clarifies the above.
13.	**New Zealand Food Safety Authority** *Carole Inkster*	**Supports Option 1** ***Public health & safety*** Considers the data is inadequate to support the addition of lutein to infant formula for the purpose of eye health, and is not a sufficient basis to permit the addition of a new substance to a food that may be consumed as the sole source or principal source of nutrition for infants. Considers that if lutein does have an important role in eye health then it should be considered for mandatory addition to infant formula.

No.	Submitter	Submission Comments
		Considers there is less reason to justify adding lutein to follow-on formula as levels in breast-milk naturally decline and commencement of follow-on formula would coincide with the introduction of foods containing lutein. ***Quality of evidence*** Concerns about the strength of science presented in the Draft Assessment Report, and do not think it is sufficient to support the addition of lutein. Notes that most of the data presented has been conducted by the Applicant and has not been reviewed or published. Considers there is insufficient baseline data - population representative data that characterise the breast milk concentration of lutein in Australian and New Zealand women and data on serum lutein for Australian or New Zealand breastfed infants or formula-fed infants. Notes that no reproduction toxicology studies were included. ***Maximum / minimum amounts and ratio*** Considers there is no sound justification for the levels proposed, which are significantly higher than in breast milk. Considers studies do not support the need for higher levels based on reduced bioavailability. Concerns that there was no consideration of a minimum effective level when setting a range for the addition of lutein. Questions if the instability of lutein and the associated losses on storage will result in manufacturers 'overdosing' to account for these losses and the impact this would have on actual lutein levels. Would like information on the natural level of lutein in cows milk based infant formula products and how this compares to the levels found in breast milk. ***Labelling / claims*** Strongly supports the prohibition of claims on infant formula products so that no marketing advantages can be sought by manufacturers. Seeks comment as to whether clause 20 of Standard 2.9.1 could be interpreted as a permission for allowing a statement such as 'contains lutein' on the label of an infant formula product. Requests that the Final Assessment Report clearly states that the addition of lutein (if permitted) cannot be claimed anywhere on the label, and that the only reference to the addition of lutein is in the ingredient list and the nutrition information panel. ***Nutritive substance*** Considers the Final Assessment Report should explain how lutein, in relation to its proposed function, fits the current definition of a nutritive substance, particularly its role in achieving a nutritional purpose.

No.	Submitter	Submission Comments
		Requests guidance on what is intended as a 'nutritional purpose' and whether it should differentiate substances added for a nutrition purpose from those which provide a perceived health benefit or support physiological function. Recommends a review of Standard 2.9.1 with a focus on compositional requirements.
14.	**Victorian Government** *Victor Di Paola*	**Supports Option 1** Supports the principle of improving infant formula and follow-on formula to better mimic human breast-milk, however, does not support Option 2. ***Quality of evidence*** Concerns regarding the proposed levels, including that: • the Application has not sufficiently demonstrated that the proposed levels are representative of breast-milk and blood levels of breastfed infants; • the content of lutein in breast-milk varies widely depending on maternal diet and the age of the breastfed infant – highest in colostrum and drops five fold over the following two-three weeks. Study by Jewel et al (2004) found nearly zero levels of lutein in breast-milk by day 12-20 of lactation; • no population representative data is available that characterises the breast-milk concentration of lutein in Australian and New Zealand women. Some data from study by Canfield (2003) that shows levels well below those proposed to be added to formula; • no data is available on blood levels of lutein in breastfed infants for Australia and New Zealand; and • there is some evidence that the bioavailability of lutein is lower from infant formula, however no studies have directly tested the relative bioavailability of lutein from breast-milk and formula. Concerns that the majority of safety data presented is from unpublished data from the Applicant. Also, the data only looks at the effects on growth, not eye health. Notes there is an ADI set for lutein and FDA has granted GRAS status in the USA. Requests assurance that the same lutein compound is being assessed in A594. Notes that data indicates the potential for nutrient interactions between carotenoids, and therefore believes that the levels and form of the nutrient should resemble that found naturally as much as possible. ***Public health & safety*** Notes the evidence for the effect of lutein on eye health is minimal, and that there are no human studies. Considers that, as both lutein and zeaxanthin are found in eye macular pigment, there is no evidence that lutein is the nutrient which potentially improves eye function and not zeaxanthin, or the ratio of the two.

No.	Submitter	Submission Comments
		Considers that if improving human infant eye health is the reason for adding lutein, then the Applicant must provide more convincing evidence for this, and be able to demonstrate the efficacy of adding lutein in the amounts and forms proposed. ***Maximum / minimum amounts and ratio*** Considers that, even allowing for reduced bioavailability, the lutein level of 250 µg/L for infant formula appears to be based on the very upper levels of lutein found in breast-milk and is more consistent with colostrum rather than mature breast-milk. Considers it is not scientifically justified to provide lutein levels for six months for formula that a breastfed infant would normally receive for only 2-3 weeks. Considers there is no justification for the level of 500 µg/L in follow-on formula – exceeds the US FDA recommendation, no data to suggest that lutein requirements double after six months of age, breast-milk content declines, and at this age infants obtain additional lutein from food. Considers there is insufficient justification for the proposed minimum level of 2 ug/100 KJ. Considers that as an objective of the Application is to possibly exert a nutritive effect, it would be appropriate to align the minimum with the lower end of the range of blood levels observed for breastfed infants. Notes that the proposed ratio of lutein:zeaxanthin is different to that found in breast-milk, and that no justification was provided for this discrepancy. Considers it unclear whether the established ADI applies to all ratios of lutein:zeaxanthin. ***Labelling / claims*** Concerns about the potential marketing of products containing added lutein. Refers to the marketing of infant formula with lutein in Indonesia, where the product package and accompanying information states that lutein helps prevent eye damage caused by blue light and oxidation. Considers these claims to be unfounded and therefore misleading. Considers the ambiguous wording of Standard 2.9.1 enables a variety of nutrient claims to be made, and notes that such claims are made on currently available products. Considers that while the proposed Nutrient and Health Claims Standard indicates infant products will be ineligible for claims, it also indicates that the existing standard be retained and hence the ineligibility for claims will be unable to be enforced. ***Recommendation*** The addition of lutein should in no way be linked to eye health, in light of the lack of evidence, and this in turn removes the requirement to show efficacy for this purpose. The Application should therefore only relate to demonstrating equivalence with breast milk.

Attachment 7

Response to Issues raised by Submitters at Draft Assessment

This attachment provides responses to issues raised by submitters at Draft Assessment. A full summary of submitter comments to the Draft Assessment Report is at Attachment 6.

Some submitters commented that health benefit/efficacy of lutein for formula-fed infants should be demonstrated and that there is currently insufficient evidence to do so. As discussed in section 6 of the main report, the regulatory approach for assessing this Application does not require a benefit of the substance in the target population to be demonstrated. In light of this approach, submitter comments relating to health benefit/efficacy are not addressed below.

Submitter issue	**FSANZ's response**
Nutritional equivalence with breast milk	
Proposed concentration of lutein is greater than found in breast milk	Some submitters expressed concern that the amount of lutein proposed for addition is greater than found in breast milk, and is comparable to colostrum which declines in the first few weeks. The maximum concentration of lutein sought by the Applicant is greater than the amounts contained in human milk. This is primarily to allow for the considerably higher bioavailability of lutein in breast milk compared with lutein added to infant formula and also to allow for losses during storage. See Section 8.1 in the main report and Section 3 in Attachment 2.
Ratio of lutein to zeaxanthin	Some submitters expressed concern over the lack of justification and uncertain significance of the difference in ratio of lutein to zeaxanthin in Tagetes erecta L. compared to breast milk. This issue is addressed in section 8.1.1 of the main report and section 4 of Attachment 2.
Potential nutrient interactions	Some submitters expressed concern over the uncertain nature of nutrient interactions between lutein and other carotenoids. There is evidence to suggest that under some circumstances there may be interactions between carotenoids when co-ingested such that the presence of one carotenoid may interfere or enhance the absorption of another. However, the nature of these interactions is not well understood as there is limited data in this area. The nutritional implication to formula-fed infants of a lutein and zeaxanthin interaction with β-carotene is unclear because, although carotenes provide a source of vitamin A precursors, there is a requirement for infant formula to contain pre-formed vitamin A. See Section 6 in Attachment 2 for further information.

Submitter issue	FSANZ's response
Equivalence with measured physiological parameters	Some submitters considered there was inadequate evidence of equivalence with measured physiological parameters such as blood levels of lutein between formula-fed and breastfed babies. The plasma/serum lutein concentrations in breastfed infants are discussed in Section 5.1 of Attachment 2. The plasma/serum lutein concentrations in formula-fed infants are discussed in Section 5.2 of Attachment 2.
Evidence	
Data on bioavailability	A number of submitters considered there was a lack of direct evidence of bioavailability of lutein and zeaxanthin in infant formula compared to breast milk. The Applicant has provided FSANZ with additional data since Draft Assessment that directly compares the bioavailability of lutein in breast milk to the bioavailability of lutein in infant formula. See Section 8.1.2.1 of the main report and Section 5.3 of Attachment 2.
Representative data for Australia and New Zealand	A number of submitters considered evidence was required on the lutein concentration in the breast milk of Australian and New Zealand women (from colostrum to mature milk) and serum lutein concentrations of Australian and New Zealand breastfed infants (at different ages). There are presently no published population representative data that characterise the breast milk concentration of lutein in Australian and New Zealand women. However, the levels of lutein in breast milk among Australian and New Zealand women are likely to be within the range of available published data based on comparable diets. See Section 3 of Attachment 2.
Lutein concentrations in formula sold in Australia and New Zealand	Some submitters considered further data on lutein concentrations in formula currently sold in Australia and New Zealand is required. There are no available data on the lutein concentrations in infant formula currently sold in Australia and New Zealand. However, information supplied by the Applicant indicated that there is about 22 µg/L of naturally-occurring lutein in one of their infant formula products. The level proposed by the Applicant relates to both naturally-occurring and added lutein.
Use of applicant funded, non-peer-reviewed studies	A number of submissions expressed concern about the use of studies conducted by the Applicant that have not been peer-reviewed and published. Applications to amend the Code must be supported by the provision of an adequate and robust data package which is frequently a combination of published journal articles and unpublished studies.

