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

6-07
3 October 2007

DRAFT ASSESSMENT REPORT

APPLICATION A594

ADDITION OF LUTEIN AS A NUTRITIVE SUBSTANCE TO INFANT & FOLLOW-ON FORMULA

DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 14 November 2007
SUBMISSIONS RECEIVED AFTER THIS DEADLINE WILL NOT BE CONSIDERED
(See 'Invitation for Public Submissions' for details)

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

EXECUTIVE SUMMARY

Food Standards Australia New Zealand (FSANZ) received a paid Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006. The Applicant has requested an amendment to the *Australia New Zealand Food Standards Code* (the Code), specifically to Clause 7 of Standard 2.9.1 – Infant Formula Products, to permit the optional addition of lutein as a nutritive substance to infant and follow-on formula.

Lutein is a plant pigment; it is a non-vitamin A carotenoid that cannot be synthesised by humans. The source of lutein in this Application is from the petals of marigold flowers (*Tagetes erecta* L) which also contain zeaxanthin, structurally a similar molecule to lutein. Plant foods rich in lutein include dark green leafy vegetables, 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. Mean lutein and zeaxanthin breast milk concentrations of women in nine countries ranged between 15 and 44 µg/L. The Applicant has requested maximum lutein concentrations of 250 and 500 µg/L in infant and follow-on formula, respectively. At these proposed levels of addition for a 3 month old infant solely fed infant formula and a 9-month old infant fed solids and follow-on formula respectively, the estimated mean intakes of lutein and zeaxanthin are 2% and 3% of the acceptable daily intake (ADI), and at the 95th percentile intake, 4% and 8% of the ADI.

In humans, lutein accumulates in the eye, specifically in an area termed the macula where it is a component of macula pigment. Lutein has proposed protective functions in the eye as an antioxidant and blue light filter. Initially, breast fed infants receive lutein in relatively high concentrations from colostrum of up to 200 µg/L and thereafter at the lower concentrations found in mature breast milk. Infant formula currently in use in Australia and New Zealand are virtually devoid of lutein. Using lutein in serum as a marker of lutein status, serum lutein increases postpartum in breast fed infants, and declines postpartum in formula-fed infants. In a trial conducted by the Applicant, it was found that infants fed formula containing sufficient lutein can achieve similar serum lutein concentrations as infants fed breast milk from mothers who regularly consume lutein-rich foods.

Preferred Approach

At Draft Assessment, the preferred regulatory approach for Application A594 is to 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.

•

FSANZ concludes that the preferred approach provides a net benefit to affected parties because it:

- does not pose any public health and safety risk to formula-fed infants;
- provides formula-fed infants and their carers with the potential to access a substance present in breast-milk, currently not available in formula in Australia and New Zealand; and

- has the potential to increase consistency with international practice and trade with those countries reported to have or pending approval of lutein enriched infant formula available on the market.

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

Consultation

At Initial Assessment, Application A594 was considered together with Application A597. Application A597 sought an amendment to the Code to permit the optional addition of lutein from marigold (*Tagetes erecta* L) as a nutritive substance in Formulated Supplementary Food for Young Children (FSFYC).

As the two Applications were jointly assessed, submitter feedback was not always specific to each individual Application. The Summary of Submissions (Attachment 6) includes comments in relation to both Applications, however any comments specific to A597 have not been considered in the body of this Draft Assessment Report.

FSANZ received 10 submissions in May 2007 in response to the Initial Assessment Report of Application A594 (and A597).

Overall, five of the 10 submitters did not indicate a preferred option, with several recommending that further assessment of safety and efficacy was required. Two submitters considered assessment should be delayed until ministerial policy guideline on the addition of substances other than vitamins and minerals (currently under development) is completed. The majority of industry submitters (including the Applicant) supported approving the addition of lutein, one noting that such support was contingent on a satisfactory safety assessment by FSANZ. Two submitters supported the *status quo* considering there was insufficient evidence at Initial Assessment to support an amendment to the Code as proposed. All the key issues raised during the stakeholder consultation are addressed in the main body of this Report.

CONTENTS

INVITATION FOR PUBLIC SUBMISSIONS

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

Written submissions are invited from interested individuals and organisations to assist FSANZ in preparing the Final Assessment of this Application. Submissions should, where possible, address the objectives of FSANZ as set out in section 18 of the FSANZ Act. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant studies, research findings, trials, surveys etc. Technical information should be in sufficient detail to allow independent scientific assessment.

The processes of FSANZ are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of FSANZ and made available for inspection. If you wish any information contained in a submission to remain confidential to FSANZ, you should clearly identify the sensitive information and provide justification for treating it as commercial-in-confidence. Section 114 of the FSANZ Act requires FSANZ to treat in-confidence, trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

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

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

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

Submissions need to be received by FSANZ by 6pm (Canberra time) 14 November 2007.

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

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

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

INTRODUCTION

Food Standards Australia New Zealand (FSANZ) received a paid Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006. The Applicant has requested an amendment to the *Australia New Zealand Food Standards Code* (the Code), specifically to Clause 7 of Standard 2.9.1 – Infant Formula Products, to permit the optional addition of lutein as a nutritive substance to infant and follow-on formula. This Draft Assessment Report discusses issues with the proposed amendment and seeks comment from stakeholders particularly in relation to expected regulatory impact(s), to assist FSANZ in making an assessment of this Application.

1. Nature of the Application

1.1 Basis of the Application

The Applicant has requested lutein be permitted as an optional nutritive substance for inclusion in the Table to clause 7 of Standard 2.9.1 with a maximum concentration of 250 µg/L (9 µg/100 kJ) in infant formula and 500 µg/L (18 µg/100 kJ) in follow-on formula. The Applicant proposes that lutein should be permitted to be added to infant and follow-on formula for the following reasons:

- lutein is naturally present in food and breast milk;
- lutein is not currently added to infant formula and follow-on formula;
- breast-fed infants have more lutein in their serum and eyes compared with
- formula-fed infants;
- lutein has potential eye health benefits to infant and young children; and
- there are potential later life effects of early lutein intake.

The Applicant requests permission to add lutein to infant formula in amounts that would provide 'comparable levels' to breast-fed infants, taking account of bioavailability and product stability factors. Current formulations of infant formula and follow-on 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 breast-fed infants. The Applicant also requests to fortify follow-on formula with lutein at a concentration that will provide a modest yet significant amount of lutein in the diet of older infants and young children, whose diets do not reliably contain dietary lutein.

The Applicant advised that lutein is approved for use in listed medicines by the Therapeutic Goods Administration (TGA) in Australia.

1.2 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 9:1.

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

1.3 Scope of Application

This Application pertains to the voluntary addition of lutein to infant formula products, principally infant formula and follow-on formula, but does not specifically pertain to 'infant formulas for special dietary use' (e.g. formulas for premature infants and/or those with specific medical conditions). However, Clauses 25 and 27(1) 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.

This Application excludes 'formulated supplementary foods for young children'[1]. A separate Application A597 has been made seeking permission to add lutein to these products.

Application A594 pertains to infant formula and follow-on formula. Infant formula and follow-on formula are defined in Standard 2.9.1 as follows:

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 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.

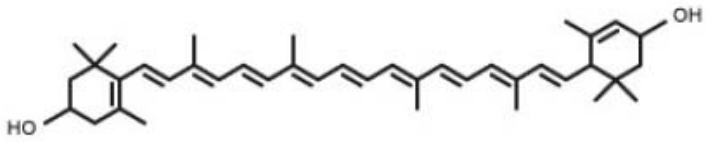
2. Background

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 synthesize 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*[2] or other dietary recommendations. Lutein and zeaxanthin contain oxygen and are referred to as xanthophyll carotenoids.

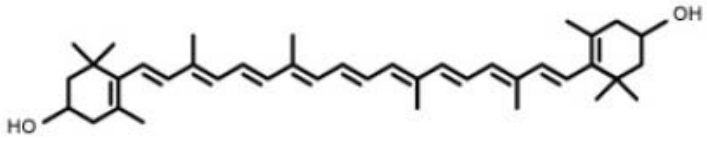
Good sources of lutein include eggs, carrots, corn, citrus fruits, avocado, broccoli and dark green leafy vegetables such as spinach. Lutein is also a food colouring agent (INS 161b) although it is not permitted to be added to infant formula products in Australia and New Zealand. Carotenoids are present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

[1] a formulated supplementary food for children aged one to three years e.g. toddler formula.
[2] This document is available online at http://www.nhmrc.gov.au/publications/synopses/n35syn.htm.

The chemical formula of lutein and zeaxanthin is $C_{40}H_{56}O_2$ and the structures are shown below. In the 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'.



Lutein



Zeaxanthin

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 (AMD).

2.1 Current Regulations

2.1.1 Domestic Regulations

2.1.1.1 Food Standards

Standards in the Code relevant to Application A594 include:

- Standard 1.1.1 – Preliminary Provisions, Division 1, clause 2 defines a nutritive substance to mean *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.*

  Division 2, clause 9 notes nutritive substances must not be added to food unless expressly permitted in the Code.

- Standard 2.9.1 – Infant Formula Products regulates the compositional and labelling requirements for infant formula products[3,4]. Division 1, clause 7 lists the permitted nutritive substances that may be voluntarily added to infant formula, the form(s) in which they may be added, the minimum amount per 100 kJ for a claim (within the meaning of 'claim' in Standard 1.1.1) 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.

- 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.

2.1.1.2 Therapeutic Goods, 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[5].

Preparations of *Tagetes erecta* that meet the definition of a herbal substance in Regulation 2 of the *Therapeutic Goods Regulations 1991* are approved for use in listed medicines[6].

2.1.1.3 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[7].

