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

21 December 2007
[9-07]

DRAFT ASSESSMENT REPORT

APPLICATION A597

ADDITION OF LUTEIN TO FORMULATED SUPPLEMENTARY FOODS FOR YOUNG CHILDREN

DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 22 February 2008
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 on 2 January 2007 (Application A597) from Wyeth Australia Pty Ltd requesting an amendment to the *Australia New Zealand Food Standards Code* (the Code). This amendment is to modify Division 4 of Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods, to permit the optional addition of lutein as a nutritive substance to formulated supplementary foods for young children (FSFYC). 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.

FSANZ is also currently assessing a request from the same Applicant to permit the addition of lutein to infant and follow-on formula (Application A594). A Draft Assessment Report for Application A594 has been released for public comment, and submissions were received in November 2007. A copy of this document can be found at http://www.foodstandards.gov.au/standardsdevelopment/applications/index.cfm.

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 high in lutein include dark green leafy vegetables, peas, carrots, corn, citrus fruits, avocado and broccoli. Lutein is also present in egg yolks, the fat of animals whose diets include lutein-rich plants and in human breast milk. Wyeth products have a small amount of lutein naturally present in the order of 20-30 µg/L.

FSANZ has undertaken a risk assessment and concluded that that there are no public health and safety concerns with the addition of lutein/zeaxanthin to FSFYC at the proposed level. Relatively large doses of lutein (6000 µg/day) have been used safely in humans over periods of several months and monkeys have received doses of tens of thousands of micrograms without ocular toxicity. The expected intake of 100–300 µg of young children consuming one to three serves of lutein-enriched FSFYC is modest in comparison.

The Applicant has sought a maximum concentration of 500 µg/L of added lutein in FSFYC, which would provide at most 100 µg of lutein in a recommended serving of 200 mL. This amount of lutein is equivalent to that contained in 4 g of peas or 14 g of boiled carrots. The estimated mean intake of lutein from non-FSFYC foods is 385 µg/d and 730 µg/d in Australian children aged 1 y and 2-3 years, respectively, and 680 µg/d in New Zealand 1-3 year olds. Despite a relatively low concentration, the proposed added lutein will enable FSFYC to act as a viable contributor to the lutein intake of children aged 1-3 years.

FSANZ has assessed the type of claims that would be permitted on FSFYC labels in respect of lutein addition. It has been determined that nutrition claims about the presence of lutein (e.g. 'source of lutein') will be permitted provided that FSFYC contain at least 30 µg/serve.

FSANZ has identified and compared two regulatory options at Draft Assessment:

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

- Option 2 – amend Standard 2.9.3 Division 4 to permit the voluntary addition of lutein as a nutritive substance at a maximum concentration of 100 µg/serve in FSFYC and to require a minimum declaration of 30 µg/serve when a nutrition claim is made.

FSANZ's comparison indicates that both maintaining the *status quo* (Option 1) and Option 2 would continue to protect the health and safety of young children who consume FSFYC. However, Option 2 is a safe and suitable option for young children, offers an added source of lutein in addition to that obtained naturally through the diet, and potentially increases opportunities for product innovation on the domestic market. Therefore, Option 2 has been assessed as providing greater net benefits to the affected parties.

Preferred Approach

Option 2 is the preferred regulatory approach for Application A597. This approach would result in an amendment to Standard 2.9.3 to permit the addition of lutein to FSFYC at no more than 100 µg/serve, and to require at least 30 µg/serve of lutein in FSFYC where a claim has been made on the presence of lutein within the product.

Reasons for the preferred approach

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

The addition of lutein to FSFYC proposed as part of Option 2:

- does not pose any health and safety risks to children aged 1-3 years;
- will be able to act as a viable contributor to the lutein intake of children aged 1-3 years;
- is consistent with relevant international regulations, and will facilitate trade; and
- as the impact analysis concludes that Option 2 provides a greater net benefit to affected parties than the *status quo* (Option 1)..

FSANZ therefore recommends the proposed draft variation to the Code that is provided in Attachment 1.

Consultation

The Initial Assessment Report sought input on both Application A594 and Application A597 together over a six-week period from 4 April to 16 May 2007. Submissions received for both applications are summarised in Attachment 6. Feedback was not always specific to each individual Application, however any comments that could be attributed directly to Application A594 have not been considered in this Draft Assessment Report.

FSANZ received nine submissions specifically commenting on A597. Overall, the majority of submitters did not provide a preferred option at Initial Assessment, whilst several recommended that further assessment of safety and efficacy is needed. Two submitters also recommended that assessment be delayed until Ministerial policy guidance on the addition of substances other than vitamins and minerals is completed.

Two industry submitters (including the Applicant) supported permitting the addition of lutein to FSFYC, however one supported this Option contingent on a satisfactory safety assessment.

Two submitters supported the *status quo* citing insufficient evidence, including a need for evidence of health benefit.

Key issues raised during the stakeholder consultation are addressed in the main body of this report.

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INVITATION FOR PUBLIC SUBMISSIONS

FSANZ invites public comment on this Draft Assessment Report based on regulation impact principles and the draft variation 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 confidential commercial information. 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) 22 February 2008.

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

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

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

INTRODUCTION

Food Standards Australia New Zealand (FSANZ) received a paid Application from Wyeth Australia Pty Ltd on 2 January 2007 (Application A597) requesting an amendment to the *Australia New Zealand Food Standards Code* (the Code). This amendment is to modify Table 3 of the Schedule of Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods, to permit the optional addition of lutein as a nutritive substance to formulated supplementary foods for young children (FSFYC). 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 that lutein be permitted as an optional nutritive substance in Division 4, *Formulated Supplementary Foods for Young Children* of Standard 2.9.3 to a maximum concentration of 500 µg/L. The Applicant proposes that lutein should be permitted to be added to FSFYC for the following reasons:

- lutein is not currently approved in the Code as a permitted nutritive substance for addition to FSFYC, but is approved as a food colour and is used as a colour in foods commonly consumed by young children e.g. flavoured milk products;
- lutein has potential eye health benefits to young children;
- there are potential later life effects of early lutein intake; and
- some of the richest food sources of lutein are often the least preferred foods of toddlers and young children.

The Applicant has requested a lutein addition at a level that will increase the existing lutein intakes within the diets of young children particularly those whose diets do not reliably contain lutein. The Applicant has claimed that at a 600 mL intake of FSFYC, young children would receive approximately 300 µg of additional lutein each day, which is equivalent to the quantity of lutein found in 50 g of green beans. FSANZ considers an intake of 600 mL FSFYC per day represents three 200 mL serves per day [1].

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 10:1.

[1] FSANZ has converted the Applicant's request for 500 µg/L into a per serve value, using a serving size of 200 mL, which is a serving size commonly attributed to FSFYC by manufacturers of toddler formula. Use of a per serve value for the addition of lutein to FSFYC is consistent with the manner in which existing compositional requirements for FSFYC are expressed in Standard 2.9.3.

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). Further details on this chemical specification are located in the Food Technology Assessment for this Application (see Section 5 below, and Attachment 5).

1.3 Scope of Application

This Application pertains to the voluntary addition of lutein to FSFYC, as defined in Clause 1 of Standard 2.9.3. Clause 1 – Interpretation of Standard 2.9.3 provides:

> ***formulated supplementary food for young children*** *means a formulated supplementary food for children aged one to three years.*
>
> ***formulated supplementary food*** *means a food specifically designed as a supplement to a normal diet to address situations where intakes of energy and nutrients may not be adequate to meet an individuals requirements.*

Other product categories mentioned in Standard 2.9.3 such as formulated meal replacements will not be affected by the amendments proposed in this Application, and therefore will not be permitted to contain added lutein.

1.4 Related Application – Application A594

FSANZ is currently assessing a request from the same Applicant to permit the addition of lutein to infant and follow-on formula as part of Application A594 – Addition of Lutein as a Nutritive Substance to Infant and Follow-on Formula. A Draft Assessment Report for Application A594 was recently released for public comment, with submissions having closed on 14 November 2007. A copy of this document can be found on the FSANZ website at http://www.foodstandards.gov.au/standardsdevelopment/applications/index.cfm.

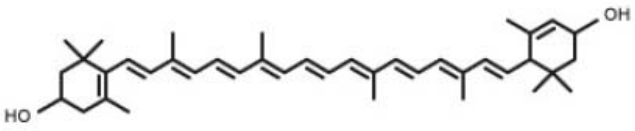
2. Background

Carotenoids are red and yellow pigments contained in animal fat and some plants. Although several hundred carotenoids have been identified, the most prevalent 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 therefore can only obtain lutein from dietary sources. Lutein 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.

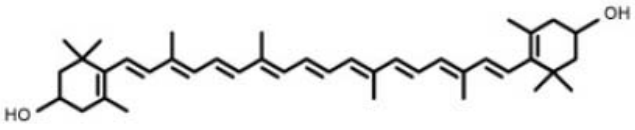
Good sources of lutein include eggs, peas, carrots, corn, citrus fruits, avocado, broccoli and dark green leafy vegetables such as spinach. Lutein is also a food colouring agent (INS 161b). Carotenoids are present in blood and adipose tissue, and concentrated in the ovaries, testes, liver, skin, breast milk, and eyes.

[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

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. 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 Food Regulations

Standard 2.9.3 contains regulations for FSFYC, with clauses 6 and 7 of this Standard specifically dealing with the composition and labelling of FSFYC respectively. Clause 6 however, details provisions on macronutrients, vitamins and minerals only, and does not make reference to other added substances.

Clause 3 of Standard 1.3.1 – Food Additives permits the addition of lutein as a food colour under Schedule 3 in processed foods specified in Schedule 1.

2.1.2 Therapeutic Goods / Medicines

In Australia, lutein is eligible for use in Listed medicines on the Australian Register of Therapeutic Goods, with no substance specific restrictions noted[3]. Preparations of *Tagetes erecta* that meet the definition of a herbal substance in Regulation 2 of the TGA regulations 1991 are approved for use in Listed medicines[4].