Submitter issue	FSANZ's response
	While there is a perception that a peer-reviewed article in a scientific journal has greater authority for a safety assessment, published journal articles also have some limitations. Efforts to minimise journal publication costs through limiting the article size has the inevitable consequence of data being presented almost exclusively in summary or minimal form. Many of the important technical details or supporting observations are not included and the 'pathway' to the conclusions is not always transparent. In some instances, the paucity of important technical detail can prevent validation of the conclusions. The peer review process which selects the articles appropriate for publication is usually based on whether the material is worthy of dissemination to other scientists. For example, it describes significant advances in the understanding of a biological process, proposes, tests or refutes hypotheses, or describes potentially useful new test methods or materials. These articles also provide a very valuable forum for the discussion of the findings in relation to other publications. Consequently investigations, such as safety studies, which may reveal no adverse findings are frequently not submitted for publication because they fail to meet the selection criteria for publication. Unpublished studies submitted by applicants are frequently performed by contract laboratories and are normally performed to reporting standards determined by Good Laboratory Practice (GLP) and Quality Assurance and are complete with individual data, summaries and statistical analysis performed by experts in the fields of toxicology, histopathology and animal science. A major benefit of GLP is to establish minimum standards of documentation, but the extent of documentation that is specified by GLP standards is too voluminous to be included in published studies. A limitation of unpublished studies can be that the results are usually discussed only within the context of that particular study and do not refer to other companion studies. The nature of these studies also sometimes necessitates that they are evaluated as 'commercial-in-confidence' but this does not devalue the quality of the data. In undertaking a risk assessment, FSANZ evaluators consider all available data. The strength or weighting of individual studies (published or unpublished) depends on whether the evaluator has access to all the data or only an abridged summary from which to make an independent evaluation and interpretation. The same issues exist for the evaluation of drugs for human or veterinary use or the use of agricultural chemicals in Australia, Europe, North America and Japan. Both published and unpublished studies have perceived limitations and benefits but all such studies are essential in establishing standards to protect public health. FSANZ needs to be able to consider the scientific merit of all available data in order to base its decisions on 'the best available evidence'.

Submitter issue	FSANZ's response
	In relation to this issue, Wyeth stated that: *Wyeth Nutrition is a division of Wyeth Pharmaceutical. Consistent with Wyeth standards as global pharmaceutical company all Nutrition manufacturing and clinical studies are conducted to the same high standard and quality as applied to Wyeth drugs and vaccines. Specifically all manufacturing is conducted consistent with Good Manufacturing Practices (GMP), all clinical studies are conducted according to International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines and all analysis of clinical samples is conducted in validated assay according to Good Laboratory Guidelines (GLP).*
Safety	
Application of JECFA ADI to infants under 12 weeks of age	A submitter noted that the ADI for lutein does not apply to infants under 12 weeks of age. FSANZ considered the ADI was suitable for infants under 12 weeks of age because investigation of the data indicated no evidence of toxicity. This issue is addressed in section 4 of Attachment 3.
Levels of lutein permitted in formula in the USA	One submitter queried why the level of lutein proposed for inclusion in follow-on formula (500 µg/L) exceeded the level stated in the US GRAS notification for use in infant formula (250 µg/L). Since Draft Assessment, the Applicant has amended their Application to request a reduced maximum concentration of lutein in follow-on formula of 250 µg/L, rather than 500 µg/L. Therefore, the requested maximum level for both infant formula and follow-on formula is consistent with the maximum level permitted in the USA.
Safety studies on growth not eye health	A concern was raised that the safety studies look at effects on growth only and not eye health. This issue has been discussed in Attachment 3.
Reproductive toxicity studies	A concern was raised that no reproductive toxicity study was considered in the risk assessment. Since the Application proposed the addition of lutein to infant formula it was considered unnecessary to define the hazard for reproductive effects in humans. Lutein occurs naturally in human milk, and the levels proposed in this Application aim to give formula-fed infants similar blood concentrations as breastfed infants. The full range of studies considered in this Application is detailed in Attachment 3.

Submitter issue	FSANZ's response
Potential allergenicity of lutein	One submitter queried if lutein from marigolds might be allergenic. All major recognised food allergens are proteins, therefore it is very unlikely that lutein has any potential to be allergenic. Further information on allergenicity is presented in Attachment 3.
Application of JECFA ADI to other ratios of lutein to zeaxanthin	One submitter queried if the JECFA ADI applies to other ratios of lutein to zeaxanthin. The JECFA ADI applies to only those lutein and zeaxanthin preparations that meet the JECFA specification. See Attachment 3 for further information.
Lutein compound	A submitter asked if the proposed lutein compound is the same as that granted GRAS status in the USA. This Application relates to lutein from marigold (Tagetes erecta L.). The material proposed for addition to the Applicant's infant formula is FloraGLO® Lutein 20% Liquid in Safflower Oil obtained from Kemin Health, L.C, and is the same material granted GRAS status in the USA.
Stability of lutein	
Stability of lutein in infant formula	One government submitter commented on the paucity of stability data and considered that data on the stability of lutein in powdered infant formula over the shelf-life of the product (up to 18 months) was required. FSANZ received a report from the Applicant late in 2007 which contained a number of further stability trials related to elucidating the stability of lutein in infant and follow-on products. This report summarised the findings from a further eleven trials undertaken by the Applicant. These stability trials included results from pilot plant, factory trials and commercially prepared Wyeth products, in both liquid (ready-to-feed) and powdered form. Product was stored at both so-called ambient conditions (27°C and 70% relative humidity (RH)) and under accelerated ageing conditions (37°C and 75% RH) and the lutein concentrations analysed every three months, up to 12 and even 18 months for the ambient conditions and till 6 months for the accelerated ageing conditions. Specifically the trials were run to determine what percentage of the original lutein was oxidised during storage. The summary and conclusions of these trials are provided in the Food Technology Report at Attachment 5 as well as in the summary provided in section 10 of the main report.
'Overdosing' to account for losses	A submitter has questioned whether with losses of lutein due to storage (related to losses analysed from stability trials) that product manufacturers will need to overdose lutein to take account of losses, and what impact this will have on actual lutein levels in product in the trade.

Submitter issue	FSANZ's response
	This idea is correct, that is that the Applicant does over dose with extra lutein after seeing the results of their stability trials. However, as stated in the Food Technology Report, manufacturers need to be aware of the requirements of the Code. That is lutein at no more than 250 µg/L in infant formula is allowed in commercial products. So manufacturers need to ensure that their products meet these regulatory limits once products are available for sale, whether the product has been on the market for only one day or at the limit of its shelf life. This is the commercial and regulatory reality which the company needs to be aware of and comply with.
Levels of addition	
Proposed concentration of lutein in follow-on formula	Some submitters considered that doubling the concentration of lutein in follow-on formula was unjustified given that older infants will be consuming a mixed diet that contains naturally occurring carotenoids. Since Draft Assessment, the Applicant has amended their Application to reduce the requested maximum concentration in follow-on formula from 500 µg/L to 250 µg/L, the same as in infant formula.
Minimum amount of lutein	Some submitters questioned the justification for the proposed minimum declaration amount, and considered that the minimum level should reflect the purpose (for example, if purpose is similar composition to breast milk then amount should reflect the lower end of the range found in breast milk). This issue is addressed in section 11.3.1 of the main report.
Labelling	
Claims	Many submitters expressed concern that Standard 2.9.1 of the Code potentially allows nutrient content claims on infant formula products to be made. This issue is addressed in section 11.3.2 of the main report.
Advice for health professionals	One industry submitter requested further guidance from FSANZ on how to differentiate advertising from advice for health professionals. FSANZ believes that the issue is dependent on whether or not health professionals would be captured as a 'food business', as defined in the Model Food Act[24], and similarly if this definition is adopted into State and Territory Food Acts. If health professionals are deemed to fall outside the definition, the statement would not be captured by the Code and hence the question concerning whether or not it is advertising becomes irrelevant.

[24] Food Business means a business, enterprise or activity (other than business, enterprise or activity that is primary food production) that involves: the handling of food intended for sale, or the sale of food regardless of whether the business, enterprise or activity is concerned of commercial, charitable or community nature or whether is involves the handling of sale of food on one occasion only.

Submitter issue	FSANZ's response
Form of lutein	
Lutein esters	One submitter requested that lutein esters as well as free lutein be permitted to be added to infant formula. The Applicant, has confirmed that their request relates to free lutein only, not lutein esters. Hence the scope of this Application, and any subsequent permission, relates to free lutein. In addition, the current specification for lutein which the Code references (being the Joint FAO/WHO Expert Committee on Food Additives (JECFA), referred to as the Compendium of Food Additive Specifications in clause 2 of Standard 1.3.4 – Identity and Purity) refers to free lutein and not lutein esters. The Applicant's lutein complies with this primary reference for specifications so no new specification is required to be written.

Attachment 8

FIRST REVIEW REPORT

CONTENTS

Executive Summary

FSANZ has considered the issues raised by the Ministerial Council in relation to Application A594 – Addition of lutein as a nutritive substance to infant formula products. The preferred option is to re-affirm the approval of the draft variation to Standard 2.9.1, subject to the following amendments as detailed below.

Decision

FSANZ re-affirms its approval of the draft variations to the *Australia New Zealand Food Standards Code* as notified to the Ministerial Council, subject to amendment (at Attachment 1).

This decision permits the voluntary addition of lutein to infant formula products because:

(a) lutein added to infant formula products is unlikely to represent a risk to formula-fed infants at the proposed maximum concentration; and

(b) based on the available evidence, the proposed concentration of lutein to be permitted will provide formula-fed infants with an infant formula product that has a concentration of lutein within the range found in breast milk.

FSANZ has made the following amendments to the draft variations:

(a) reduce the maximum concentration of lutein permitted to be added to infant formula products from the 9 µg /100 kJ (250 µg/L) proposed at Final Assessment to 5 µg /100 kJ (143 µg /L); and

(b) reduce the minimum concentration of 2µg/100 kJ (57 µg /L) proposed at Final Assessment to 1.5 µg/100 kJ (43 µg /L).