2.1.1.4 Dietary Supplements Regulations, New Zealand

The New Zealand *Dietary Supplements Regulations 1985* currently regulate food-type and therapeutic-type dietary supplements in New Zealand. As a substance normally derived from food, lutein products are permitted to be sold as nutritive supplements under the current Dietary Supplements Regulations, with products currently available on the market.

The New Zealand Food Safety Authority (NZFSA) is currently reviewing the Dietary Supplement Regulations. A discussion document released in February 2007[8] 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.

[3] Infant formula product (as defined in Standard 2.9.1) means a product based on milk or other edible food constituents of animal or plant origin which is nutritionally adequate to serve as the principal liquid source of nourishment for infants.
[4] 'Infant formula products' refers to all food regulated by Standard 2.9.1. Infant formula and follow-on formula are a subset of this formulae product.
[5] Substances that may be used in Listed medicines in Australia www.tga.gov.au/cm/listsubs.htm. Accessed 26 February 2007.
[6] Personal communication, Michele McLaughlin, Therapeutic Goods Administration, Australia, 14 March 2007
[7] Personal communication Carol Smith, Medsafe, Ministry of Health, New Zealand, 15 March 2007.
[8] New Zealand Food Safety Authority, discussion paper *Proposed Changes to the Regulation of Dietary Supplements,* Feb 2007.

2.1.2 Overseas and International Regulations

2.1.2.1 Codex Alimentarius

The recently adopted revised Codex Standard for Infant Formula[9] 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*. 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.*

2.1.2.2 United States of America (USA)

Since Initial Assessment, a generally recognised as safe (GRAS) notification for FloraGLO® Lutein 20 % Liquid in Safflower Oil has been submitted to the United States Food and Drug Administration (FDA)[10]. An Expert Panel evaluated the safety of FloraGLO® Lutein 20 % Liquid in Safflower Oil for use in infant formulas for infants from birth to 12 months and concluded it is GRAS under the intended conditions of use and the FDA's official ruling is pending. The Expert Panel concluded that if lutein is added to infant formulas from this source, the total lutein content in the finished infant formula product should not exceed 250 μg/L[11].

FloraGLO® Lutein has also received GRAS status for use as a food ingredient in specified categories of foods and beverages including infant foods and toddler foods[12].

2.1.2.3 European Union

Lutein is not currently permitted to be added to infant formula in the European Union. However, the Applicant states that an application for approval of lutein as an ingredient in infant formula is pending.

2.1.2.4 Other countries

Approval to add lutein (FloraGLO Lutein 20% Liquid in Safflower Oil) to infant formula, follow-on formula and toddler formula reportedly has been gained in the Peoples Republic of China, Indonesia, Malaysia, Kuwait, Colombia and the Philippines. Similar permissions are thought to exist in Mexico, United Arab Emirates and Hong Kong where infant formula with added lutein is currently sold.

[9] 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.
[10] GRAS Notice: GRN No. 221. Available at: http://www.cfsan.fda.gov/~rdb/opa-gras.html
[11] RM Russell, IC Munro, R Walker, SS Baker. Expert Panel Opinion Regarding the Generally Recognised as Safe Status of FloraGLO Lutein 20% Liquid in Safflower Oil for Use in Infant Formula. 21 March 2007.
[12] FDA decision for GRAS Notice: GRN No. 140. Available at: http://www.cfsan.fda.gov/~rdb/opa-g140.html

2.2 Permitted Use as a Food Colour

FSANZ is aware that lutein is permitted for use as a food colour in several international regulations but not for addition to infant formula, for example as stated in the European Council Directives[13].

2.3 Ministerial Policy Guidelines

FSANZ must have regard to any written policy guidelines formulated by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) when developing and varying food standards (see Section 4). The Ministerial Council is currently developing a policy guideline on the addition of substances other than vitamins and minerals to foods. It is unclear at this stage whether this policy guideline will apply to special purpose foods, such as infant formula products. There is no indicative timeframe for completion of this policy guideline.

2.4 Current Market

2.4.1. Domestic Market

Four major brands of infant and follow-on 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.

2.4.2 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.

Since Initial Assessment there are indications that there has been an increase in availability of infant formula containing lutein on the international market, namely in those countries noted above (see Section 2.1.2.).

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 formula contain lutein at levels similar to those proposed in this Application [14].

---

[13] 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.

[14] 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.

3. The Issue

Formatted: Bullets and Numbering

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 of the Code as a permitted nutritive substance.

4. Objectives

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives that are set out in section 18 of the FSANZ Act. These are:

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

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

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

5. Lutein as a Nutritive Substance

The Applicant has requested permission for addition of lutein to infant formula products as a nutritive substance. Nutritive substance is defined in Standard 1.1.1 of the Code 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.

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.

RISK ASSESSMENT

The following section summarises the nutrition and safety risk assessment and conclusions. The full details of the risk assessment can be found at Attachments 2, 3 and 4.

6. Risk Assessment Questions

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

1. Is lutein found in breast milk and if so, how do the concentrations in breast milk compare with those proposed for infant and follow-on formula?

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

   (a) unfortified formula?
   (b) formula fortified at the proposed concentrations?

3. Are there any risks to infants from consuming infant and follow-on formula containing lutein derived from marigold flowers at the requested concentrations?

Formatted: Bullets and Numbering

7. Risk Assessment Summary

Lutein is present in colostrum and mature human milk. During the first few days postpartum, the breast-fed infant receives a relatively high dose of lutein which is present in colostrum at concentrations several-fold greater than the concentrations found in mature breast milk. The concentration of lutein in mature human milk is variable, reflecting maternal dietary intake.

In a multinational study in which the concentrations of lutein and zeaxanthin were determined in breast milk of women living in nine countries, a group of Australian women had a concentration of 15 µg/L (Canfield et al., 2003). This value was at the lower end of the range and comparable to the lutein and zeaxanthin breast milk concentrations of women in the United States, Canada and the United Kingdom. Groups of women in China and Japan had the highest lutein and zeaxanthin concentrations in their breast milk, with mean values of approximately 44 µg/L. These values are not necessarily representative of the lutein and zeaxanthin concentration in the breast milk of women in these countries because they were taken from convenience samples of women who consumed at least 3 serves of fruit and vegetables per day. There are no population representative data that characterises the breast milk concentration of lutein in New Zealand and Australian women.

The concentrations of lutein being sought of 250 and 500 µg/L in infant and follow-on formula respectively are greater than the amounts contained in human milk. However, the bioavailability of added lutein appears to be poor and similar serum concentrations of lutein have been found in breast-fed infants from mothers having regular intakes of good dietary sources of lutein and in infants receiving formula fortified with lutein at a concentration of 250 µg/L. There is 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 nutritional implication to formula-fed infants of a lutein interaction with β-carotene is unclear because although carotenes provide a source of vitamin A precursors, industry routinely uses pre-formed vitamin A to meet the vitamin A compositional requirements for infant and follow-on formula (IFMAA, personal communication).

Lutein is proposed to function in the eye as an antioxidant and a blue light filter. An antioxidant function for lutein in the eye is indicated by *in-vitro* findings that lutein protects against photo-oxidation of photoreceptor components. The infant's eye is thought to be particularly vulnerable to blue light damage due to the greater transparency of the lens compared with older eyes. There is evidence suggestive of a blue light filtering role for lutein. Preliminary data are suggestive that the eyes of infants receiving formula unfortified with lutein are more likely to lack macular pigment than breast-fed infants (Neuringer et al, 2006). A prolonged absence of lutein and zeaxanthin has been associated with potentially detrimental changes to the eyes of primates (Rhesus monkeys) (Neuringer et al, 2003).

Lutein is a normal dietary constituent and FSANZ concludes that lutein is well tolerated and found not to have adverse effects in animal or human studies at doses up to 1000 mg/kg body weight per day. An Acceptable Daily Intake (ADI) has been established at 2 mg/kg body weight per day. The dietary exposure assessment indicated that the intake of lutein and zeaxanthin from infant and follow-on formula is well below the ADI. At the extrapolated 95th percentile intake of lutein and zeaxanthin, 3-month old infants were estimated to consume 0.09 mg/kg body weight (or 4% of the ADI) and the intake of 9-month olds was estimated to be 0.2 mg/kg body weight (or 8% of the ADI).

The data support the safety of lutein at the level of intake that would be achieved by addition to infant formula and follow-on formula at maximum concentrations of 250 µg/L and 500 µg/L, respectively. FSANZ concludes that there are no public health and safety concerns for lutein when added as a nutritive substance to infant formula and follow-on formula at the maximum levels proposed by the Applicant.

Infant formula fortified with lutein at the requested concentration of 250 µg/L will provide formula-fed infants with the opportunity to achieve serum lutein concentrations equivalent to those found in the serum of breast-fed infants whose mothers regularly consume foods rich in lutein.

The dietary intake assessment suggests that on average, older infants fed lutein in follow-on formula would double their total lutein intake by consuming about the same amount of lutein from follow-on formula as they would receive from weaning foods.

8. Food Technology

The food technology aspects of lutein used as a nutritive substance to be added to infant formula and follow-on formula have been assessed. Lutein is not being considered for an extension of use as a food additive, where it can act as a permitted colour, since its proposed use is not for this purpose. 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 of the Code so a new specification is not required to be written.

The commercial lutein preparation that is subsequently added to food is produced in vegetable oil with approved food additives; antioxidants and emulsifiers. Stability results indicate that losses of up to 40% occur after 12 months storage at ambient temperature (27°C) when the lutein preparation is added to liquid (ready-to-feed) infant formula products. For powdered infant formula products, the losses were less after 6 months at ambient temperature, with the largest being 16%. The Food Technology Report is provided at Attachment 5.

RISK MANAGEMENT

At Draft Assessment, potential risk management issues have been identified and considered along with submitter comments received during the public consultation period.