[3] Substances that may be used in Listed medicines in Australia www.tga.gov.au/cm/listsubs.htm. Accessed 26 February 2007.
[4] Personal communication, Michele McLaughlin, Therapeutic Goods Administration, Australia, 14 March 2007

Lutein is not a scheduled medicine in New Zealand and is not contained in any medicines currently registered in New Zealand[5].

2.1.3 Overseas and International Regulations

2.1.3.1 Codex Alimentarius

Codex Alimentarius regulates FSFYC under a set of guidelines titled 'Guidelines on Formulated Supplementary Foods for Older Infants and Young Children' (CAC/GL 08-1991). These guidelines do not explicitly permit the addition of lutein to FSFYC. However the guidelines do mention that *the product is intended to supply additional energy and nutrients to the staple foods used for the feeding of older infants and young children*, and that modifications may need to be made by member countries in adopting the guidelines to the unique conditions of the local environment.

2.1.3.2 United States of America (USA)

A generally recognised as safe (GRAS) notification for crystalline lutein has been submitted to the United States Food and Drug Administration (FDA)[6]. This lutein preparation is the same as that used in FloraGLO® Lutein 20% liquid in safflower oil. The FDA's response to this notice was issued on 14 June 2004, when it accepted that crystalline lutein is safe to use as a food ingredient in specified categories of foods and beverages including infant foods (for infants aged four to six months up to 12 months, excluding infant formula) and toddler foods (for children over 12 months old), at levels up to 1 mg per serve[7].

Although not directly relevant to this application (A597), a notification was also submitted to the FDA for GRAS status for FloraGLO® Lutein in infant formula to a maximum level of 250 μg/L[8]. The FDA recently responded that it had no questions about this notification. The Applicant states that for the purpose of the GRAS status, infant formula is defined as being intended for infants from birth up to 6 months of age.

2.1.3.3 European Union

Lutein is permitted for addition to foods as a food colouring agent in the European Union, but is not permitted for addition to FSFYC for any other purpose.

2.2 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. At this stage it is expected that this policy guideline will not apply to special purpose foods, such as FSFYC.

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[5] Personal communication Carol Smith, Medsafe, Ministry of Health, New Zealand, 15 March 2007.
[6] GRAS Notice: GRN No. 140. Available at: http://www.cfsan.fda.gov/~rdb/opa-gras.html
[7] FDA decision for GRAS Notice: GRN No. 140. Available at: http://www.cfsan.fda.gov/~rdb/opa-g140.html
[8] GRAS Notice No. GRN 000221

Several submitters to the Initial Assessment have requested a delay to Application A597 until the policy guideline on the addition of substances other than vitamins and minerals to foods is complete. However, FSANZ is bound by its statutory obligations to progress Application A597 and cannot postpone its assessment, especially when FSFYC are likely to no longer be captured by the policy guideline.

2.3 Current Market

2.3.1 Domestic Market

The majority of FSFYC available in Australia and New Zealand are milk-based supplementary drinks known as 'toddler formula' or 'toddler milk'. FSANZ is not aware of other products that are currently manufactured to the FSFYC provisions.

Toddler formula is generally promoted as a supplementary milk drink for children aged over 12 months of age and is recommended to be prepared with water. In addition, toddler formulas are sometimes promoted as being suitable as a replacement for milk in other foods e.g. custards. More recently a 'fresh' liquid variety of FSFYC is being marketed in Australia.

FSANZ is aware of only a small number of manufacturers/importers of FSFYC in Australia and New Zealand. On the whole, the market for these products is believed to be relatively small and discrete, although possibly growing. Generally, the manufacturers of FSFYC are also manufacturers of infant formula.

2.3.2 International Market

The Applicant has recently advised that approvals for the addition of FloraGLO Lutein 20% Liquid in Safflower Oil to FSFYC have been gained in the Peoples Republic of China, Indonesia, Malaysia, Kuwait, Colombia and the Philippines. Such products are therefore potentially available on the market in these countries.

2.4 Lutein as a Nutritive Substance

The Applicant has requested permission for addition of lutein to FSFYC as a nutritive substance. Nutritive substance is defined in Standard 1.1.1 as:

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

Clause 9, Division 2 of Standard 1.1.1 states that 'nutritive substances' must not be added to food unless expressly permitted in the Code.

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 normally consumed as a food itself 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 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 postulated to function in the eye as an antioxidant and blue light filter. It is not synthesised in the human body.

3. The Issue

The Applicant has requested that lutein be permitted as an optional nutritive substance for addition to FSFYC to a maximum concentration of 500 μg/L.

Nutritive substances must not be added to food unless expressly permitted in the Code. Standard 2.9.3 does not permit the addition of lutein to FSFYC as a nutritive substance, and therefore FSFYC products with added lutein cannot be sold within Australia and New Zealand. Permitting the addition of lutein to FSFYC would potentially provide an additional source of lutein in the diets of young children who are using FSFYC as a supplement to a normal diet when energy and nutrient intakes may not be adequate.

However allowing for the voluntary addition of lutein to FSFYC at the proposed level requires a demonstration of its safety before an amendment to the Code can be approved.

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. Food Technology Assessment

The food technology aspects of lutein used as a nutritive substance to be added to FSFYC have been assessed. The findings of this assessment are located in Attachment 5 and are summarised below.

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 so a new specification is not required.

The commercial lutein preparation that is subsequently added to food is produced in vegetable oil with approved food additives; antioxidants and emulsifiers. Stability results for powdered products, such as FSFYC, indicated good stability. Maximum losses after 12 months at ambient temperature (27°C and 70% relative humidity (RH) were determined to be 35%. The largest losses after 6 months storage under extreme conditions (37°C and 75% RH) were found to be 44%.

Manufacturers will need to be aware of losses of lutein that occur for their products with storage conditions and could apply a suitable overdosing to account for such losses. However, manufacturers also need to be aware that there are regulatory limits for lutein in formulated supplementary foods for young children proposed for the Code (i.e. no more than 500 µg/L), so they need to ensure that products commercially available for sale meet the requirements of the Code.

RISK ASSESSMENT

The following section summarises FSANZ's risk assessments and their conclusions. The full details of these risk assessments can be found at Attachments 2, 3 and 4.

6. Risk Assessment Questions

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

1. Is lutein found naturally in foods, and if so, how do the concentrations in foods compare with those proposed for FSFYC?

2. Is lutein derived from marigold flower bioavailable for young children, and is it comparable to the bioavailability of lutein from natural food sources?

3. What is the concentration of lutein in FSFYC from other ingredients?

4. What is the current dietary intake of lutein for young children in Australia and New Zealand from different sources?

5. What is the impact on lutein intakes of young children that consume FSFYC containing lutein at a maximum concentration of 500 μg/L?

6. Are there any risks to young children from consuming FSFYC containing lutein derived from marigold flowers at a maximum concentration of 500 μg/L?

7. Risk Assessment Summary

7.1 Nutrition Assessment

At the requested maximum level of 500 μg/L, FSFYC would provide at most 100 μg of lutein in a recommended serving size of 200 mL[9]. Such addition would also place FSFYC amongst foods that contain moderate amounts of lutein and zeaxanthin. As Australian and New Zealand consumers of FSFYC consume on average one serve per day, it is likely that the mean daily lutein intake from FSFYC would be comparable to the intake from, for example, 4 g of peas or 14 g of boiled carrots.

Information from the Applicant also indicates that FSFYC ingredients contain some natural level of lutein and zeaxanthin. This innate source contributes approximately 4-6 μg/serve of lutein to the total concentration of an FSFYC.

Lutein from vegetables appears to have similar bioavailability compared with lutein in supplements, assuming no losses due to processing and cooking of foods. Lutein from supplements or added to formula appears to have lower bioavailability compared with lutein contained in breast milk or eggs. As the addition of lutein to FSFYC will likely increase the mean daily contribution of FSFYC to levels comparable with moderate food sources of lutein, it is therefore considered that FSFYC will be able to act as a viable contributor to the lutein intake and lutein status of children aged 1-3 years.

7.2 Hazard Assessment

JECFA evaluated an extract of marigold (*Tagetes erecta*) at its 63rd meeting (in 2004) and established an Acceptable Daily Intake (ADI) of 2 mg/kg bw/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.

FSANZ assessed the submitted evidence on the safety of lutein as part of Application A594, and concluded that the addition of lutein to infant formula at a maximum level of 250 μg/L does not pose any public health and safety risk to formula-fed infants. The data assessed included a ninety-day, repeat-dose, toxicity study and a developmental toxicity study, both in rats, and a 52-week study in non-human primates which included comprehensive ophthalmic examinations. Two additional studies on the bioavailability of lutein from infant formula in pigs and non-human primates, and two studies on the effect of lutein-supplemented infant formula on the growth and occurrence of adverse events in human infants were also considered. No adverse effects, including those in the eye, have been observed in any of the studies on lutein and zeaxanthin. Lutein has not been found to be allergenic. Carotenodermia (skin yellowing) is observed at high doses; however this is considered harmless and is readily reversible upon discontinuation of high intakes of lutein.

[9] Refer to Footnote 1, Page 7 for clarification of serving size.

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.

7.3 Dietary Modelling

Dietary intakes were calculated using constructed theoretical diets for Australian children aged 1 year and New Zealand children aged 1-3 years. The 1995 National Nutrition survey data and the FSANZ dietary modelling computer program DIAMOND were used for the dietary intake assessment for Australian children aged 2-3 years. 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.

The highest estimated dietary lutein and zeaxanthin intake, as a proportion of the reference health standard, was the 95th percentile intake for New Zealand children aged 1-3 years following the lutein and zeaxanthin fortification of FSFYC (11% of the ADI).

At *Baseline* the major contributors (≥ 5%) to lutein and zeaxanthin intakes for Australian children aged 1 year were:

- fruit and vegetables juices (20%);
- peas, carrots, onions, sweet corn, and broccoli/cauliflower (each between 5-8%).

For Australian children aged 2-3 years, the major contributors were:

- oranges (19%);
- peas, pumpkin, sweet corn, and broccoli (each between 5-15%).

For New Zealand children aged 1-3 years, the major contributors were:

- silverbeet (23%);
- peas, pumpkin, and carrots (each between 8-10%).