In making these amendments, FSANZ is reiterating its previous decision to permit the voluntary addition of lutein to infant formula products, on the basis of safety and nutritional equivalence with breast milk. However, since Final Assessment, additional data provided and further analysis undertaken does not support an apparent four-fold difference in bioavailability between breast milk and infant formula. Therefore, FSANZ has adopted a conservative approach and reduced the lutein concentrations, from those proposed at Final Assessment, to reflect concentrations well within the range found in breast milk.

Additionally, since Final Assessment, the European Food Safety Authority[25] (EFSA) has released a scientific opinion on the suitability of lutein in infant formula and follow-on formulae which supports FSANZ's conclusion and approach at First Review.

[25] Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission on the 'suitability of lutein for the particular nutritional use by infants and young children'. The EFSA Journal (2008) 823, 1-24.

The EFSA opinion raised no safety concerns for lutein at a concentration of 250 ng/L proposed by the Applicant, but noted that a*lthough lutein bioavailability may be somewhat higher in breast milk than in formulae, the data presented do not allow a robust comparison.*

1. Introduction

On 8 September 2008, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Application A594 – Addition of Lutein as a Nutritive Substance to Infant Formula products, which seeks to permit the voluntary addition of lutein as a nutritive substance to infant formula products[26].

Due to the complexity of the science and to allow sufficient time to assess the issues highlighted by Ministers, FSANZ sought an extension from the initial three month review period. Also, this would allow FSANZ to consider the European Food Safety Authority's (EFSA) report on lutein which was due to be released at the end of October 2008. In response, the Ministerial Council granted an additional three month extension and the revised date for the completion of this First Review is 8 March 2009.

2. Objectives of Review

The objective of this Review is to reconsider the draft variation to Standard 2.9.1 in light of the Ministerial Council's concerns as outlined in Section 3.

3. Grounds for the Review requested by the Ministerial Council

A First Review was requested by the Ministerial Council on the grounds that approval of the Application:

- was not consistent with the objectives of the legislation which establishes FSANZ;
- did not protect public health and safety; and
- placed an unreasonable cost burden on industry or consumers.

Additional comments were provided by Ministers and are summarised by FSANZ as follows:

- In Application A594, the rationale presented at Final Assessment for lutein having a nutritional purpose includes that it *is proposed to function in the eye as an antioxidant*. If lutein is permitted as a nutritive substance the Applicant has not provided sufficient evidence to demonstrate the 'nutritional purpose' for which lutein is being added.

- There is a lack of representative data for Australia and New Zealand e.g. lutein concentrations in breast milk, infant formula sold in Australia and New Zealand, and food consumption data for infants from national nutrition surveys.

- There is limited data on the nature of interactions between carotenoids.

[26] 'Infant formula product', as defined in Standard 2.9.1 – Infant Formula Products, 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.

- There is limited evidence to confirm the ratio of lutein to zeaxanthin in human milk samples.

- Application A594 refers to studies that are small and 'difficult to interpret'; and there is a lack of published, independent and peer reviewed studies with a reliance on unpublished studies undertaken by the Applicant.

- The proposed concentration of lutein in infant formula products is greater than that found in breast milk based on the poorer bioavailability of lutein in formula compared to breast milk. This could potentially result in higher levels of serum lutein in formula fed infants than seen in breastfed infants. The high variability of results with regard to bioavailability between lutein in breast milk and in infant formula, and lack of information on the optimum level of dietary intake or serum levels of lutein for infants are also of concern. A conservative approach for vulnerable groups such as infants is recommended.

- The *Joint Expert Committee on Food Additives* (JECFA) ADIs are not generally intended for infants under 12 weeks.

- Manufacturers will need to 'overdose' the addition of lutein to take account of losses during storage.

- It is believed that National Agency for Drug and Food Control in Indonesia has prohibited the addition of lutein in infant formula products, which appears to conflict with information in the Final Assessment Report.

- The planned Ministerial Council policy guidance should not be pre-empted.

- In the absence of policy guidance there has been no assessment of benefit.

- The proposed approach appears to place an unreasonable cost burden on industry or consumers; however there are no quantitative values assigned to costs or benefits.

- There is concern with regard to the determination of costs associated with enforcement.

These issues are addressed under Section 6 of this Report.

4. Background

Food Standards Australia New Zealand (FSANZ) received an Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006 seeking to amend Standard 2.9.1 of the *Australia New Zealand Food Standards Code* (the Code).

Specifically, the Applicant requested permission to add lutein from marigold (*Tagetes erecta L.*) to infant formula products[27,28,29] at a maximum concentration of 250 µg/L.

[27] For the purposes of this Report, use of the term 'infant formula' refers to both 'infant formula' and 'follow-on formula', which are defined in subclause 1(2) of Standard 2.9.1.

[28] A permission to add lutein would relate to all infant formula products. Infant formula and follow-on formula are a subset of this formulae product.

The Applicant requested permission to add lutein to infant formula products in amounts that would provide 'comparable levels' to breastfed infants.

Standard 2.9.1 requires that the addition of a vitamin, mineral, food additive or nutritive substance to an infant formula product must undergo a pre-market safety assessment before such a product may be sold in Australia and New Zealand.

In determining if lutein should be permitted as a voluntary nutritive substance in infant formula FSANZ's assessment considered:

- if lutein is present in breast milk;
- whether the requested concentration of lutein in infant formula (250 µg/L) is similar to the concentrations found in breast milk (accounting for bioavailability);
- if the proposed fortification achieves a similar physiological effect for formula-fed infants compared to breastfed infants (e.g. serum lutein concentrations); and
- the safety of lutein, specifically whether there are any risks to infants from consuming infant formula containing lutein derived from *Tagetes erecta L*. at the requested concentration.

5. FSANZ Assessment of Application A594

In June 2008, FSANZ approved the voluntary addition of lutein as a nutritive substance in infant formula products at a maximum concentration of 9 µg/100 kJ (250 µg/L) with a minimum declaration of 2 µg/100 kJ. This decision was based on:

- lutein added to infant formula is unlikely to represent a risk to formula-fed infants at the requested maximum concentration. For both 3 month old infants and 9 month old infants, the estimated mean and 95th percentile intakes of lutein and zeaxanthin following fortification of infant formula were all well below the ADI; and

- the available evidence indicating that the requested concentration of lutein to be added to infant formula would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations and amounts of lutein found naturally in breast milk.

The Executive Summary and Statement of Reasons for this Application are provided at **Attachment 2**.

[29] 'Infant formula product', as defined in Standard 2.9.1 – Infant Formula Products, 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.

6. Issues addressed in the First Review

6.1 Protection of public health and safety

At the time of Initial Assessment of this Application, the Board agreed, that in the absence of Policy Guidelines, decisions about formula composition should focus on safety and the role of infant and follow-on formula as substitutes for breast milk. The Ministerial Council was informed of this approach in the Chairman's Report of October 2007 which noted that *FSANZ, in assessing the application against the objectives specified in section 18 of the FSANZ Act, is of the preliminary view that matters of efficacy or benefit are not relevant at this stage.*

6.1.1 Insufficient evidence to demonstrate nutritional purpose

The Review request states that *FSANZ's rationale for lutein having a nutritional purpose includes that it 'is proposed to function in the eye as an antioxidant'. The Applicant has not provided sufficient evidence to demonstrate the 'nutritional purpose' for which lutein is being added. It is considered that if lutein is permitted to be added as a nutritive substance, the nutritional purpose (which is one of the criteria within the definition) should be demonstrated.*

Although benefit /efficacy has not been assessed, a large body of published data shows that lutein, which cannot be synthesised by the human body, performs multiple functions consistent with it fulfilling a nutritional/physiological purpose; specifically it acts as a blue light filter and antioxidant in the eye, and as an antioxidant in the body as a whole.

Scientific observations published to date indicate a strong biological drive to ensure lutein and zeaxanthin are present in the eye. Lutein and zeaxanthin are found in many tissues that make up the human eye; they are particularly concentrated in the lens giving it the characteristic yellow colour (Bernstein *et al*., 2001; Bone *et al*., 1988; Rapp *et al*., 2000). Lutein and zeaxanthin concentrations in the eye exceed those found in serum by as much as several thousand-fold (Schmitz *et al*., 1993). They are the only carotenoids known to be highly concentrated in specific tissue (Alves-Rodrigues and Shao, 2004). Further, lutein and zeaxanthin levels in the eye are preferentially preserved over serum concentration following a decreased intake (Johnson *et al*., 2000).

The possible roles, based on published empirical evidence, of lutein and zeaxanthin in the eye fall under the categories of: protection of eye tissue from oxidation; a direct optical role such acting as a blue light filter; and a role in influencing the development of the eye early in life (Hammond 2008).

The human eye is naturally exposed to considerable oxidative stress through light, with particular sensitivity to blue light (Snodderly, 1995). Lutein has been shown to act as a filter of blue light in the eye (Junghans *et al*., 2001). Lutein and zeaxanthin also act as antioxidants in the eye (Kim *et al*., 2006), and, much like other carotenoids, more generally in the body (Lim *et* al., 1992; Trevithick-Sutton *et al*., 2006, Zhang *et al*., 1991).

Further, rhesus monkeys, a broadly accepted animal model of primate eye physiology, fed lutein free diets had no detectable macular pigment (Neuringer *et al*., 2004), and a dip in the density profile of retinal pigment epithelium cell density at the foveal centre where there would normally be a peak (Leung *et al*., 2004). This indicates an integral role of lutein and zeaxanthin in the structural development of the eye.

The published data clearly show that lutein and zeaxanthin are functional components of the macular of the human eye; no other carotenoid has been shown to be able to take their place. What remains to be more firmly established is how and to what extent these known and suggested functions of lutein influence long-term eye health in the context of infant's intakes. Corroborating the assumption that provision of dietary lutein in infancy has a beneficial long-term effect would require a large group of infants with different lutein intakes to be followed up for many decades as this is the timeframe for the development of many eye problems. Even then it would not be possible to differentiate the benefit of intakes very early in life with those from intakes in subsequent life stages.