9.1 Protection of Public Health and Safety

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

FSANZ's risk assessment has examined substantial evidence from the Applicant and other sources on the role and function of lutein in the infant as well as assessed the safety of the proposed addition of lutein to infant formula and follow-on formulas when consumed by young and older infants respectively. It concludes that there are no safety concerns for lutein when added as a nutritive substance to infant formula and follow-on formula at the maximum levels proposed, as estimated intakes of lutein and zeaxanthin are below the internationally established ADI (see Section 7).

The Applicant is seeking permissions for the addition of lutein at a maximum concentration greater than that contained in human milk.

This is considered appropriate since, based on infant serum lutein data, it appears that a higher concentration of lutein is required in infant formula to give serum concentrations in formula-fed infants comparable to those of breast fed infants of women who consume foods rich in lutein, such as dark green vegetables.

FSANZ's assessment also indicates that the specification of the lutein extract proposed is consistent with the recent JECFA specification (2004). JECFA specifications are a primary source of specifications in Standard 1.3.4 – Identity and Purity.

Therefore FSANZ proposes that lutein be permitted as an optional nutritive substance for addition to infant and follow-on formula in the permitted form described as Lutein from *Tagetes erecta L* 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, as proposed by the Applicant.

QUESTION:
Do you support setting a maximum amount of lutein in infant formula that could achieve serum lutein levels comparable with those of breast-fed infants whose mothers regularly consume lutein-rich vegetables?

9.2 Labelling Including Nutrition, Health and Related Claims

Specific labelling and packaging requirements for infant formula products, covering both infant formula and follow-on formula, are prescribed in Standard 2.9.1 of the Code. 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, i.e. to be declared only in the nutrition information table.

9.2.1 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 optional nutritive substances currently permitted in infant formula are specified in Column 3 of the Table to clause 7. FSANZ has proposed a minimum level of 2 µg/100 kJ (56 µg/L) on the same basis as previously decided during the development and review of Standard 2.9.1 (Proposal P93) i.e. that it exceeds the innate amounts in the unfortified formula and the level is present in breast milk.

9.2.2 Nutrition, health and related claims

Clause 20 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 and infant formula products for specific conditions).

Division 3 of Standard 2.9.1 (Infant Formula Products for Special Dietary Use) sets additional labelling requirements for infant formula products suitable for infants with metabolic, immunological, renal, hepatic or malabsorptive conditions (clause 28), and also for lactose free and low lactose formulas (clause 30).

FSANZ is currently considering new regulations around nutrition, health and related claims under Proposal P293, which will be contained within Standard 1.2.7. It is proposed that the current status in relation to infant formula products be maintained, with these products specifically noted as ineligible for claims under the draft Standard 1.2.7.

If lutein is permitted to be added to infant formula products, the general prohibition on nutrition, health and related claims for nutrients and nutritive substances in infant formula products that is currently in place under Standard 2.9.1, with the exceptions noted above under clauses 28 and 30, and proposed to be maintained under draft Standard 1.2.7, would apply.

9.3 Novel Foods and the Status of Lutein

One submitter raised the concern that lutein should be considered a novel food. However, as this Application is seeking the addition of lutein in infant and follow-on formula as a permitted nutritive substance, the issue of whether or not lutein is a novel food has not been addressed in this Application. The purpose of the Novel Foods Standard is to ensure that a pre-market safety assessment is conducted for novel foods before they can be sold in Australia or New Zealand. A pre-market safety assessment has been undertaken for lutein and is presented here in this Report, achieving the same level of assurance of safety as would be required for novel foods.

9.4 Consideration of Nutritional Purpose and Benefit

A number of submitters noted there was a need to consider the nutritional purpose and assess the potential benefit of permitting the addition of lutein to infant formula and follow-on formula. Section 5 of this Report outlines consideration of lutein as a nutritive substance including identifying a nutritional purpose.

FSANZ has reviewed and described the literature in relation to potential health benefit, and noted that permitting the optional addition of lutein to infant formula would provide formula-fed infants with the potential to achieve serum lutein levels comparable to breast-fed infants of women who regularly consume foods rich in lutein. This approach is consistent with existing permissions of other optional nutritive substances such as nucleotides, where the intention is to allow substances to be added where they are normally present in breast milk, where there is no evidence of toxicity or adverse interactions and when available data suggests a physiological rationale for addition.

10. Regulatory Options

At Draft Assessment FSANZ is considering two regulatory options for Application A594:

- Option 1 – maintain *status quo* by not amending the Code to permit the addition of lutein as an optional nutritive substance in infant formula and follow-on formula; and

- 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.

11. Impact Analysis

11.1 Affected Parties

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

11.2 Cost-Benefit Analysis

This analysis provides an assessment of the potential impacts of the regulatory options for Application A594 on the affected parties.

11.2.1 *Option 1- Status quo*

11.2.1.1.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 or follow-on formula currently available in Australia or New Zealand contains little or no lutein. This does not provide an opportunity for formula-fed infants to receive the substance, lutein that is naturally present in breast milk.

11.2.1.2 Industry

There are no additional benefits for industry in maintaining the *status quo.* However the reported 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 could limit potential opportunities to import infant formula containing lutein and also limit the ability to manufacture one formulation for both domestic and export markets.

11.2.1.3 Government

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

11.2.2 Option 2 – Amend Standard 2.9.1

11.2.2.1 Consumers

Permitting the addition of lutein to infant formula would provide formula-fed infants with an additional source of lutein in their diet. The addition of lutein at the levels proposed would provide a safe source of lutein for formula-fed infants.

It is unknown what additional manufacturing costs would result in the production of infant formula with added lutein and what, if any, costs could be passed on to the caregivers who choose to purchase these products.

11.2.2.2 Industry

Option 2 would allow industry to produce a new product consistent with international development for the Australian and New Zealand markets, and potentially, 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 to the countries where the addition of lutein is now approved enabling manufacturers to compete on the international market. It could also allow for the importation of formula containing lutein, and be a cost advantage for companies to manufacture one formulation for worldwide distribution.

While it is likely there would be a cost to manufacturers to add lutein to infant formula, it is unknown as to whether these costs would be passed on to consumers at the point of sale.

11.2.2.3 Government

It is expected that Option 2 would have minimal impact on government.

11.3 Comparison of Options

A comparison of the Options presented at Draft Assessment indicates that maintaining both the status quo (Option 1) and Option 2 would continue to protect the health and safety of formula-fed infants. However, evidence indicates that the addition of lutein in the form and at the levels 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 that is not currently available in infant or follow-on 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 Draft Assessment a comparison of options suggests Option 2 provides greater net benefit to the affected parties.

COMMUNICATION AND CONSULTATION

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

12. Public Consultation

The Initial Assessment Report sought input on the likely regulatory impact of both Application A594 and Application A597 together over a six-week period from 4 April to 16 May 2007.

In response FSANZ received 10 submissions. As the two Applications were presented together, submitter feedback was not always specific to each individual Application. Submissions received for both applications are summarised in Attachment 6. However, any submitter comments that were specific to Application A597 have not been considered in this Draft Assessment of Application A594.

Overall five of the ten submitters did not provide a preferred option for Application A594 at Initial Assessment, several recommending that further assessment of safety and efficacy is needed. This included four of the five government submitters and the one public health submitter.

Two submitters recommended that assessment be delayed until the ministerial policy guidance on the addition of substances other than vitamins and minerals is completed.

Of those who did indicate a preferred option, a majority of industry submitters (including the Applicant) supported permitting the addition of lutein. However one supported this Option *provided safety and efficacy is scientifically demonstrated and contingent on satisfactory safety assessment by FSANZ.*

Overall, two submitters supported the status quo citing insufficient evidence and a need for evidence of health benefit to the target group.

All the key issues raised during the stakeholder consultation are addressed in the main body of this Report.

12.1 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.

Currently other relevant overseas regulatory agencies are considering the approval of lutein for addition to infant formula (EU and US FDA). It is also reported that approvals have been granted in some other countries (Section 2.1.2.4).

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

CONCLUSION

Preferred Approach

At Draft Assessment the preferred regulatory approach for Application A594 is an amendment to 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.

FSANZ concludes that the preferred approach provides a net benefit to affected parties because it:

- does not pose any public health and safety risk to formula-fed infants;
- provides formula-fed infants and their carers with the potential to access a substance present in breast-milk, currently not available in formula in Australia and New Zealand; and
- has the potential to increase consistency with international practice and trade with those countries reported to have or pending approval of lutein enriched infant formula available on the market.

13. Implementation and Review

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

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

Attachments

1. Draft Variation to the *Australia New Zealand Food Standards Code*
2. Nutrition Assessment
3. Risk Assessment
4. Dietary Intake Assessment
5. Food Technology Report
6. Summary of Submissions to the Initial Assessment Report of A594 and A597.

Attachment 1

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

Section 94 of the FSANZ Act provides that standards or variations to standards are legislative instruments, but 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 inserting in the* Table to clause 7–

Lutein	Lutein from *Tagetes erecta L.*	2 µg	9 µg for infant formula 18 µg for follow-on formula

Attachment 2

Nutrition Assessment

Executive Summary

Lutein is present in colostrum and mature human milk. During the first few days postpartum, the breast-fed infant receives a relatively high dose of lutein which is present in colostrum at concentrations several-fold greater than the concentrations found in mature breast milk. The concentration of lutein in mature human milk is variable, reflecting maternal dietary intake. A mean combined concentration of lutein and zeaxanthin found in a Japanese group was 44 µg/L whereas in a group of 53 Australian women it was 15 µg/L (Canfield et al, 2003). However, these values may not be representative of the lutein and zeaxanthin concentration in the breast milk of women in these countries because they were taken from convenience samples. There are no population representative data that characterises the breast milk concentration of lutein and zeaxanthin in New Zealand and Australian women.