Following the fortification of FSFYC with lutein and zeaxanthin, FSFYC was also a major contributor to the lutein and zeaxanthin intakes of Australian and New Zealand children aged 1-3 years.

7.4 Risk Characterisation

In order to determine if the level of intake of lutein and zeaxanthin following fortification of FSFYC would be of concern to public health and safety, the estimated dietary intakes were compared to the ADI for lutein and zeaxanthin of 2 mg/kg bw/day.

Following the fortification of FSFYC with lutein and zeaxanthin, Australian and New Zealand children aged 1-3 years have estimated mean and 95th percentile intakes of lutein and zeaxanthin below the ADI (see Tables 4 and 5 of Attachment 4 for more detail). FSANZ has estimated that the mean lutein and zeaxanthin intakes for Australian and New Zealand children aged 1-3 years are 3-4% ADI, and 8-11% ADI at 95th percentile intakes.

The data support the safety of lutein at the level of intake that would be achieved by addition of a combination of lutein and zeaxanthin (at approximately a 10:1 ratio) to FSFYC at a maximum concentration of 500 μg/L. FSANZ concludes that there are no public health and safety concerns for lutein and zeaxanthin when added as a nutritive substance to FSFYC at the maximum levels proposed by the Applicant.

RISK MANAGEMENT

8. Risk Management Issues

8.1 Protection of Health and Safety

FSANZ's risk assessments (Attachments 2-4) indicate that there is no risk from the addition of lutein to FSFYC at the levels proposed. These assessments also concluded that lutein added to FSFYC would be no less bioavailable than that naturally occurring in vegetables, and that the quantity proposed for addition is comparable with moderate food sources of lutein. The estimated daily lutein intake from FSFYC (150-233 μg) would be comparable to the intake from a child's serving of some fruit and vegetables. Therefore lutein added to FSFYC would be a viable contributor to the lutein intake and lutein status of children aged 1-3 years.

Therefore FSANZ proposes that lutein be permitted as an optional nutritive substance for addition to FSFYC in the form described as Lutein from *Tagetes erecta L* at a maximum concentration of 100 μg/serve.

The proposed level is stated as a per serve value to ensure that the compositional requirements for the addition of lutein to FSFYC are expressed in a manner consistent with the existing requirements in Standard 2.9.3. The proposed level of 100 μg/serve is based on a serving size of 200 mL which is a size commonly attributed to FSFYC by manufacturers of toddler formula, and represents the Applicant's original request for 500 μg/L.

8.2 Labelling requirements

Standard 2.9.3 of the Code prescribes specific labelling requirements for FSFYC in relation to nutrition claims for vitamins and minerals. In addition, the label on a package of a FSFYC must also comply with general labelling provisions contained in Part 1.2 of the Code. Permitting lutein to be added to FSFYC as proposed requires consideration of both ingredient labelling and nutrition labelling.

8.2.1 Ingredient labelling

Under existing requirements, general labelling provisions contained within Standard 1.2.4 – Labelling of Ingredients applies to nutritive substances permitted for addition to FSFYC. Therefore, any addition of lutein to FSFYC will require an accompanying declaration of lutein in the statement of ingredients.

8.2.2 Nutrition labelling and health claims

Standard 1.2.8 – Nutrition Information Requirements mandates the inclusion of a nutrition information panel on FSFYC. However, there is no requirement for lutein to be listed in the nutrition information panel unless a claim is made.

Clause 4 of Standard 1.2.8 provides that where a nutrition claim is made, a nutrition information panel is required. For the purposes of making a claim, lutein would be considered a nutrient or a biologically active substance. Therefore the nutrition information requirements in Standard 1.2 8 would apply. A nutrition claim could include a reference to the presence or amount of a particular nutrient or biologically active substance[10], or it may refer to a nutritional effect, for example 'calcium builds strong bones'.

Currently, where there is no reference value for a substance (in relation to an RDI, ESADDI or a reference value in the Table to sub clause 7(3) in Standard 1.2.8), nutrition claims could be made for a nutrient or biologically active substance.

Clause 7, Division 4 of Standard 2.9.3, regulates nutrition claims on the vitamin and mineral content of FSFYC. Subclause 7(2) provides that a specified minimum amount of the vitamin or mineral must be present in a serving for a claim to be made about that vitamin or mineral.

In line with this approach, FSANZ is proposing that a claim about lutein on a FSFYC could only be made if the product contains a minimum of 30 μg/serve of lutein. This requirement for a minimum claimable amount ensures consistency with the current provisions that regulate nutrition claims for vitamins and minerals in FSFYC. The proposed minimum claimable amount of 30 μg/serve of lutein in FSFYC reflects approximately 10% of the mean dietary intake of 1 year olds in Australia, as discussed in Attachment 4. This basis is conceptually similar to the derivation of Adequate Intakes for essential nutrients when there is insufficient information to allow estimation of the average requirement. There is no known requirement for lutein.

The approach to establish a minimum claimable amount in FSFYC, as an example of a special purpose food, is different to the current general approach in the Code for making claims about nutrients and biologically active substances where no minimum claimable amount is prescribed.

8.2.3 Nutrition and health claims – Proposal P293

FSANZ is considering new regulations around nutrition and health claims under Proposal P293, which will reside in a new Standard 1.2.7 – Nutrition, Health and Related Claims.

Under draft Standard 1.2.7, where a claim is made, it is proposed that the existing requirement for a declaration of the claimed nutrient or biologically active substance in the nutrition information panel will remain.

[10] Biologically active substance is defined in Standard 1.2.8 to mean a substance, other than a nutrient, with which health effects are associated.

However, conditions for making nutrition content claims will be more stringent and additional requirements for health claims are also being proposed[11].

For example, under the proposed new regulations, where there is no established reference value for a substance in the Code, only nutrition content claims that refer to the presence of a substance would be permitted, for example 'source of lutein' or 'contains lutein'. Claims such as 'good source of lutein' or 'rich in lutein' would not be permitted. Also, as is the case now, nutrition content claims will require declaration in the nutrition information panel of the average quantity of the nutrient or biologically active substances that is claimed.

Under the proposed health claims regime, it is intended that general level health claims will be permitted, however different conditions relating to minimum claimable amounts will be required to be met. If lutein is permitted to be added to FSFYC as proposed, any established minimum claimable amount for FSFYC would take precedence over the general conditions, subject to the proposed health claims Standard being gazetted.

Question for submitters:

Noting the current and proposed regulations for nutrition and health claims, should a minimum claimable amount be established for lutein, and possibly for other future nutritive substances, in FSFYC?

8.3 Novel Foods and the Status of Lutein

One submitter to the Initial Assessment Report raised the concern that lutein should be considered a novel food. However, as this Application is seeking the addition of lutein in FSFYC 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 in this report, achieving the same level of assurance of safety as would be required for novel foods.

9. Options

At Draft Assessment FSANZ is considering two regulatory options for Application A597:

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

- Option 2 – amend Division 4 of Standard 2.9.3 to permit the voluntary addition of lutein as a nutritive substance at a maximum concentration of 100 µg/serve in FSFYC and to require a minimum declaration of 30 µg/serve when a nutrition claim is made.

[11] Further information on the proposed requirements for nutrition content claims and health claims are available from the FSANZ website at: http://www.foodstandards.gov.au/standardsdevelopment/proposals/proposalp293nutritionhealthandrelatedclaims/index.cfm. Specific discussion on the recommended approach for biologically active substances is located in Attachment 6 to the Draft Assessment Report.

10. Impact Analysis

10.1 Affected Parties

The parties affected by this Application are: **consumers** being young children who consume FSFYC and their **carers**; **industry** being Australian and New Zealand manufacturers and importers of FSFYC; and the **Governments** of Australia and New Zealand.

10.2 Cost-Benefit Analysis

This analysis provides an assessment of the potential impacts of the regulatory options for Application A597 on the affected parties.

10.2.1 Option 1 – Status quo

10.2.1.1 Consumers

It is likely that maintaining the *status quo* will have little impact on young children, as a range of safe and suitable foods will continue to be available to provide appropriate nutrition for this age group, including foods that naturally contain lutein.

10.2.1.2 Industry

There is no additional benefit for industry in maintaining the *status quo.* Maintaining the status quo is unlikely to create barriers to trade. However, while the market for FSFYC is believed to be relatively small it is possibly growing, and maintaining the *status quo* could limit industry innovation and potential markets either domestically or internationally to countries that permit the addition of lutein to FSFYC.

10.2.1.3 Government

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

10.2.2 Option 2 – Amend Standard 2.9.3 Division 4

10.2.2.1 Consumers

Permitting the addition of lutein to FSFYC would provide young children with an additional source of lutein in their diet should they choose to consume FSFYC. The addition of lutein at the levels proposed would provide a safe source of lutein, and any potential benefits obtained from additional lutein would be available to young children.

Any additional manufacturing costs that may result from the production of FSFYC with added lutein are likely to be passed on to those who purchase these products.

10.2.2.2 Industry

Option 2 would allow industry to produce new products for the Australian and New Zealand markets, and potentially, international markets.

As the addition of lutein to FSFYC would be a voluntary permission, there would not be any barriers to trade. Rather, Option 2 could potentially provide an opportunity to export FSFYC to countries where the addition of lutein is permitted, and potentially to manufacture one formulation for worldwide distribution. Option 2 would also allow for the importation of any FSFYC containing lutein.

The addition of lutein to FSFYC would also provide an opportunity for manufacturers to differentiate their products from other competitors.

10.2.2.3 Government

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

10.3 Comparison of Options

A comparison of the Options presented at Draft Assessment indicates that both maintaining the *status quo* (Option 1) and Option 2 would continue to protect the health and safety of young children who consume FSFYC.

However, FSANZ's assessment shows that the addition of lutein in the form and at the levels proposed in Option 2 is safe and suitable for young children, and would offer an added source of lutein in addition to that obtained naturally through the diet.

Option 2 also potentially increases opportunities for product innovation on the domestic market, and for increased international trade through potential importation and export of FSFYC 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 STRATEGY

11. Communication

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

FSANZ released a joint Initial Assessment Report for both Application A594 and Application A597 for a six-week consultation period from 4 April to 16 May 2007.