6.1.2 Lack of representative data for Australia and New Zealand

The Review request states that *it is considered that there is a lack of representative data for Australia and New Zealand in relation to the proposed addition of lutein to infant formula products.*

6.1.2.1 Lack of Australian and New Zealand data on lutein concentrations in breast milk

The approach taken at Final Assessment is in line with the FSANZ Act which requires that the development or review of food regulatory measures must *be based on risk analysis using the best available scientific evidence.*

FSANZ is now aware of 12 studies published to date covering 15 countries, including Australia, that have measured breast milk lutein and zeaxanthin concentrations separately or in combination (Canfield et al., 1997; Canfield et al., 2001; Canfield et al., 2003; de Azeredo & Trugo, 2008; Gossage et al., 2002; Jackson et al., 1998; Jackson & Zimmer, 2007; Jewel et al., 2004; Lietz et al., 2006; Macias & Schweigert, 2001; Menses & Trugo, 2005; Schweigert et al., 2004). One paper detailing the development of a lutein assay for milk samples reported the lutein concentration of a single New Zealand breast milk sample, but no information in relation to sampling was available e.g. days postpartum (Gill and Indyk, 2008). All of these studies used convenience samples rather than random samples, so they may not be representative of any country or region's breast milk lutein concentration. Table 1 of this Review report summarises 11 of the published studies representing breast milk data from 15 countries.

Obtaining true representative data would require samples from a random selection of a large number of breastfeeding women. There is no registry of breastfeeding women from which to select such a sample. Also, it would be unethical to insist that all selected women provide breast milk samples. Therefore, it would be logistically extremely difficult, and ethically challenging to obtain a representative sample set.

Although a broad range of concentrations has been reported in the literature, breast milk lutein and zeaxanthin concentrations are less variable than those of other carotenoids such as β-carotene and lycopene (Jackson *et al*., 1998).

Further, although collectively the evidence indicates an influence between a mothers' intake of lutein and her breast milk lutein concentration, this may not be the only factor that controls breast milk lutein concentration. For example, the higher lutein concentration reported in colostrum, relative to transition and mature milk suggests factors other than dietary intake also determine breast milk lutein concentration (Gossage *et al*. 2002; Macias & Schweigert, 2001, Schweigert *et al*., 2004).

What all the published data confirm is that lutein and zeaxanthin are natural components of breast milk in a broad range of concentrations and ratios.

In the absence of representative data, FSANZ has used the range of published breast milk lutein concentrations as a guide for setting permissions in infant formula. This approach achieves equivalence with breast milk, and ensures lutein intakes in infants given lutein enriched infant formula products do not exceed those that may be experienced by breastfed infants. See Section 6.1.7.1 for further details.

6.1.2.2 Lack of data for lutein concentrations in formula sold in Australia and New Zealand

Permissions granted for the addition of lutein to infant formula products would relate to the total lutein content. Standard 2.9.1, subclause 7 (1) of the Code intends that the maximum permitted amounts apply to the sum of the naturally occurring and added nutritive substance.

There are no data available on the lutein concentrations in infant formula currently sold specifically in Australia and New Zealand. However, information supplied by the Applicant refers to Wyeth products manufactured in other countries, not currently fortified with lutein, that may contain up to 26.0 μg /L of naturally occurring lutein. Also, the Applicant has indicated that the innate lutein concentrations in Wyeth products made overseas, would also be present in these formula products sold in Australia and New Zealand.

The concentration proposed by the Applicant relates to both naturally-occurring and added lutein.

6.1.2.3 Lack of National Nutrition Survey data for Australia and New Zealand

The purpose of the dietary intake assessment was to estimate the current and potential dietary intakes of lutein and zeaxanthin of infants. The dietary intake assessment presented in the Final Assessment Report represents a reliable estimate of lutein intake using the best available data.

As the target group was infants aged 3 months and 9 months, National Nutrition Survey data was not available. In this case, following best practice and using internationally accepted methodology, FSANZ used theoretical diets to estimate dietary intakes[30].

There may be some uncertainty with the underlying data used for the dietary intake assessment, both in relation to food consumption and lutein concentration data.

[30] The details on how the theoretical diets were derived are given in Attachment 4, Section 3.7 of the Final Assessment Report

However, slight variations in the data would not change the conclusion of the assessment that dietary intakes are well below the Acceptable Daily Intake (ADI). FSANZ estimated mean and high (90^{th} percentile) dietary intakes to be below 10% of the ADI for infants under 12 months old.

6.1.3 Use of small studies and difficult interpretations

The Review request refers to the *use of small studies and difficult interpretations.*

The conduct of small studies is a normal aspect of scientific research especially at early stages when hypotheses are being formed. Such studies are invaluable for guiding the design and conduct of subsequent larger studies. However, the reliance on small studies alone to test hypotheses and arrive at conclusions would be poor scientific practice. FSANZ affirms that the conclusions in this report have not relied solely on small studies.

FSANZ is confident that all of the available relevant scientific information has been considered in arriving at an acceptable range of concentrations for lutein in infant formula products.

FSANZ indicated in the FAR that the extent of lutein absorption in pigs and monkeys was difficult to calculate with any certainty. This was because the serum concentrations of lutein did not appear to be significantly increased following dosing. In part this may have been due to the rather large background range of serum lutein concentrations.

It is important to note that these absorption studies in pigs and monkeys are not particularly important for the purpose of determining the safety of lutein since there were no specific toxicity studies performed in these two species. It is noted however that none of the animals in the two absorption studies exhibited signs of toxicity.

6.1.4 Reliance on unpublished studies commissioned and undertaken by the Applicant; and lack of published, independent and peer reviewed research

The Review request states that *there continues to be concern about the reliance on unpublished studies commissioned and undertaken by the Applicant. There are also concerns about the overall lack of published, independent and peer reviewed research associated with this Application.*

Applications to amend the Code must be supported by the provision of an adequate and robust data package which is frequently a combination of published journal articles and unpublished studies. While there is a perception that a peer-reviewed article in a scientific journal has greater authority for a safety assessment, this must be balanced against some of the limitations due to the level of detail reported and publication bias. Efforts to minimize journal publication costs through limiting the article size, has the inevitable consequence of data being presented almost exclusively in summary or minimal form. Therefore, many of the important technical details or supporting observations are not included so that the 'pathway' to the conclusions is not always transparent. In some instances it is the paucity of important technical detail which prevents validation of the conclusions.

The peer review process which selects the articles appropriate for publication is usually based on whether the material is worthy of dissemination to other scientists to describe significant advances in the understanding of a biological process, e.g. propose, test or refute hypotheses, or describe potentially useful new test methods or materials. These articles also provide a very valuable forum for the discussion of the findings in relation to other publications. Consequently investigations, such as safety studies, which may reveal no adverse findings are frequently not submitted for publication because they fail to meet the selection criteria for publication.

Unpublished studies submitted by applicants are frequently performed by contract laboratories and are normally performed to reporting standards determined by Good Laboratory Practice (GLP) and Quality Assurance and are complete with individual data, summaries and statistical analysis performed by experts in the fields of toxicology, histopathology and animal science. A major benefit of GLP is to establish minimum standards of documentation, but the extent of documentation that is specified by GLP standards is too voluminous to be included in published studies.

The limitation of these unpublished studies can be that the results are usually discussed only within the context of that particular study and not refer to other companion studies. The nature of these studies also sometimes necessitates that they are evaluated as 'commercial-in-confidence' but this does not devalue the quality of the data.

Therefore, in undertaking a risk assessment FSANZ evaluators consider all available data in their various forms. The strength or weighting of individual studies depends on whether the evaluator has access to all the data or only an abridged summary from which to make an independent evaluation and interpretation. The same issues exist for the evaluation of drugs for human or veterinary use or the use of agricultural chemicals in Australia, Europe, North America and Japan.

Overall, the use of both published and unpublished studies have perceived limitations and benefits but all such studies are essential in establishing standards to protect public health. FSANZ needs to be able to consider the scientific merit of all available data in order to base its decisions on the best available evidence.

6.1.5 Lack of information on the optimum level of dietary intake or serum levels of lutein for infants

The Review request states that *there is no information available on the optimum level of dietary intake or serum levels of lutein for infants.*

Optimum intakes remain to be firmly established for all nutrients and are likely to be highly variable across different populations groups based on genetic and environmental factors, and nutrient interactions.

Current recommendations such as those contained in the Nutrient Reference Values for Australia and New Zealand (NRVs) are predominantly based on the prevention of deficiency across a population, not on achieving optimal intakes (NHMRC and New Zealand Ministry of Health (MoH) 2006). For infants the adequate intakes (AI)[31] are used for all macro- and micronutrients.

The AIs for infants have been set by multiplying the average intake of breast milk by the average concentration of the nutrient in question, based on available published data. Consistent with this approach, FSANZ has examined the published data to determine the range of lutein present in breast milk.

Lutein does not appear to be an essential nutrient in that it is not vital for life. Based on what is already known about its physiological functions it would likely be considered unethical to provide humans with a lutein free diet for long enough to observe deleterious effects and thereby prove essentiality or conditional essentiality. The established and likely functions of lutein are discussed in Section 6.1.1.

An absence of lutein from the diet would be rare given lutein's natural presence in a wide range of foods and use as a colour; the only situation where this might be common is during an infant's consumption of lutein free infant formula as a sole source of nutrition.

Consistent with the approach used by the National Health and Medical Research Council and New Zealand Ministry of Health (MoH) in setting AI for infants, FSANZ has considered the available data for breast milk lutein concentration alone and in combination with zeaxanthin as part of this Application; see Section 6.1.7.1 for details.

6.1.6 Limited data on carotenoid interactions

The Review request states that *the nature of these interactions (between carotenoids) is not well understood as there is limited data in this area*.

FSANZ re-affirms the decision at Final Assessment, specifically that: *The nutritional implication to formula-fed infants of a lutein and zeaxanthin interaction with β-carotene is unclear*; however *there is a requirement for infant formula to contain pre-formed vitamin A.*

Therefore, although there may be some interaction between lutein and zeaxanthin, and β-carotene, adequate provision of vitamin A is ensured by the existing Standard.