The concentration being applied for is greater than that contained in human milk. A justification for requesting greater amounts is the apparently poor bioavailability of lutein contained in formula compared with human milk. The evidence base showing a difference in bioavailability is not ideal because there are no studies in which the serum lutein concentrations of breast-fed and lutein-fortified formula-fed infants have been directly compared. However, a difference in lutein bioavailability is indicated by comparing serum lutein concentrations of breast and formula fed infants between studies. For example, in a group of North American women consuming 6 serves of dark green vegetables per day, the mean concentration of lutein in breast milk was 57 µg/L and serum lutein concentration in their infants was 126 µg/L (Wyeth Nutrition, 2006a). By comparison, consumption of formula supplemented with lutein at 289 µg/L for 5-weeks by Philippino infants resulted in a mean infant serum lutein concentration of 143 µg/L (Wyeth Nutrition, 2006b). There are no serum lutein data for Australian or New Zealand breast-fed 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 and follow-on formula to contain pre-formed vitamin A.

Lutein is proposed to function in the eye as an antioxidant and a blue light filter. An antioxidant function for lutein in the eye is indicated by *in-vitro* findings that lutein protects against photo-oxidation of photoreceptor components into degradative products. Several lines of evidence are also suggestive of a filtering role for lutein against potentially damaging blue light. The infants eye is thought to be particularly vulnerable to blue light damage due to the greater transparency of the lens compared with older eyes. Preliminary data from a small pilot study are suggestive that the eyes of infants receiving formula unfortified with lutein and zeaxanthin are more likely to lack macular pigment than breast-fed infants (Neuringer et al, 2006). The prolonged absence of lutein and zeaxanthin has been associated with potentially detrimental changes to the eyes of primates (Rhesus monkeys) (Neuringer et al, 2003).

1. Introduction

Xanthophyll carotenoids are typically present in plant chloroplasts as long chain fatty acid esters. Lutein in FloraGlo 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 & Minguez-Mosqura , 2005) and based on a study by Schweigert et al., the Applicant contends that the predominant form of lutein in human milk is also unesterified (Schweigert et al. 2000).

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

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

2.1 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 obtained samples of breast milk from five Irish mothers from day one postpartum (Jewell et al, 2004). 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.

2.2 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 (16.7) and 16.2 (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, 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: Lutein and zeaxanthin concentrations in human milk (Canfield et al, 2003)

Country	N	Lutein and Zeaxanthin µmol/L ± SEM	Lutein and Zeaxanthin[1] 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] 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 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 in U.S. women (Canfield et al, 2003). 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.

3. Comparisons between breast-fed and formula-fed infants

3.1 Serum lutein and zeaxanthin concentration in breast-fed infants

A range of serum lutein and zeaxanthin combined concentrations shown in Table 2 have been found in groups of breast-fed 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 breast-fed 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 breast-fed infants by which to assess where in the range Australian and New Zealand infants might lie.

3.2 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 SMA formula was 17.9 (2.9) µg/L. In contrast, the serum lutein and zeaxanthin concentrations in breast-fed 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 randomized 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 (fortified with 47 µg/L), and 143.2 µg/L (fortified with 289 µg/L).

3.3 Macular pigment

A novel photographic technique suitable to measure macular pigment optical density in the eyes of infants has been developed (Neuringer et al, 2006).

In a pilot study, it was found that three of four breast fed infants aged 4-5 months had macular pigment, whereas macular pigment was absent in one of the infants. In formula-fed infants receiving formula without added lutein and zeaxanthin, macular pigment was absent in three of four infants. Over a period of several years, an absence of dietary lutein and zeaxanthin has been associated with detrimental effects to the eyes of Rhesus monkeys (Neuringer et al, 2003; Leung et al, 2004).

The data indicate that infants fed formula fortified with lutein and zeaxanthin at the lower concentration proposed in this Application (250 µg/L) had a mean serum lutein and zeaxanthin concentration comparable to that of North American breast-fed infants whose mothers were generally high consumers of lutein-rich foods. Plasma concentrations of lutein and zeaxanthin have been found to increase postpartum in breast-fed infants and to decline in infants fed formula devoid of lutein and zeaxanthin to concentrations below those at the low end of the breast-fed range. Preliminary data indicate that macular pigment is likely to be absent in the eyes of infants fed unfortified formula.

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

We are not aware of trials in which the relative bioavailability of lutein from human milk or formula has been directly tested. Data on human milk and infant serum lutein and zeaxanthin combined concentrations are available from cross-sectional analyses.

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

Reference	Human milk	Formula	Infant serum
Canfield, 2001	9		~50
Wyeth Nutrition, 2006a	57		126
Wyeth Nutrition, 2006b		20	17.3
Wyeth Nutrition, 2006b		47	30.2
Wyeth Nutrition, 2006b		289	143.2

The data suggest that the lutein and zeaxanthin concentration in formula milk needs to be considerably higher than the concentration in human milk to achieve comparable lutein concentrations in infant serum. Supplemental lutein has also been found to have lower bioavailability than an equivalent amount of lutein contained in egg yolks (Chung et al, 2004).

3.5 Interaction of lutein and zeaxanthin with other carotenoids

Data from a trial 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 β-carotene AUC 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 another trial were indicative of lutein and zeaxanthin interfering with the absorption of β-carotene because of decreases in both the area under the curves of β-carotene and retinyl palmitate. 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 randomized 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 natures of these interactions are not understood.

3.6 Antioxidant activity

Oxidative stress in the retina appears to promote the formation of degradation products that accumulate with age (Katz & 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 & 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).

3.7 Macular pigment optical density

A proposed role for lutein is as a blue light filter in the eye (Ahmed et al, 2005) and the Applicant proposes that blue light may pose a particular hazard to infants because of greater light transmission to the back of the eye in the younger compared with the older eye (Dillon et al, 2004). A filtering effect has been shown *in-vitro* using liposomes enclosing a fluorescent dye (Junghans et al, 2001). When lutein was incorporated into the lipophilic membrane, fluorescence emission was lower than in lutein-free controls when exposed to blue light, indicating a filter effect. In primates, foveal protection associated with macular lutein status has been found in rhesus monkeys (Barker et al, 2005). Photochemical damage caused by exposure to low-power laser energy was evident to the same degree in the foveal and parafoveal regions of monkeys fed lifelong xanthophyll-free diets.

In a control group of monkeys whose diets included xanthophyll carotenoids, there was a higher threshold to photochemical damage in the xanthophyll-rich area of the fovea compared with the parafovea. The authors attributed the protection to the presence of the carotenoids lutein and zeaxanthin.

These data are supportive of a role for lutein and zeaxanthin in providing a filter to potentially damaging blue light.

REFERENCES

Adelekan D, Northrop-Clewes CA, Owa J, Oyedeji A, Owoeye A, Thurnham DI. Use of biomarkers of sub-clinical infection, nutrition and neonatal maturity to interpret plasma retinol in Nigerian neonates. *Br J Nutr.* 2003;90:353-361.

Ahmed SS, Lott MN, Marcus DM. The macular xanthophylls. Surv Ophthalmol. 2005;50:183-93.

Ausich LA, Sanders DJ. Process for the formation, isolation and purification of comestible xanthophyll crystals from plants. US Patent Number 5,648,564 Issued on July 15, 1997.

Barker F, Neuringer M, Johnson E, Schalch W, Koepcke W, Snodderly DM. Dietary zeaxanthin or lutein improves foveal photo-protection from blue light in xanthophyll-free monkeys [abstract]. *Invest Ophthalmol Vis Sci.* 2005;46:E-abstract 1770.

Bone RA, Landrum JT, Guerra LH, Ruiz CA. Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. *J Nutr.* 2003;133(4):992-998.

Canfield L, Kaminsky R, Taren D, Shaw E, Sander J. Red palm oil in the maternal diet increases provitamin A carotenoids in breastmilk and serum of the mother-infant dyad. *Eur J Nutr.* 2001;40:30-38.

Canfield L, Clandinin M, Davies D, et al. Multinational study of major breast milk carotenoids of healthy mothers. *Eur J Nutr.* 2003;42(3):133-141.

Chung HY, Rasmussen HM, Johnson EJ. Lutein bioavailability is higher from lutein-enriched eggs than from supplements and spinach in men. J Nutr. 2004;134:1887-93.

Dancheck B, Nussenblatt V, Kumwenda N, et al. Status of carotenoids, vitamin A, and vitamin E in the mother-infant dyad and anthropometric status of infants in Malawi. *Journal of Health, Population & Nutrition.* 2005;23(4):343-350

Delori FC, Staurenghi G, Arend O, Dorey CK, Goger DG, Weiter JJ. In vivo measurement of lipofuscin in Stargardt's disease--Fundus flavimaculatus. Invest Ophthalmol Vis Sci. 1995;36:2327-31.

Dillon J, Zheng L, Merriam J, Gaillard E. Transmission of light to the aging human retina: possible implications for age related macular degeneration. *Exp Eye Res.* 2004;79:753-759.

Eldred GE, Lasky MR. Retinal age pigments generated by self-assembling lysosomotropic detergents. Nature. 1993;361:724-6

Feeney-Burns L, Hilderbrand E, Eldridge S. Aging human RPE: Morphometric analysis of macular, equitorial and peripheral cells. *Invest Ophthalmol Vis Sci.* 1984;25:195-200.

Gossage C, Deyhim M, Yamini S, Douglass L, Moser-Veillon P. Carotenoid composition of human milk during the first month postpartum and the response to b-carotene supplementation. *Am J Clin Nutr.* 2002;76:193-197.