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

Overall, the majority (five of the nine submitters) did not provide a preferred option for Application A597 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. Also, 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, three industry submitters (including the Applicant) supported permitting the addition of lutein to FSFYC. However, one supported this Option contingent on satisfactory safety assessment by FSANZ.

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

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.

As the proposed addition of lutein to FSFYC would be a voluntary permission, the amendments to the Code would not create any barriers to trade. Also, the proposed permissions would harmonise with those countries that have reportedly gained approval to add lutein to toddler formula and provide some opportunities for international trade.

It is expected that the proposed amendments to the Code permitting voluntary addition of lutein to FSFYC will harmonise Australian and New Zealand standards with some overseas practice, and will not result in a potential barrier to trade. As such, WTO member nations will not be notified of the proposed amendment to Standard 2.9.3 under either the Technical Barriers to Trade or Sanitary and Phytosanitary Agreements.

CONCLUSION

13. Conclusion and Preferred Approach

Preferred Approach

Option 2 is the preferred regulatory approach for Application A597. This approach would result in an amendment to Standard 2.9.3 to permit the addition of lutein to FSFYC at no more than 100 µg/serve, and to require at least 30 µg/serve of lutein in FSFYC where a claim has been made on the presence of lutein in the product.

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

The addition of lutein to FSFYC proposed as part of Option 2:

- does not pose any health and safety risks to children aged 1-3 years;

- will be able to act as a viable contributor to the lutein intake and lutein status of children aged 1-3 years;

- is consistent with relevant international regulations, and will facilitate trade; and

- as the impact analysis concludes that Option 2 provides a greater net benefit to affected parties than the *status quo* (Option 1).

FSANZ therefore recommends the proposed draft variation to the Code that is provided in Attachment 1.

14. Implementation and Review

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

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

ATTACHMENTS

1. Draft variation to the *Australia New Zealand Food Standards Code*
2. Nutrition Assessment
3. Hazard Assessment
4. Dietary Intake Assessment
5. Food Technology Report.
6. Summary of submissions on the Initial Assessment Report for Applications A594 and A597.

Attachment 1

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

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

To commence: on gazettal

[1] ***Standard 2.9.3*** *of the Australia New Zealand Food Standards Code is varied by inserting –*

6A Lutein

(1) Lutein from *Tagetes erecta L*. is a nutritive substance which may be added to a formulated supplementary food for young children, provided the total of the naturally occurring and added amounts of lutein is no more than 100µg per serving.

(2) The label on a package of formulated supplementary food for young children must not include any words indicating, or any other indication, that the product contains lutein unless the total amount of lutein is no less than 30µg per serving.

Attachment 2

Nutrition Assessment

Summary

The Applicant has requested the addition of lutein to FSFYC to a maximum of 500 µg/L. At this level of addition, FSFYC would provide at least 100 µg of added lutein in a recommended serving of 200 mL. The addition would also place FSFYCs amongst foods that contain moderate amounts of lutein and zeaxanthin. For Australian and New Zealand consumers of FSFYC who consume on average one serve per day, it is likely that the mean daily lutein intake from FSFYC (150-233 µg; see Attachment 4) would be comparable to the intake from a serve of some fruit and vegetables, such as 4 g peas or 14 g boiled carrots.

Information from the Applicant also indicates that FSFYC ingredients contain some natural level of lutein and zeaxanthin. This innate source contributes approximately 4-6 µg/serve of lutein to the total concentration of a FSFYC.

Lutein from supplements or added to formula appears to have lower bioavailability compared with lutein contained in breast milk or eggs. Lutein from vegetables appears to have similar bioavailability compared with lutein in supplements, assuming no losses due to processing and cooking of foods. As the addition of lutein to FSFYC will likely increase the mean daily contribution of FSFYC to levels comparable with moderate food sources of lutein, it is therefore considered that FSFYC will be able to act as a viable contributor to the lutein intake and lutein status of children aged 1-3 years.

1. Introduction

This Nutrition Assessment examines the likely impact on the nutritional status of children aged 1-3 years from lutein added to formulated supplementary foods for young children (FSFYC) in its free (unesterified) from.

There is limited data on children of 1-3 years in scientific discussions on lutein's nutritional characteristics. Therefore, data on adults or older children have been considered, as these age groups consume a varied diet similar to children aged 1-3 years. Data on infants has been used sparingly, as the eating patterns of this age group have not progressed to a full diet. *In vitro* and animal data have also been considered where the evidence base is not strong enough to use more applicable information.

Three broad areas have been considered in this assessment:

- the concentration of lutein in the general foods and in FSFYC;
- the nutritional function of lutein; and
- the bioavailability of supplemental and added forms of lutein.

2. Concentration of lutein and zeaxanthin in general foods and in formulated supplementary foods for young children.

Lutein can be found in foods either as lutein or as its isomer, zeaxanthin. The amount of lutein in fruits and vegetables tends to predominate over zeaxanthin. In spinach for example, lutein was present at a concentration of 58.7 mg/kg compared with zeaxanthin at 1.4 mg/kg; a lutein:zeaxanthin ratio of approximately 40:1 (Chitchumroonchokchai *et al*., 2004). However, food composition tables usually do not provide separate values for lutein and zeaxanthin because the laboratories supplying the data have measured total xanthophyll carotenoids i.e. lutein plus zeaxanthin combined. The United States Department of Agriculture (USDA) has published a data set (United States Department of Agriculture, 2005) containing information on the combined lutein and zeaxanthin concentrations of American foods. Data on the lutein and zeaxanthin concentrations for Australian and New Zealand foods is not available but the US database lists foods similar to those consumed in Australia and New Zealand.

The lutein and zeaxanthin contents of selected foods are presented in Table 1. The data shows that vegetables, especially green leafy vegetables, have the greatest lutein and zeaxanthin contents. Some fruits and corn-based cereal items also have moderate lutein and zeaxanthin concentrations. In contrast, meat, dairy and non-corn cereal products are at the lower end of the scale, with nil lutein/zeaxanthin contents (data not shown).

Table 1: USDA lutein and zeaxanthin concentrations in selected foods

Food item	Lutein and zeaxanthin (µg/100g)
Kale, cooked, boiled, drained, without salt	18246
Spinach, cooked, boiled, drained, without salt	11308
Peas, green, frozen, cooked, boiled, drained, without salt	2400
Lettuce	2313
Broccoli	1403
Brussels Sprouts, cooked, boiled, drained, without salt	1290
Breakfast Cereal, Corn Flakes	977
Corn, sweet, yellow, cooked, boiled, drained, without salt	949
Carrots, cooked, boiled, drained, without salt	687
Beans, green, cooked, boiled, drained, without salt	564
Egg, whole, cooked, hard boiled	354
Egg, whole, raw, fresh	331
Celery	283
Wheat flour, wholegrain	220
Nectarines	130
Oranges	129
Tomatoes, red, ripe	123
Orange juice	115
Peaches	91
Bread, wheat	48
Pears, canned in juice	34
Cucumber, with peel	23

The Applicant has stated that FSFYC will likely contain close to a maximum of 500 µg/L of added lutein, which would provide at least 100 µg of added lutein in a recommended serving of 200 mL. This is a modest amount of lutein, equivalent to that contained for example in 4 g of peas or 14 g of boiled carrots.

As well as the proposed lutein addition to FSFYC, information from the Applicant indicates that FSFYC ingredients contain some natural level of lutein and zeaxanthin (Kemin Health, 2005). This innate source would contribute approximately 20 - 30 μg/L of lutein to the total concentration of an FSFYC.

3. Nutritional function of lutein

Data is not available on nutritional function of lutein specific to children of young ages, or specific to the consumption of FSFYC. *In vivo* data on infants and animals, and *in vitro* data is the only identified material that assesses the nutritional role of added forms of lutein.

3.1 Antioxidant activity

Lutein and zeaxanthin have the ability to act as anti-oxidants in the human body, in addition to their other nutritional functions. In particular, it has been suggested that lutein and zeaxanthin can protect against oxidative damage to the retina (Chong *et al*., 2007).

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

3.2 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 and young children, as light transmission to the back of the eye is a function of age, and is more pronounced in the younger eyes compared with those of older ages (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.

4. Relative bioavailability of added forms of lutein

There is scant information on the bioavailability of lutein added to a milk-based formula relative to other foods. In infants receiving formula, it took approximately five times the concentration of lutein to achieve similar plasma lutein concentrations compared with breast-fed infants.

Study	Milk source	n	Age (wk)	Milk lutein + zeaxanthin concentration (μg/L)	Infant serum lutein + zeaxanthin concentration (μg/L)
Wyeth Nutrition (2006a)	Breast	41	8	57	126
Wyeth Nutrition (2006b)	Formula	21	5	289	143

Note: Serial blood samples were not taken and it is therefore unknown whether steady state serum concentrations had been reached over the duration of the studies.

There are limited data on the relative bioavailability of supplemental lutein compared with lutein contained naturally in food. Using a randomized crossover design, nine healthy young adults received 1.7 mg lutein/d from eating foods made with carrots or from a lutein supplement (Molldrem *et al*., 2004). Over a 14 day period, participants consumed their allocated treatment for 7 days followed by 7 day washout. Serum lutein concentrations were determined over the 14 days and expressed as area under the curve (AUC).

Study	n	Treatment	Mean (SD) 14 day AUC (μmol/L·d)	Difference between treatments
Molldrem *et al.* (2004)	9	1.7 mg from foods made using cooked carrots	1.36 (0.53)	P < 0.004
		1.7 mg in oil (supplied by Kemin)	2.09 (0.58)	

In this study, supplemental lutein was well absorbed compared with lutein contained in foods made with cooked carrots.

In a crossover study, 10 healthy men received for nine days a lutein supplement, lutein-enriched eggs, or spinach, each providing 6 mg lutein; blood samples were taken intermittently over the treatment periods. The greatest differences among treatments occurred on day 10, the day after cessation of treatment.