6.1.7 Proposed concentration of lutein in infant formula compared to breast milk

The Review request states that *there is concern about the proposed concentration of lutein being greater than that found in breast milk and is comparable to colostrum which declines in the first few weeks.*

[31] Adequate intake (used when a recommended dietary intake cannot be determined) – The average daily nutrient intake level based on observed or experimentally-determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate.

Also, that ***a justification for requesting the greater amounts of lutein for infant formula is based on the apparent poor bioavailability of lutein contained in formula compared with human milk.***

And ***the high variability of the results raised concern regarding the four fold difference in bioavailability between lutein in breast milk and lutein in infant formula used for calculating lutein levels in the Final Assessment Report.***

The Review request also states that ***the draft standard proposes the voluntary addition of lutein to infant formula that may result in a higher level of serum lutein in infants fed such formula,*** **and that** ***225 μg/L…is higher than any of the serum lutein levels observed in breastfed infants.***

6.1.7.1 Lutein concentrations in breast milk

Studies of lutein, and lutein and zeaxanthin concentrations in breast milk (see Table 1) and infant serum (see Table 2) have reported a broad range of concentrations. Excluding colostrum and transition milk by only considering milk obtained at least 21 days postpartum, the mean combined lutein and zeaxanthin concentrations from published studies ranges from 6.9 μg/L in samples (n=18) from Honduras (Canfield *et al.*, 2001), to 199 μg/L in samples (n=25) from Tanzania (Lietz *et al.*, 2006). The available reports indicate that even within countries, breast milk lutein and zeaxanthin concentrations vary.

This is illustrated by the four separate reports for the United States indicating a mean lutein and zeaxanthin concentration ranging from 11.4 μg/L to 54.0 μg/L (Canfield *et al.*, 1997; Canfield *et al.*, 2003; Gossage *et al.*, 2002, Jackson *et al.*, 1998); this does not include values from milk obtained within six days postpartum and therefore does not include colostrum. Table 1 provides mean results of breast milk combined lutein and zeaxanthin concentrations reported in published studies.

Table 1: Mean Lutein and Zeaxanthin Concentrations in Breast Milk

Reference	Country	n	Treatment‡	Days Postpartum†	Lutein & Zeaxanthin (□g/L)	Sample Collection*
Canfield *et al*, (1997)	United States	6 6	60 mg β-carotene 210 mg β-carotene	≤6 months	11.4 18.8	Afternoon single complete expressions
Canfield *et al*, (2001)	Honduras	18	control	baseline final	1-24 months	10.6 6.9	Morning spot sample of foremilk
Canfield *et al*, (2003)	Australia Canada Chile China Japan Mexico Philippines United Kingdom United States	53 55 51 52 51 50 60 50 49	none (cross-sectional)	1-12 months	15.4 17.1 32.4 43.2 43.8 25.0 19.9 15.4 14.8	Afternoon single complete expressions

Reference	Country	n	Treatment‡	Days Postpartum†	Lutein & Zeaxanthin (□g/L)	Sample Collection*
de Azeredo & Trugo	Brazil	72	none (cross-sectional)	30-120	14.2	Morning single complete expression
Gossage *et al*, 2002	United States	21	none (cross-sectional)	0 3 6 9 12 15 20 27	136.5 130.8 91.0 76.8 59.7 48.4 48.4 54.0	Single complete expression; time of day unspecified
Jackson *et al*, (1998)	United States	23	none (cross-sectional)	6-16 weeks	38.7	Afternoon single complete expression
Jackson & Zimmer, 2007	Japan Mexico United Kingdom	20 20 20	none (cross-sectional)	1-12 months	63.9 68.6 30.5	Afternoon single complete expression
Lietz *et al*, (2006)	Tanzania	25-28	control	1 month 3 months	147.9 199.1	Morning pooled foremilk sample from both breasts
Macias & Schweigert, 2001	Cuba	21	none	1 7 15	44.1 30.2 20.1	Single complete expressions ; time of day unspecified
Meneses & Trugo, (2005)	Brazil	49	none (cross-sectional)	30-120	34.1	Single complete expression; time of day unspecified
Schweigert *et al*, (2004)	Germany	21 13 12	none	4 19 65-77 93-105	112.1 61.4 21.9 23.8	Single complete expression; time of day unspecified

‡ For completeness both cross-sectional and longitudinal studies with and without dietary intervention in mothers have been included. None of the dietary interventions were intended to increase lutein and/or zeaxanthin concentrations. However, two report statistically significant differences in lutein and zeaxanthin concentration between control and intervention groups (Canfield *et al.*, 2001; Lietz *et al.*, 2006); results for intervention groups have therefore not been included or considered for these two studies.

† Days, weeks, or months post partum gives an indication of whether measurements are for colostrum, transition, or mature milk. Where a range of days postpartum is provided lutein and zeaxanthin concentrations were measured at one point in time per mother but not all mothers were the same in terms of time postpartum.

*A number of breast milk sampling protocols have been employed; those involving complete expression of one breast are more indicative of average concentrations than partial samples as fore, mid, and hind milk have been shown to contain differing lutein and zeaxanthin concentrations (Jackson *et al.*, 1998).

A study by Jewell *et al*. (2004) also reported breast milk lutein and zeaxanthin concentrations, but expressed the results per gram of fat.

The study did not report the fat content of milk; without that information all the results could not be converted to μg/L for inclusion in Table 1. However, the authors did report in their text that: *the median concentration in Irish samples was 145 nmol/L* [82.5 μg/L] *(48-339 nmol/L)* [i.e. 27-193 μg/L], *but this fell approximately five-fold in the next 12-21 days* [postpartum].

The reported range in mean serum and plasma lutein and zeaxanthin concentrations is 47.8 μg/L in a group 28 infants from Honduras (Canfield *et al.*, 2001), to 143 μg/L in a group of 10 infants from the United States (Johnson *et al*., 1994). These are shown in Table 2.

The Applicant has asked for permission for the addition of lutein to infant formula products, although the product to be added is approximately 10% zeaxanthin. It is therefore appropriate to determine a concentration of lutein that is equivalent to the range of values in mature breast milk. Table 3 summarises the results of studies that published breast milk lutein concentrations separate to zeaxanthin concentrations of mature milk; i.e. at least one month postpartum.

Table 2: Serum and Plasma Lutein Concentrations in Breastfed Infants

Reference	Country	n	Age‡	Lutein & Zeaxanthin (μg/L)
Johnson *et al*., 1994	United States	10	1 month	143.0
Canfield *et al*., 2001	Honduras	28	1-24 months	51.2
		28		47.8
		10		55.7
Dancheck *et al*., 2005	Malawi	173	12 months	168.4
Wyeth Nutrition, 2006a	United States	41	58 days	125.9
				Geometric Mean
Adelekan *et al*., 2003†	Nigeria	192	0-20 days	45.5
Wyeth Nutrition, 2007	United States	14 (at baseline)	9-21 days	81.0
		13 (after 12 weeks)	93-105 days	69.3

‡ The age of measurement gives an indication of whether infants were likely to be exclusively breastfed or also receiving complementary feeding.
† The majority of infants were exclusively breastfed, but 20 were given both breast milk and infant formula.

Table 3: Mature Breast Milk Lutein Concentrations

Reference	Country	n	Treatment	Days Postpartum	Lutein (μg/L)	Zeaxanthin (μg/L)
Jackson & Zimmer, 2007	Japan	20	none cross-sectional	1-12 months	51.1	12.8
	Mexico	20			47.9	20.7
	United Kingdom	20			21.8	8.7
Lietz *et al*, (2006)	Tanzania	25-28	red palm oil	1 month	125.2	17.1
				3 months	142.2	17.1
		25-28	control	1 month	130.8	17.1
				3 months	176.3	22.8

The women in the study by Jackson and Zimmer (2007) reported having at least three servings of fruits and vegetables combined per day. The difference in breast milk lutein concentrations suggests carotenoid rich food intake was greater in Japanese and Mexican women than those from the United Kingdom.

The women in the study by Lietz *et al* (2006) reported having a low intake of carotenoid rich foods. Despite this they had comparatively high breast milk lutein concentrations similar to the higher end of the range in colostrum and transition milk in Irish mothers (Jewell *et al*., 2004).

These two studies suggest that to achieve compositional equivalence with breast milk, infant formula products should contain between 21.8-176.3 μg/L.

6.1.7.2 Limited evidence regarding ratio of lutein to zeaxanthin in human milk

The Review request states that t*he ratio (of lutein to zeaxanthin) can vary over a wide range reflective of the diet but there is very limited evidence to confirm this in human milk samples*.

Five published studies and one unpublished report assessing breast milk from 214 mothers report mean ratios of lutein to zeaxanthin ranging from approximately 2.5:1 to 8:1 (Jackson and Zimmer 2007; Jewell *et* al., 2004; Lietz *et al*., 2006; Schweigert *et al*., 2004; Wyeth, 2006).

The broadest reported range in individuals was between 1:1 and 33:1 (Jewel *et al*., 2004). No appreciable change in the ratio of lutein to zeaxanthin in breast milk has been observed over time (Schweigert *et al*., 2004; Lietz *et al*., 2006).

These findings show that lutein usually predominates over zeaxanthin in breast milk, but with considerable variation in the specific ratio across and within study groups. Therefore, the ratio of lutein to zeaxanthin of approximately 10:1 found in *Tagetes erecta L.* is consistent with the predominance of lutein in breast milk and within the range reported for breast milk.

6.1.7.3 Bioavailability of lutein

The studies originally submitted by the Applicant provided information on the lutein concentrations in plasma/serum from infants exclusively fed breast milk or infant formula. The lutein concentrations in breast milk and infant formula covered a wide range of concentrations. The analyses provided in the submitted reports indicated that similar lutein concentrations in breast milk and infant formula resulted in approximately 4-fold lower concentrations in infant plasma/serum in formula-fed infants compared to breastfed infants. Thus, the bioavailability of lutein in infant formula products at Final Assessment was considered to be approximately 4-fold lower than lutein in breast milk. This provided justification for proposing to permit higher concentrations of lutein for addition to infant formula products as compared to concentrations in breast milk.