Hogg RE, Anderson RS, Stevenson MR, Zlatkova MB, Chakravarthy U. In vivo macular pigment measurements: a comparison of resonance Raman spectroscopy and heterochromatic flicker photometry. Br J Ophthalmol. 2007;91:485-90.

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.

Johnson L, Norkus E, Abbasi S, Gerdes JS, Bhutani VK. Contribution of beta carotene (beta-C) enriched formulae to individual and total serum carotenoids in term infants. 104th Annual Meeting of the American Pediatric Society and the 63rd Annual Meeting of the Society for Pediatric Research 1994. Abstract 1869.

Junghans A, Sies H, Stahl W. Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. Arch Biochem Biophys. 2001;391:160-4.

Katz ML, Eldred GE, Robison WG Jr. Lipofuscin autofluorescence: evidence for vitamin A involvement in the retina. Mech Ageing Dev. 1987;39:81-90.

Katz ML, Robison WG Jr. What is lipofuscin? Defining characteristics and differentiation from other autofluorescent lysosomal storage bodies. Arch Gerontol Geriatr. 2002;34:169-84.

Mata NL, Weng J, Travis GH. Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration. Proc Natl Acad Sci U S A. 2000;97:7154-9.

Neuringer M, Wallace P, Bone R. Results summary of a pilot study for the measurement of macula pigment in infants' eyes; human milk-fed or formula-fed infants. Wyeth Nutrition, 2006, unpublished.

Kim S, Nakanishi K, Itagaki Y, Sparrow J. Photooxidation of A2-PE, a photoreceptor outer segment fluorophore, and protection by lutein and zeaxanthin. *Exp Eye Res.* 2006;82(5):828-839.

Kostic DS, White WS, Olson JA. Intestinal absorption, serum clearance, and interactions between lutein and B-carotene when administered to human adults in separate or combined oral doses. *Am J Clin Nutr*. 1995;62:604-610.

Leung IY, Sandstrom MM, Zucker CL, Neuringer M, Snodderly DM. Nutritional manipulation of primate retinas, II: effects of age, n-3 fatty acids, lutein, and zeaxanthin on retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 2004;45(9):3244-3256.

Micozzi MS, Brown ED, Edwards BK, Bieri JG, Taylor PR, Khachik F, Beecher GR, Smith JC Jr. Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. Am J Clin Nutr. 1992 Jun;55(6):1120-5.

Neuringer M, Wallace P, Billingslea A, Gold J, Weleber R. Incidence of drusen-like changes in a rhesus monkey colony: effects of age, gender and dietary carotenoids [abstract]. *Invest Ophthalmol Vis Sci.* 2003;44:E-abstract 4949.

Perez-Galvez A, Minguez-Mosqura MI. Esterification of xanthophylls and its effect on chemical behaviour and bioavailability of carotenoids in the human. *Nutr. Res. 2005;25:631-40*.

Rapp L, Maple S, Choi J. Lutein and zeaxanthin concentrations in rod outer segment membranes from perifoveal and peripheral human retina. *Invest Ophthalmol Vis Sci.* 2000;41:1200-1209.

Schweigert FJ, Hurtienne A, Bathe K. Improved extraction procedure for carotenoids from human milk. *Int J Vitam Nutr Res.* 2000;70:79-83.

Schweigert FJ, Bathe K, Chen F, Buscher U, Dudenhausen J. Effect of the stage of lactation in humans on carotenoid levels in milk, blood plasma and plasma lipoprotein fractions. *Eur J Nutr.* 2004;43:39-44.

Taylor HR, Keeffe JE, Vu HTV, Wang JJ, Rochtchina E, Pezzullo ML and Mitchell P. Vision loss in Australia. *Med J Aust*. 2005;182: 565–568

van den Berg H, van Vliet T. Effect of simultaneous, single oral doses of beta-carotene with lutein or lycopene on the beta-carotene and retinyl ester responses in the triacylglycerol-rich lipoprotein fraction of men. *Am J Clin Nutr.* 1998;68(1):82-89.

van den Berg H. Carotenoid interactions. *Nutr. Rev.* 1999;57:1-10.

Wing G, Blanchard G, Weiter J. The topography and age relationship of lipofuscin concentration in the retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 1978;17(7):601-607.

Wyeth Nutrition. Sub-analysis of lutein results: Effects of infant formula supplementation with beta-carotene and other carotenoids compared to breast-fed infants. 1994.

Wyeth Nutrition. Analysis of the lutein concentrations in infant plasma and expressed human milk – Clinical Study Report 9041A1-904, 2006a.

Wyeth Nutrition. Effect of lutein in S-26 Gold on infant plasma lutein concentration – Clinical Study Report 9041A1-903, 2006b.

Attachment 3

Risk Assessment

Executive Summary

This Application seeks permission for lutein to be added to infant formula, intended for infants from birth to twelve months, to give a final level of lutein in the ready-to-drink formula of 250 µg/L. Addition of lutein to follow-on formula, intended for infants 6 – 12 months is also requested, to give a final concentration of lutein at 500 µg/L.

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*) 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. 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 submitted as part of this Application.

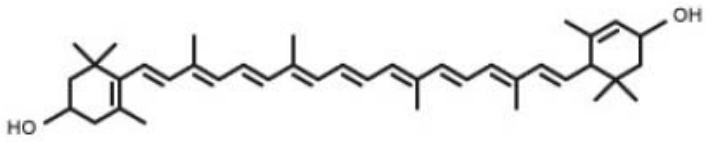
JECFA evaluated this lutein and zeaxanthin preparation at its 63rd meeting (in 2004) and established an Acceptable Daily Intake (ADI) of 2 mg/kg bw per day. This was based on the highest dose tested in a ninety day repeat dose toxicity study in rats and includes a safety factor of 100. The ADI set by 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. In addition to the clinical trial in human infants, the database included a developmental toxicity study in rats and a 52-week toxicity study in non-human primates which also indicated no adverse effects at the highest doses tested (up to 1000 mg/kg bw/day in the developmental toxicity study). FSANZ considers that lutein in infant formula at the levels which are proposed in this Application does not represent a risk to young infants.

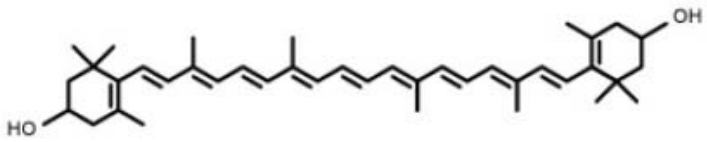
Background

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*) 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.

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 crustacea, 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.

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.

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.

<u>Aims of the current assessment</u>

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.

SUMMARY OF SUPPLEMENTARY DATA

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.

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.

Human studies

Unpublished Wyeth study. (2006) Effect of Lutein in S-26 Gold on Infant Plasma Lutein Concentration. Protocol n. 904A1-903 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 200µg 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 19.8µg lutein/L, so the two test formulas contained 47.4 and 288.5µg/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.

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.

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 ul/L results in growth equivalent to that of infants fed non-fortified S-26 Gold formula.

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.

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 breast-fed 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 Island, 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 levels which are proposed in this Application.

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 does not represent a risk to young infants at the levels which are proposed in this Application.

REFERENCES

Institute of Medicine (2000) β-carotene and other carotenoids. *In Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids.* Washington, DC. Institute of Medicine (IOM) National Academy Press (NAP), pp 325-382.

Canfield, L.M., Clandinin, M.T., Davies, D.P., Fernandez, M.C., Jackson, J., Hawkes, J., Goldman, W.J., Pramuk, K., Reyes, H., Sablan, B., Sonobe, T., and Bo, X. (2003). Multinational study of major breast milk carotenoids of healthy mothers. Eur J Nutr 42(3):133-141.

JECFA (1986) Principles for evaluating risks from chemicals during infancy and early childhood: the need for a special approach. World Health Organization, Geneva. http://www.inchem.org/documents/ehc/ehc/ehc59.htm#PartNumber:6 Accessed 9 August 2007

JECFA (1987) Environmental Health Criteria 70: Principles for the safety assessment of food additives and contaminants in food. World Health Organization, Geneva. http://www.inchem.org/documents/ehc/ehc/ehc70.htm#SectionNumber:5.5 Accessed 9 August 2007

JECFA (Joint FAO WHO Expert Committee on Food Additives) 2004. *Compendium of food additive specifications* FAO Food and Nutrition 2004. Paper 52 Addendum 12:35-37

JECFA (2006) *Safety evaluation of certain food additives (Sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives). (lutein from* Tagetes erectus*)*. WHO Food Additive Series 54, WHO, Geneva.

Jewell, V.C., C.B.D. Mayes, T.R.J. Tubman, C.A. Northrop-Clewes and D.I. Thurnham (2004) A comparison of lutein and zeaxanthin concentrations in formula and human milk samples from Northern Ireland mothers. European Journal of Clinical Medicine 58(1):90-97

Annex 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.

Kruger C.L., M. Murphy, Z. DeFreitas, F. Pfannkuch, and J. Heimbach (2002) An innovative approach to the determination of safety for a dietary ingredient derived from a new source: case study using a crystalline lutein product. Food and Chemical Toxicology 40:1535-1549.

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.

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. A pproximately 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 Report

EXECUTIVE 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 (at up to 250 µg/L) and to follow-on formula (at up to 500 µg/L). 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 9:1.

As the Acceptable Daily Intake (ADI) [14] 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.

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).

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).

[14] 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).

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.

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.

DIETARY MODELLING CONDUCTED TO ESTIMATE LUTEIN AND ZEAXANTHIN INTAKES

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.

Population groups assessed

The primary target group was identified as infants aged up to 1 year. Within this population group, dietary lutein and zeaxanthin intakes were investigated for:

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

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).

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

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

Scenarios for dietary intake assessments

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

'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.

'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.