Study	n	Treatment (6 mg)	Mean[1] change (SD) from baseline at day 10 (nmol/[L·mg dose])	Difference between egg and other treatments
Chung *et al.* (2004)	10	Supplement (Vitamin power)	21.7 (3.5)	P< 0.001
		Enriched eggs (Kemin)	67.3 (8.2)	
		Spinach	31.7 (4.6)	P < 0.005

[1] Geometric mean

These data indicate that lutein is more bioavailable from eggs compared with a lutein supplement or spinach. There was no difference in the apparent bioavailability of lutein from a supplement or spinach.

Lutein from supplements or added to formula appears to have lower bioavailability compared with lutein contained in breast milk or eggs. Lutein from vegetables appears to have similar bioavailability compared with lutein in supplements, assuming no losses due to processing and cooking of foods.

4.2 Interaction of lutein and zeaxanthin with other carotenoids

There are some data to suggest that large doses of purified β-carotene may impair the intestinal absorption of lutein and zeaxanthin. An early trial in which subjects 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).

Following the trial by Micozzi *et al.* (Micozzi *et al*., 1992), several other studies were undertaken to examine the possible interaction between lutein and β-carotene. Kostic *et al.* (1995) investigated the effects on serum lutein following single oral doses of lutein and zeaxanthin, β-carotene, or both. 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 incomplete β-carotene conversion to vitamin A in the presence of the xanthophyll carotenoids. It should be noted that supraphysiological amounts of lutein and β-carotene were used. The dose used was 0.5 μmol/kg body weight, equivalent to a range of lutein supplementation of 15,000 to 26,000 μg/d, dependent upon the body weights of the participants. Data from another trial (Van den Berg and Van Vliet, 1998) 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.

The Applicant has also 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). The mean post-supplementation plasma *cis* β -carotene concentration was higher in the group receiving the greatest amount of lutein, but there was no difference in the plasma concentrations of all *trans* β-carotene or α-carotene between groups.

The interaction of lutein (and β-carotene) with lycopene has been studied by Riso *et al.* (2004). This study involved the comparison of spinach consumption alone (a source of lutein and β-carotene), and its consumption with tomato puree (a source of lycopene). Both of these test foods were given with a low carotenoid diet to 9 healthy adults over 21 days (crossover with a 14 day washout period). The results showed that serum lutein levels were not significantly different ($p<0.05$) between the spinach and spinach-tomato diets (mean 1.59 μmol/L and 1.55 μmol/L respectively).

Although interactions have been found that affect the absorption of carotenoids taken in large doses, these findings have not been replicated when carotenoids have been consumed from vegetables or supplemented formula.

4.3 Interaction of lutein with fat intake

Lutein is a fat soluble substance, and can be influenced by a number of dietary factors related to fat intake. In particular, the concurrent presence of fats and oils in the intestinal lumen may have an effect on the bioavailability of lutein.

The impact of fat intakes on lutein has previously been demonstrated in a randomised crossover trial. Roodenburg *et al.* (2000) compared the effect of different levels of concurrent fat intake on the serum levels of lutein, vitamin E, α-carotene, and β-carotene of 60 healthy adults. Subjects were given a supplement of either vitamin E, α/β-carotene, lutein or a placebo in the presence of a low (3 g) or high (36 g) fat spread over 14 days. The results showed that serum lutein increased by 158 nmol/L and 365 nmol/L for the low and high fat intakes respectively ($p<0.001$). In contrast, the higher concurrent fat intake had no appreciable impact ($p>0.05$) on vitamin E, α-carotene, or β-carotene status.

5. Conclusion

The available evidence indicates that the addition of lutein to FSFYC will provide at least the same level of nutrition as lutein available from natural sources. As the addition of lutein to FSFYC will likely increase the mean daily contribution of FSFYC to levels comparable with moderate food sources of lutein (based on dietary modelling results in Attachment 4), it is therefore considered that FSFYC will be able to act as a viable contributor to the lutein intake of children aged 1-3 years.

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Attachment 3

Hazard Assessment

Summary

This Application seeks permission for lutein and zeaxanthin to be added to formulated supplementary food for young children (FSFYC), intended for infants from one to three years old. The main food in this category is milk-based supplementary drinks, known as 'toddler formula'. Addition of lutein and zeaxanthin to FSFYC is requested to give a final concentration of lutein in these products of 500 µg/L.

Lutein and zeaxanthin are naturally occurring xanthophyll carotenoids. Lutein and zeaxanthin are normal constituents of the diet, are 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 (~96%) with a small amount of zeaxanthin (~4%). The extract is present at approximately 20% in safflower or other edible oil.

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/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.

FSANZ assessed the submitted evidence on the safety of lutein as part of Application A594, and concluded that the addition of lutein to infant formula at a maximum level of 250 µg/L does not pose any public health and safety risk to formula-fed infants. The data assessed included 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 considered. No adverse effects have been observed in any of the studies on lutein and zeaxanthin. Carotenodermia (skin yellowing) is observed at high doses; however this is considered harmless and is readily reversible upon discontinuation of high intakes of lutein.

Relatively large doses of lutein (6000 µg/d) have been used safely in humans over periods of several months as an exploratory treatment for age-related macular disease (Bartlett & Eperjesi, 2007). Other primates (Rhesus Macaque monkeys) have received even larger doses of either lutein or zeaxanthin equivalent to 28,000 to 44,000 µg of the carotenoids per day, dependent upon the weight of the monkey, again over a period of several months without ocular toxicity (Khachik et al., 2006). The expected intake of 100 – 300 µg of young children consuming lutein-enriched FSFYC is modest in comparison.

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.

1. Assessment

FloraGLO® Lutein 20% Liquid in Safflower Oil is a purified extract combined with vegetable oil (e.g. safflower oil) to give a preparation containing approximately 20% lutein. The Applicant has provided statements that their product 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.

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

The Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) first considered xanthophylls obtained from *Tagetes erecta* L. petals at its 31st meeting, in 1987. At that time, no toxicological data was available; however, tentative quality specifications were prepared. *Tagetes* extract containing low concentrations of lutein was considered by JECFA at its 55th and 57th meetings, in 2001 and 2002 respectively, at which time the tentative specifications were superseded by full specifications. These specifications relate to the low concentration lutein preparations only, not the high lutein concentration preparation under consideration in this Application.

1.1.1 Sixty third meeting of JECFA, 2004

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

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

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

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

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

1.2 Aims of the current assessment

FSANZ assessed the safety of lutein as part of Application A594 – Addition of lutein as a nutritive substance to infant and follow-on formula. This report is publicly available at http://www.foodstandards.gov.au/_srcfiles/DAR_A594_%20Lutein.doc.

Therefore, the aims of the current assessment were to:

- Review the assessment conducted as part of A594; and
- Determine the safety of lutein and zeaxanthin added to FSFYC.

2. Summary of studies considered for A594

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

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

Parameter	332 µg lutein/kg bw	1660 µg 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.

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

This study aimed to determine the absorption of lutein by two groups of three 13-week old infant rhesus monkeys (*Rhesus macaques*) when administered in infant formula. On the day of dosing, infants were separated from their mothers and fasted for six hours. Monkeys were given a single dose of either 166 µg lutein/kg bw or 1660 µg lutein/kg bw in S-26 Gold infant formula via gavage. Blood was drawn at 0, 1, 2, 4 and 6 hours after formula administration and serum prepared. Serum lutein, cholesterol and triglycerides were measured. For lutein, measured by HPLC, the mean C_{max}, mean T_{max}, and mean AUC were calculated and are shown in the table below.

Parameter	166 µg lutein/kg bw ± SD*	1660 µg 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.

2.3 Human studies

2.3.1 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 200 μg lutein/L for 36-37 days. The lutein source used for fortification contained lutein and zeaxanthin in a ratio of approximately 13:1. The S-26 Gold formula naturally contains 19.8 μg lutein/L, so the two test formulas contained 47.4 and 288.5 μg/L respectively (added to 150% of the label claim to account for manufacturing and storage shelf life losses). It was calculated that plasma lutein concentrations would have reached a steady state within this time period. In addition to lutein, other carotenoids (alpha- and beta-cryptoxanthin, cis- and trans-beta carotene, lycopene, zeaxanthin and cis-lutein/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/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.

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

A prospective, randomised, controlled, double-blind study was conducted in healthy <14 day old Philippine infants.

The addition of lutein to infant formula at a level of 200 μg/L was evaluated with regard to growth, incidence of adverse events, blood chemistry, general eye health and visual acuity.

230 infants (118 females and 112 males) were randomised into one of two formula groups: control formula (S-26 Gold) and experimental formula (S-26 Gold with 200 µg/L lutein). Formula was provided for four months. Subjects were weighed and measured at weeks 0, 4, 8, 12 and 16. Formula intake over three days was recorded during weeks 4, 8 and 12. Temperament scales were completed by the parent/caregiver in weeks 8 and 12. Infant health history and physical examination, including fundoscopic exam was conducted at week 0 and 16. Visual acuity measurements were conducted at week 16, followed by the collection of infant blood samples. Any adverse events that occurred throughout the study were recorded.

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

3. Discussion

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

FSANZ considered data submitted by the Applicant in support of A594, which 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.

An ADI was set for lutein at 2 mg/kg bw per day, on the basis of the 90-day, repeat-dose toxicity study in rats, with a safety factor of 100. Although the ADI was not set for infants below 12 weeks of age, lutein was considered safe for addition to infant formula (suitable for infants 0-12 months) at the level proposed (250 µg/L). Several issued were considered in for in coming to this conclusion including:

- The presence of lutein in breast milk. 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. 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.

In regard to the safety of lutein and zeaxanthin for young children aged one to three years, similar issues have been considered. FSFYC does not represent the sole source of nutrition for young children, who will also be exposed to lutein from other foods in their diets (e.g. fruit, vegetables and eggs). Therefore it is important to include these sources in dietary intake assessment. However, no adverse effects have been associated with lutein in any of the studies conducted, either in animals or in humans, and there is no indication that effects might be expected in young children. Therefore, FSANZ considers the ADI of 2 mg/kg bw per day set for Application A594, is applicable to young children aged one to three years. Intakes of lutein at or below this level represent no risk to young children.