To fully address the concerns raised at First Review regarding bioavailability, FSANZ requested additional information from the Applicant. This included the handling and preparation of breast milk and infant plasma/serum samples and the analytical methods used to measure the concentration of lutein in these samples.

After extensive analysis of the information provided, FSANZ is now of the opinion that the information does not support the concept that lutein bioavailability from breast milk is higher than from infant formula products.

Several specific aspects of the Wyeth studies are considered to be problematic.

These concerns are based around sample storage, handling and preparation, and the assays used for the measurement of lutein concentrations in breast milk, infant plasma and infant serum samples. Also, there are large discrepancies in the two studies on infant formula (Wyeth 2006b and Wyeth 2007) when the mean infant serum/plasma data are plotted against infant formula concentration.

As presented, these two studies would indicate that the bioavailability of lutein in infant formula from the Wyeth (2007) study is approximately twice that of lutein in infant formula from the Wyeth (2006b) study.

The specific reasons for the conflicting results obtained in these infant formula studies can be speculated upon, but in the absence of additional studies, cannot be confirmed. Variations in sample storage, handling and preparation and analytical assays are possible confounding factors. The variability identified in the infant formula data raises the question of how much of the variability in the breast milk data (Wyeth 2006a and Wyeth 2007 studies) could be due to these uncharacterised factors. FSANZ considers it may be possible, but is not able to confirm that sample storage / handling may have contributed to erroneous conclusions being drawn from the data.

Because of the discrepancies identified in these studies, FSANZ considers that the data are not adequate to support substantially greater lutein concentrations in infant formula products relative to the range of concentrations reported in breast milk. Thus, the bioavailability of lutein in infant formula products has been considered by FSANZ to be the same as the bioavailability of lutein from breast milk.

FSANZ also appreciates that some published studies may be similarly prone to such deficiencies in some instances. However, the same level of scrutiny is not possible to apply to the limited data presented in published studies. For example, the studies by Canfield et al. (2003) and de Azeredo & Trugo (2008) use an assay method which suffers from unknown extraction efficiency and poor recovery (Liu et al., 1998). Therefore, lutein concentrations were probably underestimated in these studies, which is consistent with the relatively low concentrations of breast milk lutein reported in these studies (Table 1).

Because of the large variation in the assay methods used in published studies, FSANZ has considered the totality of reported breast milk lutein concentrations in determining the minimum and maximum concentrations of lutein for addition to infant formula products for this Application.

The revised maximum lutein concentration for infant formula products proposed at First Review is well within the range reported in breast milk to date.

The anticipated serum lutein resulting from consumption of infant formula products containing the revised maximum lutein concentration would likewise be within the reported mean ranges.

6.1.7.4 European Food Safety Authority scientific opinion

Since the Final Assessment of Application A594, the recent scientific opinion of the European Food Safety Authority[32] (EFSA) has been released on the suitability of lutein in infant formula products.

The EFSA report raised no safety concerns about lutein at the concentration of 250 µg/L proposed by the Applicant. However, the EFSA report also questioned the reliability of the data provided in the Application under their consideration noting:

The results obtained in infants fed formulae with added lutein do not support the use of a concentration in the range of 250 - 300 µg/L in infant formulae to obtain the closest correspondence with the distribution and range of plasma lutein in breast fed infants. According to the data provided by the applicant, a concentration of about 120 µg/L could be sufficient to achieve this aim. The Panel concludes that the results obtained in formula-fed infants do not support a 200 microgram/L lutein target concentration in infant formulae.

Although the EFSA opinion raised no safety concerns for lutein at the concentration of 250 µg/L proposed by the Applicant, it also noted that *'although lutein bioavailability may be somewhat higher in breast milk than in formulae, the data presented do not allow a robust comparison'.* This EFSA scientific opinion therefore supports FSANZ's conclusion and approach at First Review.

6.1.8 Level of overage

The review request states there *is concern that manufacturers will need to overdose lutein to take account of losses incurred during storage,* and notes that the level requested by the Applicant *includes 250% overdosing to ensure the product will always have at least 100µg/L lutein.*

The review request asks *how manufacturers will ensure that their products will contain no more than 250 µg/L lutein, particularly if it is placed into the market place the day following manufacture.*

In the Final Assessment Report, FSANZ supported the maximum permitted concentration of lutein in infant formula as requested by the Applicant, at 250 µg/L. The Food Technology Report (Attachment 5 to the Final Assessment Report) provides the justification for the overage of 250%, that is, a maximum permitted concentration of 250 µg/L for a label declaration of 100 µg/L.

This overage takes account of lutein losses during storage over time to the end of shelf life of the product. Stability studies showing losses with storage over time and at different temperatures were provided by the Applicant.

[32] Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission on the 'suitability of lutein for the particular nutritional use by infants and young children'. The EFSA Journal (2008) 823, 1-24.

The Applicant's request for this level of overage was also to ensure that the product would always be manufactured to contain lutein at a concentration within the permitted range. The Applicant provided data on the initial levels of lutein in their commercially produced product. The results indicated, at a 99% confidence level, that the product would always be produced with lutein below the maximum permitted. The data indicated that the commercially produced product had a maximum concentration of 190% of the label declaration i.e. 190 µg/L; this was well under the permitted maximum proposed at Final Assessment of 250 µg/L.

Manufacturers of infant formula are required to produce their product to ensure that lutein concentrations in commercial product are always between the regulatory ranges of minimum and maximum limits.

Since the First Review Request, the Applicant has provided more recent information on storage and shelf life, and initial production levels of lutein in infant formula, in addition to the data that was available at Final Assessment. The Applicant states the more recent data is based on two and a half years of production of infant formula products containing added lutein.

The more recent data provided to support an overage of 250%, relates to actual variability in commercial product. The Applicant has provided a summary of commercial production data of initial lutein concentrations compared to target levels. More extensive shelf life storage trials than those provided at Final Assessment have also been provided. Statistical calculations were performed by the Applicant on the results to further explain the rationale.

FSANZ believes the Applicant's production results are quite comparable to those of typical production facilities that dose relatively low levels of a substance into commercial food products.

The additional long term shelf life storage studies recently provided indicate that less lutein is lost with long term storage than originally indicated at Final Assessment. Average losses due to long term storage to the end of shelf life (two years for powdered product and one year for liquid product) are now understood to be 28%. This is compared to the 41-55% losses after 12 months for liquid and powdered products respectively, as reported at Final Assessment. Most of this loss is due to oxidation of lutein within the first 3 months, with a slower reduction over the remaining shelf life.

6.1.9 Joint Expert Committee on Food Additives (JECFA) ADIs are not intended for below 12 weeks of age

The Review request states that *it is noted that the Joint Expert Committee on Food Additives (JECFA) indicates that ADIs are generally not intended to be applied to infants below 12 weeks of age. This would strengthen the case for using a more conservative approach to setting a maximum level in infant formula.*

As stated at Final Assessment, FSANZ acknowledges that JECFA ADIs do not generally apply to infants below 12 weeks of age. However, the available data for lutein indicate that the ADI is applicable for the most sensitive segments of the population, including infants below 12 weeks of age. No toxicity has been reported in animal studies even at very high of intake (1000 mg/kg/day).

No adverse effects have been observed in clinical studies with lutein fortified infant formula. The ADI is therefore considered to be conservative and highly protective for infants below 12 weeks of age. It is also relevant that neonates receive large amounts of lutein via colostrum relative to the intake from subsequent breast milk. Therefore, FSANZ's approach at First Review to reduce the maximum permitted concentration of lutein in infant formula is not based on safety concerns. Rather it is to permit lutein at concentrations within the range observed in breast milk from healthy mothers.

6.1.10 Lack of assessment of benefit

The Review request states *that in the absence of policy guidance there has been no assessment of benefit of the addition of lutein to infant formula to the child. FSANZ has indicated that adding up to 280 µg/L lutein to infant formula would be safe according to toxicology reports.*

FSANZ re-affirms the position taken at Final Assessment noting that in the absence of Ministerial policy guidelines at that time, the approach to the assessment of this Application has focussed primarily on the safety of lutein (see also Section 6.1.1). The findings of the safety assessment concluded that lutein added to infant formula products is unlikely to represent a risk to formula-fed infants at the requested maximum concentration.

The potential for the addition of lutein to infant formula products to provide a long-term health effect for formula-fed infants has not been included in consideration of this Application.

Rather, as infant formula products are used as a substitute for breast milk and in some instances as the sole source of nutrition for formula-fed infants, FSANZ has considered nutritional equivalence with breast milk.

The revised maximum lutein concentration for infant formula proposed at First Review is well within the range reported in breast milk to date.

As the bioavailability of lutein in infant formula products is taken to be similar to that in breast milk, it is anticipated that the serum lutein of infants consuming infant formula products with lutein at the revised concentration would likewise be within the reported ranges of breast fed infants.

In the absence of policy guidance this is consistent with the approach historically taken with existing permissions for voluntary nutritive substances in Standard 2.9.1, for example *nucleotides.*

6.2 Absence of Policy Guidance

The Review request states that *although the Ministerial Council has agreed to commence work on policy guidance on infant formula, the timing of the completion of this policy guidance is not yet known and the absence of this policy guidance creates uncertainty. In light of this uncertainty, policy guidance should not be pre-empted.*

In March 2008, the Food Regulation Standing Committee (FRSC) established a Working Group to develop a Policy Guideline on the intent of Part 2.9 of the Code – Special Purpose Foods. A Consultation Paper[33] was released for public comment in January 2009, with submissions due in early March 2009.

In June 2008, FRSC established a separate Working Group to develop a Policy Guideline on Infant Formula Products covered under Standard 2.9.1 of the Code. This policy guidance has not become available within the statutory timelines for this Application, therefore FSANZ has progressed Application A594 according to the statutory requirements.

This approach is consistent with FSANZ's consideration of other Applications in the absence of policy guidance (see Section 6.1.1).

6.3 Indonesian prohibition of lutein in infant formula products

The Review request states that *it is believed that the National Agency for Food and Drug Control, Republic of Indonesia – Regulation concerning the addition of nutrients and no-nutrients into food products has prohibited the addition of lutein into infant formula and follow-on formula*.