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:

95^{th} percentile intake = mean intake x 2.5

Australian and New Zealand infants aged 3 months

The recommended energy intake for a three-month-old boy (FAO, 2004) at the 50^{th} 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

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 50^{th} 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 50^{th} 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.

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.

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.

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).

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).

DIETARY INTAKE ASSESSMENT RESULTS

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%).

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 95thpercentile 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)

REFERENCES

ACT Community Care. (2000) From Milk to More Introducing foods to your baby. Publishing Services, Canberra.

Ahmed, S.S., Lott, M.N. and Marcus, D.M. (2005) The Macular Xanthophylls. *Survey of Ophthalmology* 50(2):183-193.

FAO (2004) *Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation, Rome, 17-24 October 2001. FAO Food and Nutrition Technical Report Series No 1*. FAO, Rome. ftp://ftp.fao.org/docrep/fao/007/y5686e/y5686e00.pdf. Accessed on

Hitchcock, N.E., Gracey, M., Gilmour, A.I. and Owler, E.N. (1986) Nutrition and growth in infancy and early childhood: a longitudinal study from birth to five years. *Monographs in Paediatrics* 19:1-92.

Joint FAO/WHO Expert Committee on Food Additives (2005) *Evaluation of certain food additives: sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives (WHO technical report series; 928)*. http://whqlibdoc.who.int/trs/WHO_TRS_928.pdf. Accessed on 17 August 2007.

Joint FAO/WHO Expert Committee on Food Additives (2007) *Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives* . http://jecfa.ilsi.org/section1.htm#5. Accessed on 17 August 2007.

National Health and Medical Research Council. (2001) Dietary Guidelines for Children and Adolescents In Australia Incorporating Infant Feeding Guidelines For Health Workers (Draft). (Unpublished Work) .

U.S.Department of Agriculture (2005b) *Composition of Foods Raw, Processed, Prepared: USDA National Nutrient Database for Standard Reference, Release 18*.

U.S.Department of Agriculture (2005a) *Composition of Foods Raw, Processed, Prepared: USDA National Nutrient Database for Standard Reference, Release 18*.

USDA (2005) *USDA National Nutrient Database for Standard Reference*. 2 May 2005.

WHO (1985) *Guidelines For The Study of Dietary Intakes of Chemical Contaminants*. WHO Offset Publication. 87, World Health Organisation, Geneva.

WHO (2007) *The WHO Child Growth Standards*. http://www.who.int/childgrowth/standards/WFA_boys_0_5_percentiles.pdf. Accessed on 14 June 7 A.D.

Attachment 5

Food Technology Report

EXECUTIVE SUMMARY

The food technology aspects of lutein used as a nutritive substance to be added to infant formula and follow-on formula have been assessed. Lutein is not being considered for an extension of use as a food additive, where it can act as a permitted colour, since its proposed use is not for this purpose. 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 in the Code so a new specification is not required to be written.

The commercial lutein preparation that is subsequently added to food is produced in vegetable oil with approved food additives; antioxidants and emulsifiers. Stability results indicate that losses of up to 40% occur after 12 months storage at ambient temperature (27°C) when the lutein preparation is added to liquid (ready-to-feed) infant formula products. For powdered products, such as infant formula, follow-on formula and products produced for children aged 1-3 and 3-7 years, the losses were less after 6 months at ambient temperature, with the largest being 16%.

INTRODUCTION

FSANZ has received an Application from Wyeth Pty Ltd seeking permission to add lutein as a nutritive substance to infant formula and follow-on formula (A594).

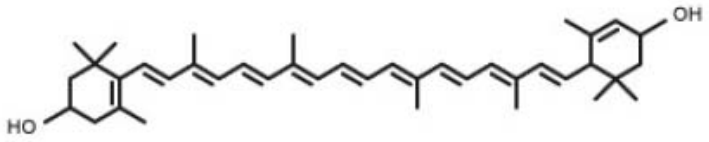
This Food Technology Report aims to address the chemistry of lutein, how it is manufactured, and more specifically the stability of lutein in the relevant food matrices, i.e. in liquid and powdered milk products. The Application is seeking permission for lutein as a nutritive substance not as a food additive where it has the technological function of a colour.

BACKGROUND

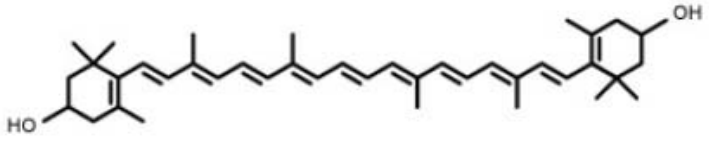
Lutein is a carotenoid (of the oxygenated carotenoid family called xanthophyll) found in many yellow and dark green vegetables including maize, spinach and green peas. More than 600 carotenoids have been isolated and characterised from natural sources and are characterised as brightly coloured plant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

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 zeaxanthin (an isomer of lutein) are shown below 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. 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.

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 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.

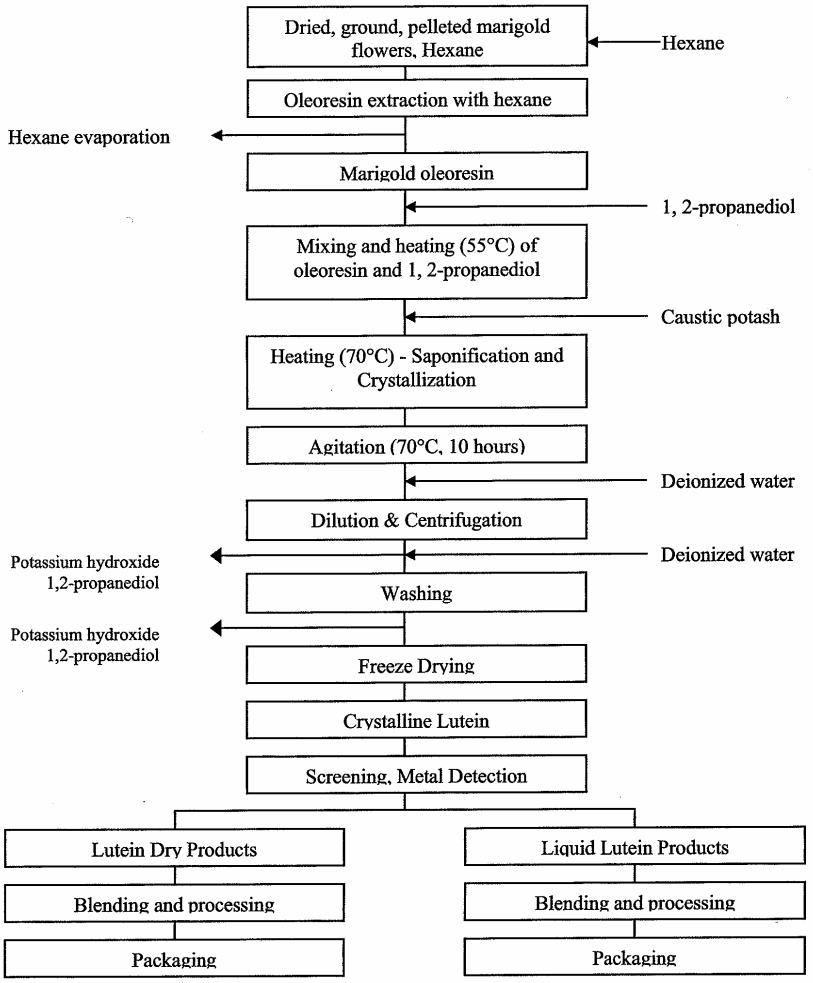


Figure 2: Schematic of the lutein preparation manufacturing process

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 1) 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.

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 – Identity and Purity. This means the specification of the lutein extraction is currently consistent with the Code, and a new specification is not required to be written.

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 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
Odor	Bland
Colour	Orange-red
Ash	Max. 1%
Aerobic plate count	Max. 100 cfu/g
E. coli enrichment	Negative/10g
Listeria monocytogenes	Negative/25g
Salmonella	Negative/10g
Staph enrichment	Negative/10g
Coliform enrichment	Negative/25g
Yeast count	Max. 100 cfu/g
Mould count	Max. 100 cfu/g

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 non-fat strawberry yoghurt and some other foods, but more importantly for the Application, its stability in liquid and solid infant formula type products.

The Applicant performed stability trials on lutein concentration in commercially prepared products (both solid and liquid) specific for the Application and the results are reported in the Application. The important results are summarised here.

For ready-to-feed (RTF, liquid products) products with lutein added at target levels of 25, 100 and 200 µg/L, there was up to a 40% loss of lutein after 12 months storage at ambient conditions (27°C). The losses were a lot less (only up to 7% loss) after storage of product for 3 months at elevated temperature (37°C). The Applicant explains that the lower losses at the elevated temperature storage is unusual compared to the experience with other carotenoids, where 3 months elevated temperature storage is usually a good indicator for 12 months ambient storage losses. However, they currently use 40% overdosing of carotenoids to take account of losses with storage, and these figures indicate such numbers are reasonable to still meet their targeted levels.

For powdered product similar stability trials were performed with trials at 27°C and 37°C for 6 months for infant formula, follow-on formula and what they refer to as international formula for children both 1-3 years and 3-7 years, with targeted 25 ug/l (for infant formula) and 200 ug/L (for the other products). After 6 months at 27°C there were only slight losses with the largest being 16% for infant formula.

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

CONCLUSION

This review of the food technology aspects of using lutein as a nutritive substance for infant formula and follow-on 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* meets the JECFA specification. This specification is referenced in the Code so no new specification needs to be written if the Application is approved. Lutein has reasonable stability in the commercial liquid and powdered products, with the largest losses being 40% in liquid products after storage of 12 months at ambient (27°C), which manufacturers can account for by over dosing with lutein.