4. Conclusions

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.

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 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 adverse effects were observed in the available animal and human studies. 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.

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Attachment 4

Dietary Intake Assessment Report

Summary

Dietary intakes were calculated using constructed theoretical diets for Australian children aged 1 year and New Zealand children aged 1-3 years. The 1995 National Nutrition survey data and the FSANZ dietary modelling computer program DIAMOND were used for the dietary intake assessment for Australian children aged 2-3 years. 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.

Estimated mean and 95th percentile dietary lutein and zeaxanthin intakes were below the ADI for Australian children aged 1 year and 2-3 years and for New Zealand children aged 1-3 years. The highest estimated dietary lutein and zeaxanthin intake, as a proportion of the reference health standard, was the 95th percentile intake for New Zealand children aged 1-3 years following the lutein and zeaxanthin fortification of Formulated Supplementary Foods for Young Children (FSFYC) (11% ADI). The ADI for lutein is for added sources only. FSANZ has compared intakes of total lutein and zeaxanthin from naturally occurring and added sources to the ADI, therefore this will result in an overestimate of the level of risk.

At *Baseline*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes for Australian children aged 1 year were:

- fruit and vegetables juices (20%);
- peas (8%)
- carrots (7%)
- onions (7%)
- sweet corn (6%); and
- broccoli/cauliflower (5%).

For Australian children aged 2-3 years, the major contributors were:

- oranges (19%);
- peas (15%);
- pumpkin (9%);
- sweet corn (6%); and
- broccoli (5%).

For New Zealand children aged 1-3 years, the major contributors were:

- silverbeet (23%);
- peas (10%);
- pumpkin (9%); and
- carrots (8%).

Following the fortification of FSFYC with lutein and zeaxanthin, FSFYC was also a major contributor to the lutein and zeaxanthin intakes of Australian and New Zealand children aged 1-3 years.

1. Background

An Application was received by FSANZ to amend the Code to allow the addition of lutein from marigold (*Tagetes erecta* L.), as a nutritive substance, to Formulated Supplementary Foods for Young Children (FSFYC) at up to 500 µg/L.

Lutein is an oxygenated carotenoid (xanthophyll pigment) which occurs naturally with the isomer zeaxanthin in many foods such as vegetables and fruits (Joint FAO/WHO Expert Committee on Food Additives, 2005). Carotenoids are synthesized by all plants and some microorganisms (Ahmed *et al*., 2005). Rich sources of lutein and zeaxanthin include kale, spinach, cress, Swiss chard, green peas, lettuce, zucchini, Brussels sprouts, broccoli and corn (maize) (U.S.Department of Agriculture, 2005).

2. Dietary intake assessment provided by the Applicant

Dietary intake assessment data for lutein and zeaxanthin were provided by the Applicant (see Table). The Applicant estimated mean baseline lutein intakes to be 636 µg/day for American (USA) children aged 1-3 years and 344 µg/day for Australian children aged 1-3 years. These intakes excluded the intake of lutein and zeaxanthin from formula. The Applicant stated that older infants and children consuming 600 mL of lutein-fortified follow-on formula would increase lutein intakes by approximately 300 µg/day. The dietary intake assessment for American children was undertaken using national survey data from the National Health and Nutrition Examination Survey (NHANES 2001-2, released 2004), which included two 24-hour recalls for collecting food consumption data, and the USDA National Nutrient Database for Standard Reference (Release 17, 2004). The dietary intake assessment for Australian children was undertaken using the Food Intake and Nutrition Status (FINS) Study (FINS 2005-2006, pilot results released Feb 2006), which included a three day weighed record for collecting food consumption data, and the USDA National Nutrient Database for Standard Reference (Release 17, 2004).

Whilst it is not stated clearly that the intakes presented in Table 1 are 'baseline' intakes, it is assumed that this is the case given text provided in the application that states 'In order to estimate current lutein intakes amongst Australian toddlers…', and that the section following this in the application then refers specifically to 'Potential lutein intake from proposed products' with quantitative intakes provided.

The dietary intakes estimated by the Applicant at the mean for Australia were around half of that estimated for children in the USA of the same age (1-3 years). Different dietary surveys were used for these assessments, however, the mean would not be expected to be influenced by the number of days of dietary survey duration, however, it would be expected that a survey of longer duration would result in lower high percentile intakes, which is the case for the 90th percentile results. In addition to this, the same concentration dataset was used for both studies.

Therefore, the difference in the estimated mean intakes between Australian and American children could be attributed to the way in which concentrations were assigned to food groups (for which no further details are provided to confirm this assumption) or differences in food consumption amounts for different foods. Food consumption amounts and major contributing foods were not provided in the results which could assist in demonstrating this.

Table 1: Estimated mean and 90th percentile daily intake of lutein and zeaxanthin at baseline for USA and Australian children aged 2 months – 8 years, as provided by the Applicant

Country	Age Group	Number of respondents	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

* Uses NHANES 2001-2, released 2004 and the USDA National Nutrient Database for Standard Reference (Release 17, 2004).
# Uses the Food Intake and Nutrition Status (FINS) study consumption data (2006 release) and the United States Department of Agriculture (USDA) National Nutrient Database for Standard Reference (Release 17, 2004).

Based on dietary intake data for the USA assuming a high intake percentile and low percentile body weight for the age group, the Applicant estimated that lutein intake for a child aged 1-3 years would be 9% of the JECFA ADI of 2000 µg/kg bw/day. Using similar assumptions for the Australian estimates, including the highest recommended formula consumption, the applicant estimated dietary intakes equivalent to 7% of the ADI. For an average consumer it was estimated that intakes would be around 1% of the ADI.

A dietary intake assessment was considered necessary to be conducted by FSANZ 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 FSFYC on public health and safety. While data were provided by the Applicant on estimated dietary intakes for Australian children, data were not provided for New Zealand children aged 1-3 years. Intake assessments needed to be conducted for both the Australian and New Zealand populations. Since the ADI relates to lutein and zeaxanthin rather than lutein only, all dietary intake assessments in this report refer to lutein and zeaxanthin.

3. Dietary modelling conducted by FSANZ to estimate lutein and zeaxanthin intakes

3.1 What is dietary modelling?

Dietary modelling is a tool used to estimate dietary exposure to (or intake of) food chemicals, including nutrients, 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 documents all such decisions, model assumptions and data limitations to enable the results to be understood in the context of the data available and so that FSANZ risk managers can make informed decisions.

3.2 Population groups assessed

The target group was identified as children aged 1-3 years as this is the age group for which FSFYC are targeted.

3.3 Dietary survey data

DIAMOND contains dietary survey data for both Australia and New Zealand; the 1995 NNS from Australia that surveyed 13,858 people aged 2 years and above, and the 1997 New Zealand NNS that surveyed 4,636 people aged 15 years and above. Both of these surveys used a 24-hour food recall methodology. FSANZ does not currently hold food consumption data in DIAMOND in the correct format from the 2002 New Zealand National Children's Nutrition Survey (CNS) to enable dietary intake assessments to be conducted. The 2002 NZ CNS surveyed 3,275 New Zealand children aged 5-14 years. The Australian NNS data were used in the assessment of lutein and zeaxanthin intakes for Australian children aged 2-3 years.

Since the target group was identified as children aged 1-3 years, the data from the NNSs could not be used directly in assessment for Australian children aged 1 year and New Zealand children aged 1-3 years. Theoretical diets were constructed to estimate dietary lutein and zeaxanthin intakes for Australian children aged 1 year and New Zealand children aged 1-3 years (see Section 3.7.1).

3.4 Dietary intake assessment approach

Lutein and zeaxanthin intakes were estimated by combining usual patterns of food consumption, as derived from either NNS data or theoretical diets, with current concentrations of lutein and zeaxanthin in foods and the current and proposed levels of use of lutein and zeaxanthin in FSFYC.

Dietary Intake = nutrient concentration x food consumption amount

3.5 Lutein and zeaxanthin concentration data

The levels of lutein and zeaxanthin in foods that were used in the dietary intake assessment were derived from the Application and from the U.S. Department of Agriculture (USDA) nutrient database (U.S.Department of Agriculture 2005) in the absence of data for these substances being available for Australia and New Zealand.

Concentrations of lutein and zeaxanthin were assigned to each of the food groups in the theoretical diets and to food groupings in the Australian NNS. Concentrations of lutein and zeaxanthin were assigned to food groups in the NNS using DIAMOND food classification codes, based on raw agricultural commodities.

The Applicant provided proposed maximum concentrations of lutein in FSFYC. 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 material proposed by the Applicant for addition to FSFYC is a purified extract of lutein from marigold oleoresin which contains both lutein and its isomer zeaxanthin in a ratio of approximately 10:1). The lutein and zeaxanthin concentration for FSFYC that was used in the dietary intake assessments was 550 µg/L.

3.6 Scenarios for dietary intake assessments

3.6.1 *Baseline* model

This model represents estimated lutein and zeaxanthin intakes for each population group, assessed in the current regulatory environment (i.e. before permission to add lutein and zeaxanthin FSFYC 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 currently used in some brands of FSFYC.

3.6.2 *Scenario* model

This model represents estimated lutein and zeaxanthin intakes for each population group after permission to add lutein and zeaxanthin to FSFYC is in effect in Australia and New Zealand. As for *Baseline*, the model took into account naturally occurring lutein and zeaxanthin in food but not lutein and zeaxanthin intakes from the use of supplements.

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

3.7.1 Australian children aged 1 year and New Zealand children aged 1-3 years

Research conducted by UMR Research and the New Zealand Food Safety Authority (NZFSA) reported that, for children aged 1-3 years who consume at least 200 mL of toddler milk (FSFYC) per day (18% of all 1-3 year old children; 85% of those who consume FSFYC), the average consumption of FSFYC was 460 mL per day (New Zealand Food Safety Authority, 2006).

The theoretical diet for Australian children aged 1 year contained 423 g/day of milk; the theoretical diet for New Zealand children aged 1-3 years contained 267 g/day milk and approximately 15 g/day of infant formula/ follow on formula. In the theoretical diets used in this assessment, it was assumed that there was complete replacement of milk, infant formula and follow-on formula with FSFYC. In the assessments conducted using the 1995 NNS, it was assumed that FSFYC replaced all full fat and unspecified fat content milk.