The Final Assessment Report stated that Wyeth had gained product registration approval for lutein-containing infant formula products in various countries including Indonesia. Since the Final Assessment, a Regulation [34] was enacted in Indonesia on 10 July 2008 concerning *the addition of nutritive and non-nutritive materials to food products*. Article 5 of the Regulation states (from an English translation obtained by FSANZ) that *the addition of lutein to baby formula and 'extension' formula (i.e. formula for older babies -6 months and older) is prohibited*.

Exceptions from the provisions made in Article 5 may be considered *if shown scientifically to be safe for the consumer and to confer a benefit through a procedure for study as determined by the head of the Agency*. The Regulation also states *that food products that are on the market at the time of entry into effect of these regulations will be allowed a period not exceeding 12 (twelve) months to be brought into conformity with them.*

FSANZ understands that the National Agency for Food and Drug Control (NAFDC) in Indonesia has enacted this prohibition to align with the Codex Standard on Infant Formula which does not specifically permit lutein, as Indonesia adopts the Codex guidelines. NAFDC have also indicated that there is no scientific supporting data for Indonesia to permit the use of lutein. However, it is not for FSANZ to determine the appropriateness of or the rationale for the Indonesian regulation.

[33] Department of Health and Aging, Special Purpose Foods Consultation Paper on Food Regulation Policy Options. http://www.health.gov.au/internet/main/publishing.nsf/Content/foodsecretariat-pgdev

[34] Regulation of the Head of Medicines and Foodstuffs Control Agency Republic of Indonesia (Number: HK 00.05.1.52.3572).

6.4 Cost burden on industry or consumers

The Review request states that ***the Cost Benefit Analysis (CBA) is entirely qualitative with no quantitative values assigned to the costs or benefits to the various stakeholders. The possible increased costs to caregivers of product with added lutein is a concern, particularly when the FAR states 'it could also allow for the importation of formula with added lutein, and be a cost advantage for companies to manufacture <u>one</u> formulation for worldwide distribution"***

FSANZ does not support the suggestion that the addition of lutein to infant formula products would place an unreasonable or additional cost burden on industry or consumers. The addition of lutein to infant formula products would be a voluntary, not mandatory permission so both manufacturers and consumers could choose to manufacture or purchase respectively products with added lutein.

The Applicant has advised FSANZ that only 'Gold' (premium) infant formula products (both liquid and powder) would contain lutein at this time, as part of their existing premium category of infant formula products. As it is not planned to add lutein to standard formula, a choice of product and price would continue to be available to caregivers. FSANZ is unaware if this would also be the case if other manufacturers of infant formula products took up the voluntary permission.

The Gold range of products currently sells at a higher price than standard formula. However the Applicant has indicated, that based on the information available to date, they do not anticipate a price increase due solely to the addition of lutein. They also note that price increases are reviewed regularly and in response to market conditions. The cost for any such products will be determined by market forces or the demand and supply for this category of products.

Moreover if the addition of lutein harmonises local production with the applicant's export and international products then there may be economies of scale for industry as one formulation of formula with added lutein could be used for their worldwide market. Manufacturing savings could potentially be passed on to the consumers, and consumers would continue to have the benefit of a choice of products available.

6.5 Costs associated with enforcement

The Review request states that ***FSANZ is requested to provide advice on how costs associated with the enforcement by jurisdictions were determined and how these costs were agreed upon in regard to this Application.***

Qualitative assessment suggests that amending Standard 2.9.1 to permit the voluntary addition of lutein in infant formula products as proposed would not have a major impact on Government. However, during the public consultation period, no quantitative data regarding enforcement costs was provided in response to the assessment reports to allow FSANZ to determine the specific costs of enforcement.

The applicant has advised that lutein will be added to their Gold category of products only and not to their standard products. Therefore compliance costs would only apply to this limited range of products.

As this is a voluntary permission the extent of addition by manufacturers will be limited to products only when it is commercially viable. However the potential uptake of the voluntary permission by other manufacturers is unknown.

FSANZ understands that there are existing measures for monitoring compliance of infant formula products in place and that these measures could be supplemented (e.g. through additional questions or inspection of documentation) in relation to lutein, so limiting additional enforcement costs.

In light of the above circumstances, and in the absence of further information, FSANZ understands that there would be no significant additional costs for enforcement in regard to addition of lutein in infant formula products as proposed at First Review.

FSANZ consulted the Office of Best Practice Regulation (OBPR) during Final Assessment of the Application. The OBPR plays a central role in promoting the Council of Australian Government's objective of improving the effectiveness and efficiency of regulation. Their advice concurred with FSANZ's assessment that the proposed changes are of a machinery of government nature and do not substantially alter existing arrangements. OBPR advised that no further regulatory impact assessment was required.

FSANZ has also advised the OBPR of the Review of this Application and the revised levels of lutein proposed. The OBPR have confirmed that their previous advice that a Regulation Impact Statement is not required still stands.

7. Proposed amendments to the draft variation

7.1 Lutein concentration permitted in infant formula products

7.1.1 Bioavailability

FSANZ has considered the concerns expressed in the First Review Request regarding the concentration of lutein being greater than lutein concentrations in breast milk, based on the apparent lower bioavailability of lutein in infant formula products compared with breast milk (see Section 6.1.7.3).

FSANZ's safety assessment reaffirms the conclusion at Final Assessment that the concentration proposed is unlikely to pose any safety concerns for formula-fed infants.

At Final Assessment, the proposed maximum and minimum concentrations were based on data provided by the Applicant which indicated a higher bioavailability of lutein from breast milk than from infant formula, with approximately a four-fold difference.

Section 6.1.7 outlines FSANZ's conclusions following a request for further information from the Applicant in relation to the bioavailability studies provided, and analysis of the submitted data. FSANZ concludes that the apparent difference in bioavailability is not supported by the additional data provided.

FSANZ considers the additional bioavailability data is not sufficiently robust as a basis upon which to formulate a regulatory decision.

Consequently, the relative bioavailability of lutein in infant formula products and breast milk has been assumed as equivalent at First Review (see Section 8).

FSANZ concludes it is appropriate to take a conservative approach at First Review and permit minimum and maximum lutein concentrations in infant formula products that are comparable to the range in breast milk (refer to Section 6.1.7.1).

7.1.2 Minimum and maximum levels of lutein

FSANZ is recommending a reduction in the maximum concentration of lutein permitted to be added to infant formula products from 9 µg /100 kJ (250 µg/L) proposed at Final Assessment to 5 µg /100 kJ (143 µg /L).

A reduction in the minimum concentration of lutein permitted to be added to infant formula products from 2µg/100 kJ (57 µg /L) to 1.5 µg / 100 kJ (43 µg /L) is also recommended.

In recommending this revised maximum concentration of lutein, FSANZ has considered the range (21.8 – 176.3 µg/L) of mean lutein concentrations in breast milk (see Section 6.1.7.1) and selected a manufacturing target of 100 µg/L, which sits approximately mid-way within the range of mean lutein concentrations in breast milk.

FSANZ has undertaken a statistical analysis of the recent data provided by the Applicant using the typical normal distribution of the initial lutein concentrations and a manufacturing target of 100 µg/L.

A minimum concentration of 48 µg/L (taking account of storage losses) at the end of shelf life and a maximum permitted concentration of lutein of 134 µg/L at the time of manufacture is expected at the 95% confidence limits. Both these limits are within the proposed regulatory limits (that is 43 µg/L and 143 µg/L). **Attachment 3** provides the calculations for information. As the regulatory limits are listed in the Code in units of µg/100 kJ, the figures have been rounded to the nearest half whole number and therefore the range is slightly larger than the range calculated above.

This analysis ensures that commercial product could comply with the proposed regulatory limits throughout product shelf life, taking into account storage losses. Also, this approach would result in an infant formula product at the end of shelf life with an average lutein concentration that remains within the range reported in breast milk to date, is biologically plausible and is unlikely to pose any safety concerns for formula-fed infants. The anticipated serum lutein concentrations in infants consuming infant formula product containing the revised maximum lutein concentration would be within the reported mean ranges for breast fed infants.

The requirement for a minimum concentration allows for the declaration on the label of the presence of lutein. The minimum amount of 2µg/100 kJ (57 µg /L) proposed at Final Assessment ensured that the lutein content in the fortified product was above the innate levels in infant formula products. The proposed lower concentration of 1.5µg/100 kJ (43 µg /L) still exceeds the innate amounts of lutein found in unfortified formula (see Section 6.1.2.2). The minimum requirement also ensures that the declaration of lutein occurs only when lutein is added to infant formula and therefore is not misleading for consumers. In addition, it is within the range of mean lutein concentrations found in breast milk.

8. Review Options

There are three options proposed for consideration under this Review:

1. re-affirm approval of the draft variation to Standard 2.9.1 as notified to the Ministerial Council; or

2. re-affirm approval of the draft variation to Standard 2.9.1, subject to any amendments FSANZ considers necessary; or

3. withdraw approval of the draft variation to Standard 2.9.1 as notified to the Ministerial Council.

9. Decision

FSANZ has considered the issues raised by the Ministerial Council in relation to Application A594 – Addition of Lutein as a Nutritive Substance to Infant Formula Products.

The First Review concludes that the preferred review option is Option 2.

This Option re-affirms the approval of the draft variation to Standard 2.9.1 of the Code subject to any amendments FSANZ considers necessary, as detailed in **Attachment 1**.

Decision

FSANZ re-affirms its approval of the draft variations to the *Australia New Zealand Food Standards Code* as notified to the Ministerial Council, subject to amendment (at Attachment 1).

This decision permits the voluntary addition of lutein to infant formula products because:

(a) lutein added to infant formula products is unlikely to represent a risk to formula-fed infants at the proposed maximum concentration; and

(b) based on the available evidence, the proposed concentration of lutein to be permitted will provide formula-fed infants with an infant formula product that has a concentration of lutein within the range found in breast milk.

FSANZ has made the following amendments to the draft variations:

(a) reduce the maximum concentration of lutein permitted to be added to infant formula products from the 9 µg /100 kJ (250 µg/L) proposed at Final Assessment to 5 µg /100 kJ (143 µg /L); and

(b) reduce the minimum concentration of 2µg/100 kJ (57 µg /L) proposed at Final Assessment to 1.5 µg/100 kJ (43 µg /L).