REFERENCES

Joint FAO/WHO Expert Committee on Food Additives (JECFA) (1992) Compendium of Food Additive Specifications, FAO Food and Nutrition Paper 52 Addendum 12 (2004), also found at http://www.fao.org/ag/agn/jecfa-additives/specs/Monograph1/Additive-255.pdf Accessed on 10 May 2007.

Merck Index, 13th edition, Merck and Co. Ltd. Whitehouse Station, N.J. (2001).

Encyclopedia of Food Sciences and Nutrition, (2003), Second Edition, *Carotenoids*, Academic Press, pp 927-943 and 287-289.

Attachment 6

Summary of submissions from the Initial Assessment Report for Applications A594 and A597

EXECUTIVE SUMMARY OF SUBMISSIONS

The Initial Assessment Report sought input on the likely regulatory impact of both Application A594 and Application A597. In May 2007, FSANZ received 10 submissions in response to the Initial Assessment Report for:

- Application A594 – Consideration of an amendment to Standard 2.9.1 of the Code to permit the addition of lutein as a nutritive substance at a maximum concentration of 250 µg/L in infant formula and 500 µg/L in follow-on formula; and

- Application A597 - Consideration of an amendment to Standard 2.9.3 of the Code to permit the addition of lutein as a nutritive substance at a maximum concentration of 500 µg/L in Formulated Supplementary Foods for Young Children (FSFYC).

As the two Applications were presented together, submitter feedback was not always specific to each individual Application. Therefore, this summary of submissions includes submitter comments in relation to both Applications. However any comments that are specific to Application A597 have not been considered in the body of this Draft Assessment Report for Application A594.

Formatted: Bullets and Numbering

At Initial Assessment two options were proposed for each Application namely:

Application A594:
Option 1 – maintain the s*tatus quo*;
Option 2 – amend Standard 2.9.1

Application A597:
Option 1 – maintain the s*tatus quo*;
Option 2 – amend Standard 2.9.3

The majority of submitters provided comment on both Applications combined, while some comments were received relevant to one specific Application.

Submitters' views were mixed in relation to a preferred regulatory option,

- Of the (4) industry submitters a majority (3 including the Applicant) supported Option 2 – however one supported this Option '*provided safety and efficacy is scientifically demonstrated and contingent on satisfactory safety assessment by FSANZ'*

- Four of the five Government submitters did not state a preferred Option at this stage noting further assessment of safety and efficacy is needed. A delay until FSANZ Policy Guidelines on the addition of substances other than vitamins and minerals are completed was recommended by two of the Government submitters. One Government submitter supported the *status quo*.

- The one public health submitter did not state a preferred option at this stage and included points requiring further assessment.

Overall five of the ten submitters did not provide a preferred option at initial assessment considering further assessment of safety and efficacy was needed.

KEY ISSUES IDENTIFIED FROM SUBMISSIONS

1. Regulatory options

Reasons for and against each of the regulatory options included:

1.1 Option 1 – maintaining the status quo

Support:

- insufficient evidence to support the addition of lutein (efficacy, levels, safety);
- evidence of clear health benefit is needed;
- recommended delay until FSANZ Policy Guidelines are completed;
- considers lutein a novel food;
- potential for health claims; and
- JECFA ADIs are not applicable to less than four months of age.

1.2 Option 2 – amending Standard 2.9.1 and 2.9.3 to permit lutein

Support:

- sufficient evidence to demonstrate benefits to eye health;
- is a nutrient found in breast milk;
- recent US Expert Panel Opinion supports lutein in infant formula and granted GRAS status; and
- is currently approved for addition to infant formula in some other countries.

Against:

- insufficient evidence to support addition of lutein (efficacy, levels, safety);
- evidence of clear health benefit needed; and
- recommended delay until FSANZ Policy Guidelines completed.

1.3 *No preferred Option at this time*

Formatted: Bullets and Numbering

- Policy Guidelines are needed;
- further assessment of safety and efficacy is required;
- composition of formula must not provide additional benefits over breast milk;
- does lutein meet definition of a nutritive substance;
- what are the levels and variability in breast milk, formula and mixed diet, interactions with other nutrients;
- content or health claims should not be permitted for FSFYC; and

- information needed on the similarities and differences between lutein in breast-milk and the proposed form.

Ref	Submitter	Submission Comments in response to IAR
	Industry	
	Food Technology Association of Victoria Inc. **David Gill**	**A594 only - Supports Option 2** No supporting information provided. No reference to A597.
	Nestlé Australia Ltd **Kirsten Grinter**	**A594 and A597 - Supports Option 1** ***Safety / benefits*** Considers the scientific evidence available to date is not sufficient to support the addition of lutein to infant formula products. Is not aware of any published studies that have evaluated the effect on growth and development, or the beneficial effects of formulae or foods supplemented with lutein in infants and young children. Also, there are no experimental or epidemiological published data on the influence of lutein on visual development or visual function in infants. This would require large scale studies with long-term supplementation. Considers measurement of changes in macular carotenoid levels raises a major technical hurdle in infants. Plasma levels are an indirect measure and have an uncertain association with macular concentrations of lutein. ***Levels*** The absence of studies makes it impossible to establish whether there is an optimal intake, or a minimum effective level for the target population, or if the proposed form of lutein is bio available or effective for the target group. Suggests the levels present in breast milk would provide an indication. Also considers it is not possible to establish the risks for the target population in the absence of published data. Notes JECFA established an ADI for lutein from tagetes erectes and synthetic zeaxanthin for use as a colour, linked to specifications (lutein content) of a particular extract. However notes ADIs are not applicable to infants less than 4 months of age. For these infants suggests if levels of lutein + zeaxanthin in formula were similar to those in breast milk, safety concerns would be reduced. Notes that surveys (internal Nestle studies) conducted on infant formula show those formula containing predominantly milk fat or vegetable fat may naturally contain lutein levels within the range of human milk.

Ref	Submitter	Submission Comments in response to IAR
		Comparison to breast milk. Notes at present only minimal scientific data is available which documents lutein levels found in human milk and infant formulae. Notes the combined lutein/zeaxathin in breast milk varies amongst populations. Provides figures of a median combined lutein/zeaxathin content of breast milk of 20 micrograms/L (range 15-44). Refers to a recent study reporting a lutein content of 50 micrograms / L in a breast milk sample collected 19 days post partum and a zeaxanthin level of 11 micrograms/L, indicating a lutein:zeaxanthin ratio of 4.5 (Schweigert et al 2004).The authors showed levels decrease significantly from first lactation to mature milk, but the ratio remains relatively stable. Also refers to a study showing median lutein concentrations in human milk of 4.79 nmol/gfat (range 0.42-9.98). Notes breast milk concentrations of lutein differ greatly between individuals and this study indicated by day 12-20 of lactation concentrations had dropped to almost zero (Jewell et al 2004). Notes cows milk also contains lutein and zeaxanthin with levels depending on feeding practice. Consequently milk-based infant formulas also contain variable lutein levels. Refers to an internal Nestle study reporting lutein levels ranging from 2-33 micrograms/L (Perrin 2004). ***Nutrient claims*** Consider nutrition and health claims should be permitted where they are scientifically substantiated. ***Impact on industry*** There would be no direct impact if the status quo remains, however this would not support industry innovation which is appropriate if safety and efficacy data can be scientifically substantiated.
	AFGC **Kim Leighton**	**A594 and A597: Supports Option 2** ***provided safety and efficacy is scientifically demonstrated and contingent on satisfactory safety assessment by FSANZ*** ***Safety / benefits*** Considers evidence provided by the Applicant demonstrates the addition of lutein to infant formula helps ensure formula-fed infants derive the acute benefits of lutein, especially pertinent to premature infants. Also considers the Applicant has shown that ensuring sufficient intake of lutein in infancy and early childhood has the potential to significantly reduce cumulative effects of oxidative damage to the retina and lens. Notes the presence of lutein in breast milk demonstrates that lutein has a nutritive effect and is a natural and normal constituent of an infants food supply. Considers there is sufficient weight of evidence to demonstrate benefits of lutein exist including its role in eye health.

Ref	Submitter	Submission Comments in response to IAR
		Notes JECFA at its 63rd meeting established an ADI for lutein derived from marigold flowers and synthetic zeaxanthin of 2 mg/kg bw/day for use as a nutrient supplement. Considers this supports that supplemental free lutein is accepted as a safe compound for humans. However, notes ADIs are not applicable to infants under 4 months of age, but supports the addition of lutein and zeaxanthin at levels that closely match those in breast milk. Notes USFDA confirmed JECFA's ruling that lutein and zeaxthanin are safe (GRAS) for human consumption. However this did not specify inclusion of lutein in infant formula, and a level of 1 mg/reference amount were specified for infant and toddler foods. Refers to a risk assessment published in 2006 that notes data for intakes above 2 mg/kg bw / day is insufficient for long term safety assessment. ***Claims / Levels*** AFGC considers, as a principle, that general and high level health claims should be permitted where scientifically substantiated, and content claims where they accurately reflect a product composition. Is not aware of studies specifically determining upper and lower limits for infants, but notes the Observed Safe Level risk assessment method indicates the evidence of safety is strong at intakes up to 20 mg/d for lutein.
	Wyeth Australia Pty Ltd **Jeanette Fielding**	**A594 and A597: Supports Option 2** Provides additional information to support the original Application. ***Safety*** Notes at IAR lutein was GRAS in the US for use in specified categories of foods including 'infant and toddler foods' but not infant formula. Since then (March 2007) the US Expert Panel Opinion regarding the GRAS status of FloraGLO Lutein 20% liquid in safflower oil for use in infant formula has been released. The panel determined that '*overall when viewed in its entirety the scientific evidence presented provides no indication that FloraGLO Lutein 20% Liquid in Safflower Oil will produce adverse effects on human health when consumed under the intended conditions of use in infant formulas'.* This safety evaluation was based on a total lutein content, in finished infant formula product, not to exceed 250 micrograms/L. Notes for the purpose of the US opinion, infant formula is defined as a breast-milk substitute suitable from birth to six months of age. At the time of this submission, this opinion was within its 90 day evaluation period.