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

95th percentile intake = mean intake x 2.5

3.7.1.1 Australian children aged 1 year

The theoretical diet for Australian children aged 1 year was based on information on recommended energy intakes, mean body weight, the proportion of milk and solid foods in the diet for a 1 year old child, and data from the 1995 NNS on foods consumed by a 2 year old child.

The recommended energy intake for a one year old boy (FAO, 2004) at the 50th percentile weight (WHO, 2006) was used as the basis for the theoretical diet. Boys' weights were used because boys tend to be heavier than girls at the same age and therefore have higher energy and food requirements. The body weight of a 50th percentile one year old boy was 9.6 kg.

It was assumed that 35 per cent of energy intake was derived from milk and 65 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 1 year old's diet. Certain foods such as nuts (excluding peanut butter), 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).

A detailed description of the theoretical diet used for Australian children aged 1 year can be found in Table A1.1 in Appendix 1.

3.7.1.2 New Zealand children aged 1-3 years

The Simulated Diet for 1-3 year old toddlers that was used in the analysis of the 2003/04 New Zealand Total Diet Survey (NZ TDS) was used to estimate the mean dietary lutein and zeaxanthin intake in this assessment. The Simulated Diet was a 14-day diet constructed to represent average consumers and was derived from regional studies, rather than national studies of food and nutrient consumption (Vannoort and Thomson, 2005) and did not included the consumption of FSFYC. In order to assume a 'worst-case' scenario, the body weight of a 1 year old child (9.6 kg) was used in the calculations of lutein and zeaxanthin intakes, where lutein and zeaxanthin intakes were expressed in mg/kg bw/day.

A detailed description of the theoretical diet used for New Zealand children aged 1-3 years can be found in Table A1.2 in Appendix 2.

3.7.2 Australian children aged 2-3 years

No FSFYC were consumed in the 1995 Australian NNS and, as a consequence, assumptions were made about the consumption of FSFYC in the dietary intake assessment process. It was assumed that 2-3 year old children would replace 100% of full fat and unspecified fat content fluid cow's milk (plain and commercially flavoured) consumption, including that used in cooking, with FSFYC – 93% of 2-3 year old Australian children were consumers of these milks or foods containing milks in the NNS. Therefore, it was assumed that 93% of 2-3 year old children were consumers of FSFYC for the purpose of this assessment. Cheeses, ice creams and ice confections, yoghurts and reduced and low fat milks were not replaced with FSFYC.

As discussed previously, research conducted by UMR Research and the New Zealand Food Safety Authority (NZFSA) reported that, for children aged 1-3 years who consume at least 200 mL of toddler milk (FSFYC) per day the average consumption of FSFYC was 460 mL per day. In the 1995 NNS, the average consumption of full fat and unspecified fat content fluid cow's milks (and therefore of FSFYC in this assessment) was 403 grams/day for those 2-3 year old children consuming these foods.

Lutein and zeaxanthin intakes were calculated for each individual child aged 2-3 years in the NNSs using their individual food consumption records from the dietary survey. The DIAMOND program multiplied the specified concentration of lutein and zeaxanthin for an individual food by the amount of the food that an individual consumed in order to estimate the intake of lutein and zeaxanthin from each food. Once this had been completed for all of the foods specified to contain lutein and zeaxanthin, the total amount of lutein and zeaxanthin consumed from all foods was summed for each individual. Population statistics (such as mean and 95th percentile intakes) were then derived from the individuals' ranked intakes.

3.7.2.1 How were the percent contributors calculated?

Percentage contributions of each food group to total estimated lutein and zeaxanthin intakes were calculated by summing the intakes for a food group from each individual in the population group who consumed a food from that group and dividing this by the sum of the intakes of all individuals from all food groups containing lutein and zeaxanthin, and multiplying this by 100.

4. Assumptions used in the dietary intake assessment

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

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

4.1 Consumer behaviour

- Consumption of foods as recorded in the NNSs represent current food consumption amounts;

- consumption of foods as outlined in the theoretical diets represent current food consumption amounts for Australian children aged 1 year and New Zealand children aged 1-3 years;
- 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;
- in the theoretical diets, all children aged 1-3 years consume FSFYC;
- in the assessment that used the 1995 NNS, all children aged 2-3 years who consumed full fat or unspecified fat content milk will replace these milks with FSFYC;
- children aged 1-3 years consume FSFYC in addition to solid foods; and
- the substitution of FSFYC for milk is on a 'volume for volume' basis rather than on an energy basis.

3.2 Concentration Data

- It was assumed that USA data (from the United States Department of Agriculture) (U.S.Department of Agriculture 2005) on the lutein and zeaxanthin concentrations in foods were representative of Australian and New Zealand foods;
- where a food was not included in the intake assessment, it was assumed to contain a zero concentration of lutein and zeaxanthin;
- the lutein and zeaxanthin concentration of FSFYC is currently 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).

3.3 General

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

5. Limitations of the dietary modelling

Dietary modelling based on 1995 or 1997 NNS food consumption data provides the best estimate of actual consumption of a food and the resulting estimated dietary intake of a nutrient for the population. However, it should be noted that the NNS data do have limitations. These limitations relate to the age of the data and the changes in eating patterns that may have occurred since the data were collected. Generally, consumption of staple foods such as fruit, vegetables, meat, dairy products and cereal products, which make up the majority of most people's diet, is unlikely to have changed markedly since 1995/1997 (Cook *et al*., 2001a; Cook *et al*., 2001b).

Over time, there may be changes to the ways in which manufacturers and retailers make and present foods for sale. Since the data were collected for the Australian and New Zealand NNSs, there have been significant changes to the Food Standards Code to allow more innovation in the food industry.

As a consequence, a limitation of the dietary modelling is that some of the foods that are currently available in the food supply were either not available or were not as commonly available in 1995/1997 (e.g. FSFYC). No FSFYC were consumed in the 1995 Australian NNS and, as a consequence, assumptions were made about the consumption of FSFYC in the modelling process. In the dietary intake assessment for lutein and zeaxanthin, it was assumed that 2-3 year old children would replace all of their full fat and unspecified fat content fluid cow's milk (plain and commercially flavoured) consumption, including that used in cooking, with FSFYC.

Additionally, since the data were collected for the NNSs, there has been an increase in the range of products that are fortified with nutrients. FSANZ does update the food composition database through analytical programs and scans of the market place. However, with the market place continually changing it is difficult to account for all fortified products at a given point in time.

A limitation of estimating dietary intake over a period time using information from a recall method is that people may over- or under-report food consumption, particularly for certain types of foods. Over- and under-reporting of food consumption has not been accounted for in this dietary intake assessment.

Since the 1995 Australian NNS does not report on respondents aged below 2 years, the 1997 New Zealand NNS does not report on respondent aged below 15 years and the 2002 New Zealand CNS does not report on respondents aged below 5 years, theoretical diets were used to estimate dietary lutein and zeaxanthin intakes for children in the target group of up to 3 years. Theoretical diets for Australian children aged 1 year and New Zealand children aged 1-3 years were used in this assessment. Mean food consumption amounts in the theoretical diets are used to represent food consumption patterns for an age group as a whole and may not be as accurate as the data derived for other population groups from the NNSs that use food consumption data of individuals.

Although some data on the use of complementary medicines (Australia) or dietary supplements (New Zealand) were collected in the NNSs, data were either not in a robust enough format to include in the theoretical diet assessments or in DIAMOND, or have simply not been included in the DIAMOND program to date. Consequently, intakes of substances consumed via complementary medicines or dietary supplements could not be included directly in the dietary intake assessments conducted using the theoretical diets or DIAMOND.

While the results of national nutrition surveys can be used to describe the usual intake of groups of people, they cannot be used to describe the usual intake of an individual (Rutishauser, 2000). In addition, they cannot be used to predict how consumers will change their eating patterns as a result of an external influence such as the availability of a new type of food.

6. Dietary intake assessment results

6.1 Estimated intakes of lutein and zeaxanthin

Dietary intakes of lutein and zeaxanthin were estimated for Australian children aged 1 year, New Zealand children aged 1-3 years and Australian children aged 2-3 years (see Table 2 and Table 3).

Table 2: Estimated dietary intakes of lutein and zeaxanthin for Australian children aged 1 year and New Zealand children aged 1-3 years, as assessed using theoretical diets

Country	Age (years)	Estimated dietary intake of lutein and zeaxanthin (µg/day)			
		Mean		95th percentile	
		Baseline	***Scenario***	***Baseline***	***Scenario***
Australia	1	385	618	962	1,544
New Zealand	1-3	680	835	1,701	2,088

Table 3: Estimated dietary intakes of lutein and zeaxanthin for Australian children aged 2-3 years, as assessed using NNS data

Age (years)	Estimated dietary intake of lutein and zeaxanthin (µg/day)			
	Mean		95th percentile	
	Baseline	***Scenario***	***Baseline***	***Scenario***
2-3	730	936	2,261	2,462

The estimated mean baseline dietary intakes predicted by FSANZ for Australian children 1 year was 385 µg/day and was 730 µg/day for 2-3 years. The Applicant predicted mean baseline intakes for Australian children 1-3 years to be 344 µg/day. Therefore the FSANZ estimates are comparable for 1 year olds and around double that predicted by the Applicant for 2-3 year olds. The FSANZ assessment is based on a 24-hour recall and the Applicants assessment is based on a three-day weighted food record, however mean intakes would not be expected to be strongly influenced by the number of days of dietary survey data. The FSANZ predicted intakes for the 1 year old being similar to those based on a more comprehensive food consumption study show that the theoretical diet used for predicting dietary intakes is a sound methodology. The composition data sets were based primarily on the same data source, therefore the way in which the concentration data were assigned to food groups and the food consumption amounts could be the reason why the estimated intakes for Australian children are different for 2-3 year olds.

Using USA consumption data (see Table 1), the Applicant estimated mean lutein and zeaxanthin intakes for 1-3 year old children as 636 µg/day at baseline.