In making these amendments, FSANZ is reiterating its previous decision to permit the voluntary addition of lutein to infant formula products, on the basis of safety and nutritional equivalence with breast milk. However, since Final Assessment, additional data provided and further analysis undertaken does not support an apparent four-fold difference in bioavailability between breast milk and infant formula. Therefore, FSANZ has adopted a conservative approach and reduced the lutein concentrations, from those proposed at Final Assessment, to reflect concentrations well within the range found in breast milk.

Additionally, since Final Assessment, the European Food Safety Authority[35] (EFSA) has released a scientific opinion on the suitability of lutein in infant formula and follow-on formulae which supports FSANZ's conclusion and approach at First Review.

The EFSA opinion raised no safety concerns for lutein at a concentration of 250 µg/L proposed by the Applicant, but noted that a*lthough lutein bioavailability may be somewhat higher in breast milk than in formulae, the data presented do not allow a robust comparison.*

10. Implementation and review

The draft variation to Standard 2.9.1 will come into effect on the date of gazettal.

11. References

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Attachments

1. Draft variation to the *Australia New Zealand Food Standards Code*
2. Executive Summary and Statement of Reasons from the Final Assessment Report
3. Statistical calculations explaining the overage required

Attachment 1

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

Standards or variations to standards are considered to be legislative instruments for the purposes of the Legislative Instruments Act (2003) and are not subject to disallowance or sunsetting.

To commence: on gazettal

[1] ***Standard 2.9.1*** *of the Australia New Zealand Food Standards Code is varied by -*

[1.1] *omitting the column headings from the* Table to clause 7, *substituting –*

Column 1	**Column 2**	**Column 3**	**Column 4**
Nutritive substance	**Permitted forms**	**Minimum amount per 100 kJ**	**Maximum amount per 100 kJ**

[1.2] *inserting in the* Table to clause 7 –

Lutein	Lutein from *Tagetes erecta L.*	1.5 µg	5 µg

Attachment 2

Executive Summary and Statement of Reasons from the Final Assessment Report

Food Standards Australia New Zealand (FSANZ) received an Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006 seeking to amend the *Australia New Zealand Food Standards Code* (the Code), to permit the voluntary addition of lutein as a nutritive substance to infant formula products[36].

Specifically, the Applicant has requested permission to add lutein from marigold (*Tagetes erecta L.*) to infant formula[37,38] at a maximum concentration of 250 µg/L. The Applicant requests permission to add lutein to infant formula in amounts that would provide 'comparable levels' to breastfed infants.

Lutein is a plant pigment; it is a non-vitamin A carotenoid that cannot be synthesised by humans. Plant foods rich in lutein include dark green leafy vegetables, peas, carrots, corn, citrus fruits, avocado and broccoli. Lutein is also present in egg yolks, the fat of animals whose diets include lutein-rich plants and in human breast milk.

This Final Assessment Report discusses issues such as safety and nutritional equivalence with breast milk, including those issues raised in submissions, regarding this Application to permit the voluntary addition of lutein to infant formula. The approved draft variation to Standard 2.9.1 – Infant Formula Products is provided at Attachment 1.

Regulatory Approach

In the absence of Ministerial policy guidance FSANZ has adopted, in accordance with the section 18 objectives of the *Food Standards Australia New Zealand Act 1991*, the following approach to the assessment of this Application.

This assessment of whether lutein should be permitted as a voluntary nutritive substance in infant formula has considered:

- if lutein is present in breast milk;
- whether the requested concentration of lutein in infant formula (250 µg/L) is similar to the concentrations found in breast milk (accounting for bioavailability);
- if the proposed fortification achieves a similar physiological effect for formula-fed infants compared to breastfed infants (e.g. serum lutein concentrations); and

[36] 'Infant formula product', as defined in Standard 2.9.1 – Infant Formula Products, 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.
[37] For the purposes of this Report, use of the term 'infant formula' refers to both 'infant formula' and 'follow-on formula', which are defined in subclause 1(2) of Standard 2.9.1.
[38] A permission to add lutein would relate to all infant formula products. Infant formula and follow-on formula are a subset of this formulae product.

- the safety of lutein.

This approach recognises that the health effect of many substances in breast milk is not well understood.

The above approach does not require a benefit of lutein in the target population to be demonstrated. This is consistent with the approach historically taken with existing permissions for voluntary nutritive substances in Standard 2.9.1, for example nucleotides. Accordingly, the potential health benefit of lutein to the formula-fed infant has not been assessed in this Report.

Risk Assessment

At Final Assessment, the key risk assessment findings include:

- lutein is present in breast milk, with mean values ranging from 15-57 µg/L depending on maternal lutein intake;

- the ratio of lutein to zeaxanthin found in *Tagetes erecta L.* is within the range of ratios of lutein to zeaxanthin found in breast milk; noting considerable variability among individuals;

- lutein added to infant formula is unlikely to pose any safety concerns for formula-fed infants at the requested maximum concentration of 250 µg/L;

- lutein in breast milk is considerably more bioavailable than lutein added to infant formula, with evidence indicating a four-fold difference;

- the requested concentration of lutein to be added to infant formula would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found in breast milk; and

- some losses of lutein from both liquid 'ready-to-feed' and powdered infant formula products occur during storage.

The key risk assessment issues are discussed in section 8 of this Report. Full details of the risk assessment are found at Attachment 2 – Nutrition Assessment, Attachment 3 – Hazard Assessment, Attachment 4 – Dietary Intake Assessment and Attachment 5 – Food Technology Assessment.

Risk Management

This Final Assessment Report considers, in the context of the findings from the Risk Assessment, a number of issues relevant to permitting the addition of lutein to infant formula including:

- the appropriateness of the requested maximum concentration to be added to infant formula (250 µg/L), in relation to the concentration of lutein in breast milk and serum lutein concentrations, and safety;

- the minimum amount required for labelling declaration of lutein in infant formula; and
- the immediate and potential impacts of each regulatory option on affected parties.

Decision

To amend Standard 2.9.1 to permit the voluntary addition of lutein as a nutritive substance in infant formula products at a maximum concentration of 9 µg/100 kJ (250 µg/L) with a minimum declaration of 2 µg/100 kJ required for labelling purposes.

In addition, to make a minor consequential amendment to wording in the heading of column 3 in the Table to clause 7 of Standard 2.9.1 for clarification regarding labelling for nutrition declaration purposes.

Reasons for Decision

FSANZ has undertaken an assessment, using the best available evidence, of permitting the addition of lutein to infant formula, and recommends the draft variation to the Code as at Attachment 1 be approved for the following reasons:

- Lutein added to infant formula at a maximum concentration of 250 µg/L is unlikely to pose any safety concerns for formula-fed infants and would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found naturally in breast milk.
- The minimum level for declaration of lutein of 2 µg/100 kJ (57 µg/L) exceeds the innate amounts of lutein found in unfortified formula and equates to the lower mean concentration present in breast milk (accounting for bioavailability).
- The amendment to the Table to clause 7 would clarify that the minimum amount relates to the minimum amount required for labelling declaration purposes only.
- Overall, permitting the addition of lutein to infant formula will provide a net-benefit. Specifically, the decision will provide formula-fed infants with a source of lutein (a substance naturally present in breast milk), and potentially provide increased opportunities for international trade.

Consultation

During the assessment of this Application, two rounds of public consultation have been undertaken, as well as targeted consultation with representatives from the Australian State and Territories and New Zealand Governments.

FSANZ received 14 submissions in response to the Draft Assessment Report. Industry submitters, in general supported the Applicant's request to add lutein to infant formula, however, no Government submitters expressly supported this option.

A summary of submissions to the Draft Assessment Report is at Attachment 6. Key issues raised by submitters at Draft Assessment are addressed in this Report, either in the main report and/or in Attachment 7 – Response to Issues raised by Submitters at Draft Assessment.

At Final Assessment, FSANZ undertook additional targeted consultation with jurisdictions. This was to discuss and explain the rationale to the approach taken for the assessment of this Application, and our consideration of and response to issues they have raised.

Implementation and Review

Following consideration and approval of the draft variation to the Code by the FSANZ Board, notification of the Board's decision will be made to the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council). Subject to any request from the Ministerial Council for a review, the amendments to the Code with respect to Standard 2.9.1 will come into effect upon gazettal.

Attachment 3

Statistical calculations explaining the overage required

In explaining the range of lutein concentrations expected, the Applicant performed a natural log transformed analysis of their initial lutein concentrations. However, FSANZ does not believe such an analysis is required so used the typical normal distribution statistical analysis which yielded similar results to those provided by the Applicant.

The following calculation explains the derivation of the maximum (143 µg/L, equivalent to 5 µg/100 kJ) and minimum (43 µg/L, equivalent to 1.5 µg/100 kJ) that FSANZ determined should be regulated for the lutein concentration in infant formula products as determined in section 7.

Although the provision in Standard 2.9.1 is expressed as µg/100 kJ, the explanation is given using µg/L to avoid the need to use decimals. The following calculations are based on a manufacturing target of 100 µg/L to yield a range based on a maximum in fresh product on the shelf to a minimum after losses on storage.

The mean of the normal distribution of the finished final product is 100 µg/L, and the coefficient of variation is 17% (as provided by the Applicant from the analysis of their production results), giving the standard deviation of 0.17 µg/L. The minimum at manufacture is the mean minus 2 times the standard deviation that is approximately 66 µg/L. At a confidence level of 95.4% the initial concentration of lutein is between 66 and 134 µg/L, for a dosing target of 100 µg/L. Allowing for losses of 28% due to storage losses, 95% of the product would contain lutein between 48 and 96 µg/L at the end of shelf life. Also the maximum lutein content when product is first put on the shelf would be 134 µg/L at 95% confidence limit.

These calculations indicate that it would be expected that the Applicant would be able to commercially produce product that would always contain lutein within these regulatory limits when purchased.

It would be up to the manufacturer to decide what lutein concentration they would initially target to ensure all commercial product should always be within the regulatory limits.