Ref	Submitter	Submission Comments in response to IAR
		International regulations Since the original Application approval for the addition of lutein (as FloraGLO Lutein 20% liquid in safflower oil) to infant formula and toddler milks had been gained by China, Indonesia, Malaysia, Kuwait, Colombia and the Philippines. Notes application approvals are pending in the EU. Provides copy of a letter from Dr A Lucas and T Michaelson in support of the European application to add lutein to infant formula and follow-on formula. ***International Market*** Notes infant formula, follow-on formula and toddler milks with lutein (FloraGLO Lutein 20% liquid in safflower oil) launched in 2006, have been marketed in Mexico, United Arab Emirates and Hong Kong. ***Claims*** Supports the addition of a lutein content claim to the label, on the basis of enabling consumers to choose and identify lutein within supplementary toddler milks, which may offer reassurance to parents of 'fussy eaters' who may be consuming a limited number of foods. Refers to a government survey from UK that has reported 81% of children aged 2-3 years consume fruit once a day or less frequently, and 88% consume vegetables once a day or less. Refers to lutein dietary intake data for toddlers in US showing mean and 90th percentile lutein intakes for toddlers 1-3 years are 636 micrograms/day and 1194 micrograms/day respectively. Notes these estimates are higher than reported for Australian toddlers in a Wyeth pilot trail. ***Claims*** Believes the amount approved for a nutrition source claim should be similar to the amount typically found in one serve of a food that naturally contains the nutritive substance. Recommends a nutrient claim for toddler milks be made at 95 micrograms / serve for toddlers. The maximum lutein concentration for toddler milk proposed in Application 597 in a 200 ml serve would equal 100 micrograms, hence would be able to make a claim. ***Levels*** Considers maximum concentration of lutein permitted should be based on the JECFA ADI. Refers to the maximum level of lutein recommended for infant formula and toddler milks in the Applications. Notes there is no observed colour change at the levels proposed. ***Impacts on consumers*** Considers the benefit to formula –fed infants is the inclusion of a nutrient that is found in breast milk, thereby improving nutritional status. The addition of lutein to the toddler diet especially when vegetable consumption is poor is anticipated to improve nutritional status.

Ref	Submitter	Submission Comments in response to IAR
	Government	
	Dept Health South Australia **Elena Anear**	**A594 and A597: Supports Option 1** Considers lutein derived from marigolds is not a usual diet constituent and should therefore be considered a novel food. Notes lutein is not regarded as a vitamin and is not covered by NRVs or other dietary recommendations. ***Safety / benefits*** Notes that while there is some evidence of the role of lutein in preventing and slowing macular degeneration, this is an aging condition. Considers sufficient evidence is required of a clear health benefit to the target group (infants and children to 3 years of age). ***Policy*** Notes the Ministerial Council is considering a policy guideline on the addition of substances other than vitamins and minerals which will assist assessment of such applications. Recommends that until these guidelines are completed this application should not be approved, and that the status quo be maintained. ***Claims*** Concerned about potential for health claims to be permitted on foods regulated by Std 2.9.2 and 2.9.3 e.g. if the addition of lutein is permitted. Strongly believes foods covered by these standards should be ineligible to carry any claims. Notes clinical colleagues have expressed concern about proliferation and marketing of 'follow-on' formulae and believe this should not be permitted. Provided an extract from the P293 PFAR which notes: *The Ministerial guidelines require the exclusion of infant foods from health claims: yet both the P293 DAR and PFAR only exclude infant formula. Considers this should be extended to cover foods regulated under 2.9.2 Foods for Infants and 2.9.3 Division 4 FSFYC, except where a claim is specifically allowed under these standards. Refers to the National Health and Medical Research Council's Dietary Guidelines for Children, and the WHO recommendations re breastfeeding. Notes there should be no threat to this critical period of development posed by additional permissions for food manufacturers to make claims on foods regulated by these two standards.*
	NZ Food Safety Authority **Carole Inkster**	**A594 Infant Formula: preferred option not stated at IAR** ***Scope and intent of Standard 2.9.1*** Prefers a conservative approach when considering infant formula. Strongly supports MOH nutrition policy including promotion of breastfeeding. ***Safety / benefits*** Believes the composition of infant formula should not exceed or provide additional benefits over breast milk.

Ref	Submitter	Submission Comments in response to IAR
		Lutein from marigold needs an appropriate safety assessment that applies to infants and infant formula. Notes the establishment of an ADI by JECFA normally does not apply to infants younger than 12 weeks. The DAR needs to consider what safety data is available and whether this is sufficient to infants, at the levels proposed. The safety assessment should also include allergenicity. Notes the Application is based on the role of lutein in supporting eye health and aims to provide formula-fed infants with lutein at levels comparable to breast-fed infants. Considers the Draft assessment report needs to establish the content of lutein in breast milk, and its role in infant nutrition. In addition, the efficacy of lutein from marigold, compared to dietary sources, would need to be considered. ***Health claims*** Supports the proposed approach in the Code of Standard 1.2.7 – Nutrition Health and Related Claims, which prohibits claims on infant and follow-on formula in relation to any nutrient or nutritive substance, such as lutein. Considers there will be no marketing advantage if lutein is permitted to be added to infant formula as it will only be referenced on the ingredient list and possibly the nutrition information panel. ***Definition of a Nutritive substance*** Refers to the Code definition of a nutritive substance (Clause 2 Standard 1.1.1). Requests comment in the DAR as to whether a substance added to infant formula to 'support eye health' provides a physiological benefit rather than a *nutritional purpose*. Queries whether lutein falls outside the definition of a nutritive substance, and if so how would any permission be managed in Standard 2.9.1. ***Review of Standard 2.9.1*** Notes there appears to be an increasing number of Applications seeking permission to allow addition of new substances to infant formula. Believes it is timely for FSANZ to consider a proposal to look more broadly at Standard 2.9.1, and in particular the compositional requirements. **A597 – FSFYC: preferred option not stated at IAR** ***Safety / benefits*** Believes lutein from marigold should be subjected to a safety assessment at the levels proposed for FSFYC. Does not consider the Applicants comment that 'some of the richest sources of lutein are some of the least preferred foods of young children' is justification for addressing poor dietary habits through the addition of nutritive substances to FSFYC. ***Claims*** Is still considering the issue of whether FSFYC with lutein added should be permitted to make nutrition content claims and / or health claims.

Ref	Submitter	Submission Comments in response to IAR
		Supports further discussion on the merits of specific labelling requirements for FSFYC with added nutritive substances or substances added for physiological benefit.
	Victorian Dept. Human Services **Fiona Jones**	**A594 and A597: Recommends delay** ***Policy*** Considers the preparation of this assessment should be delayed until the policy guidelines for addition of substances other than vitamins and minerals has been completed and endorsed by the Australian NZ Food Regulation Council. ***Safety*** Requests the following issues also be addressed at draft assessment: • the biological differences and similarities between the proposed form of lutein and the lutein in breast milk; and • the efficacy of the proposed form of lutein in the target population. ***Levels*** Notes no information on levels of lutein in breast milk has been provided. Does not consider the IAR provides sufficient information to comment on proposed levels of addition. ***Claims*** Understands that claims on infant formula will continue to be prohibited, and considers nutrition content or health claims for lutein should not be permitted for FSFYC. Considers lutein is an obscure substance with any potential benefit probably unknown to consumers, so a content claim is of no marketing advantage to a manufacturer without a health claim.
	NSW Food Authority **David Cusack**	**Preferred option not stated at IAR**. Supports progression of these applications to Draft Assessment subject to consideration of issues *summarised* below. ***Safety / benefits*** Requests FSANZ careful consideration of these specific issues and notes support for these applications is dependent on positive results arising from this investigation: • clear identification of a beneficial dose / response relationship in the target population; • clear toxicological data demonstrating that lutein in pure form and in the form proposed by the Applicant is not associated with any detrimental effect to the target population, inclusive of acute and long term toxicity, growth and development, and normal metabolism; • identification of a daily threshold level of lutein (if applicable to the dose and serving size proposed by the Applicant);

Ref	Submitter	Submission Comments in response to IAR
		• bioavailability of the proposed form of lutein to the target population; and • identification of any issues for the target population associated with consumption of lutein from food vehicles proposed by the Applicant in conjunction with all other sources of lutein in the diet, including breast milk.
	Queensland Health **Tenille Fort**	**A594: preferred option not established.** Has not yet established a position in relation to A594. Will review the Draft assessment report and provide comment at that time. **A597: preferred option not stated** and no comment provided.
	Health Professionals	
	Dietitians Assoc Australia **Kate Poyner**	**A594 and A597: preferred option not stated.** Supports FSANZ decision to accept Application 594 and 597 for assessment. ***Safety / benefits*** In addition to the key Assessment Questions posed at IAR, DAA request consideration of: • what is the level and variability of lutein in breast milk in different population groups? • what is the level and variability of lutein in breast milk over the duration of lactation? • what is the level and variability of lutein in infant formula available in Australia? • what is the intake of lutein in young children consuming a mixed diet? and • how is lutein availability and function affected by the dietary intake and levels or other carotenoids? ***Claims*** DAA would support a content claim if there was international consensus amongst health authorities in the area of infant and early childhood nutrition as to the recommended intake for lutein. Notes no claim would be permissible for infant formula. DAA would support a general level health claim for lutein in FSFYC and eye function if there was strong evidence on the function of lutein in young children.