With the Applicants estimated intake of lutein from formula being an additional 300 µg/day, this would result in total mean intakes of around 940 µg/day for American children aged 1-3 years. In the FSANZ assessment, estimated mean lutein and zeaxanthin intakes were 618 µg/day for 1 year old Australian children, 835 µg/day for New Zealand children aged 1-3 years, and 936 µg/day for Australian children aged 2-3 years, following the fortification of FSFYC (and follow-on formula for New Zealand) with lutein and zeaxanthin.

6.2 Major contributors to lutein and zeaxanthin intakes

6.2.1 Australian children aged 1 year

For consumers of FSFYC, the major contributors from food (≥ 5%) to lutein and zeaxanthin intakes at *Baseline* for Australian children aged 1 year were fruit and vegetables juices (20%), peas (8%), carrots (7%), onions (7%), sweet corn (6%) and broccoli/cauliflower (5%).

Under the fortification *Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were FSFYC (38%), and fruit and vegetables juices (13%).

6.2.2 New Zealand children aged 1-3 years

For consumers of FSFYC, the major contributors from food (≥ 5%) to lutein and zeaxanthin intakes at *Baseline* for New Zealand children aged 1-3 years were silverbeet (23%), peas (10%), pumpkin (9%) and carrots (8%). Under the fortification *Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were silverbeet (19%), FSFYC (19%), peas (8%), pumpkin (7%) and carrots (7%).

6.2.3 Australian children aged 2-3 years

For consumers of FSFYC, the major contributors from food (≥ 5%) to lutein and zeaxanthin intakes at *Baseline* for Australian children aged 1 year were oranges (19%), peas (15%), pumpkin (9%), sweet corn (6%) and broccoli (5%). Under the fortification *Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were FSFYC (22%), oranges (15%), peas (12%) and pumpkin (7%).

7. Comparison of intakes with reference health standards

In order to determine if the level of intake of lutein and zeaxanthin following fortification of FSFYC will be of concern to public health and safety, the estimated dietary intakes were compared to the ADI for lutein and zeaxanthin of 2 mg/kg bw/day (see Attachment 3 for details). The ADI for lutein is for added sources only. FSANZ has compared intakes of total lutein and zeaxanthin from naturally occurring and added sources to the ADI, therefore this will result in an overestimate of the level of risk.

For Australian and New Zealand children aged 1-3 years, the estimated mean and 95th percentile intakes of lutein and zeaxanthin were all below the ADI (see Table 4 and Table 5). The FSANZ assessment estimated mean lutein and zeaxanthin intakes for Australian and New Zealand children aged 1-3 years at 3-4% ADI following the fortification of FSFYC with lutein and zeaxanthin, with estimated 95th percentile intakes being 8-11% ADI. There is a limitation associated with the lack of detailed food consumption data from NNSs for children less than two years of age and the use of theoretical diets in estimating dietary intakes for this age group.
However, it would not be expected that if more detailed consumption data were available from an NNS, that estimated intakes would approach the ADI. This is demonstrated by the estimated intakes for 2-3 year olds using NNS data where estimated dietary intakes for high consumers of lutein and zeaxanthin following fortification of FSFYC are only at 8% of the ADI.

The Applicant estimated lutein exposure for high lutein consumers to be at 10% of the ADI for American (U.S.A.) children aged 1-3 years and 6% ADI for Australian children aged 1-3 years. The results for Australian children that were provided by the Applicant are similar to those estimated by FSANZ for Australian and New Zealand children.

Table 4: Estimated mean and 95th percentile intakes of lutein and zeaxanthin for Australian children aged 1 year and New Zealand children aged 1-3 years, as a percentage of the ADI

Country	Age (years)	Estimated dietary intake of lutein and zeaxanthin^ (%ADI*)			
		Mean		95th percentile	
		Baseline	*Scenario*	*Baseline'*	*Scenario*
Australia	1	2	3	5	8
New Zealand	1-3	4	4	9	11

^ Estimated using theoretical diets.
* ADI for lutein and zeaxanthin = 2 mg/kg bw/day

Table 5: Estimated mean and 95th percentile intakes of lutein and zeaxanthin for Australian children aged 2-3 years, as a percentage of the ADI

Age (years)	Estimated dietary intake of lutein and zeaxanthin# (%ADI*)			
	Mean		95th percentile	
	Baseline	*Scenario*	*Baseline*	*Scenario*
2-3	2	3	7	8

Estimated using 1995 NNS.
* ADI for lutein and zeaxanthin = 2 mg/kg bw/day

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Appendix 1

Theoretical diets used in the risk assessment

Table A1.1: Theoretical diet for Australian children aged 1 year

Food/Food Group	Food Consumption Amount (grams per day)
Apples, pears and quince	26.6
Avocado	0.4
Bacon and cured pork	0.2
Baked beans	4.4
Bananas, kiwifruit, figs, passionfruit	13.9
Beans, green, snake and butter	0.7
Beef and veal	1.6
Beer	0
Beetroot	0.6
Berries	1.2
Biscuits, savoury	1.7
Breakfast cereal, single grain	4.7
Broccoli and cauliflower	3.0
Butter	0.5
Cabbage, kale and Jerusalem artichoke	0.5
Cakes and sweet muffins	3.9
Carrots, parsnips, radishes and cassava	4.0
Celery and other stem vegetables	0.7
Cheese, processed	2.1
Cheese, ripened (e.g. cheddar)	3.1
Cheese, unripened (e.g. cottage)	0.2
Chicken, duck, quail and emu	4.8
Chocolate and chocolate confectionery	3.0
Citrus fruits	12.2
Coconut flesh and liquid	0.7
Cream	1.3
Crustacea (e.g. prawns)	0.1
Cucumber, capsicum, eggplant, artichoke and choko	1.5
Dairy blend	0.1
Dried fruits	2.3
Eggs	3.3

Food/Food Group	Food Consumption Amount (grams per day)
Fish fillets, not canned, battered or crumbed	0.5
Fish, battered	0.6
Fish, canned (except salmon)	0.5
Fish, crumbed	0.2
Fruit and vegetable juices, fruit juice drinks and cordials	163.8
FSFYC	423.1
Grapes	3.7
Ham and deli meats	2.5
Hamburgers and meat patties	0.05
Herbs	0.01
Ice cream, ice confections and frozen desserts	8.0
Infant cereal	0
Infant dessert, dairy based	1.3
Infant dessert, fruit based	1.1
Infant dinner	1.3
Infant formula	0
Lamb	0.9
Lettuce and snow pea sprouts	1.1
Liver and pate	0.03
Mango, pawpaw, pepino, rambutan and tamarillo	0.9
Margarine or margarine spread	2.1
Melons	3.2
Milk, full fat	0
Milk, modified, low fat	0
Mixed grain breakfast cereals, breakfast bars and muesli bars and slices	4.3
Multigrain breads	1.5
Mushrooms	0.6
Oats, rolled	1.5
Oil, vegetable/nut/seed	0.5
Olives	0
Onions, leeks and shallots	2.5
Pasta and noodles	10.1
Peanuts and peanut products	0.9
Peas and snow peas	1.8
Pineapple	1.6

Food/Food Group	Food Consumption Amount (grams per day)
Pizza	0.6
Plain sweet biscuits, slices and scones	3.9
Pork (except cured products)	0.6
Potato crisps and extruded snacks	3.3
Potato, sweet potato and turnip	17.8
Pumpkin, marrow, squash and zucchini	2.5
Rice, rice noodles and rice crackers	12.6
Salmon, canned	0
Sauce, tomato and barbeque	1.3
Sausages, sausage patties, frankfurts and saveloys	3.5
Savoury pastries (e.g. pies)	4.6
Seaweed	0.0
Soft drinks	23.2
Soy beverage, soy cheese & soy ice confection	0
Spinach, silverbeet and watercress	0.1
Stone fruits	4.0
Stone fruits, canned	4.9
Sugar, confectionery, toppings, jams, fruit spreads and jelly	8.4
Sweet corn	2.5
Tea and coffee	0
Tomatoes	6.2
Tree nuts	0
White breads, muffins, crumpets, buns, doughnuts and pancakes	21.6
Wholemeal and ryes breads, rolls, muffins, crumpets and buns	5.0
Wine, white	0
Yoghurt, yoghurt beverages and dips	14.5

Table A1.2: Theoretical diet for New Zealand children aged 1-3 years

Food	Food Consumption Amount (grams per 14 days)	Food Consumption Amount (grams per day)
Apple-based juice	380	27
Apples	350	25
Apricots, canned	60	4.3
Avocado	20	1.4
Bacon	30	2.1
Banana	490	35
Beans	15	1.1
Beans, baked	100	7.1
Beef, mince	120	8.6
Beef, rump	50	3.6
Beer	0	0
Beetroot	0	0
Biscuit, chocolate	115	8.2
Biscuit, cracker	60	4.3
Biscuit, plain sweet	165	12
Bran flake cereal, mixed	30	2.1
Bread, mixed grain	30	2.1
Bread, wheatmeal	115	8.2
Bread, white	425	30
Broccoli/Cauliflower	70	5.0
Butter	55	3.9
Cabbage	15	1.1
Caffeinated beverage	0	0
Cake	60	4.3
Capsicum	10	0.7
Carbonated drink	300	21
Carrot	115	8.2
Celery	15	1.1
Cheese	145	10
Chicken	60	4.3
Chicken nuggets	50	3.6
Chinese takeaway dish	0	0
Chocolate beverage	300	21
Chocolate, plain milk	20	1.4
Coffee beans, ground	0	0

Food	Food Consumption Amount (grams per 14 days)	Food Consumption Amount (grams per day)
Coffee instant	0	0
Confectionery	35	2.5
Corn, canned	30	2.1
Corned beef	35	2.5
Cornflakes	60	4.3
Courgette	10	0.7
Cream	20	1.4
Cucumber	15	1.1
Dairy dessert (child)	460	33
Egg	110	7.9
Fish fingers (child)	40	2.9
Fish in batter	45	3.2
Fish, canned	20	1.4
Fish, fresh	30	2.1
Flavoured snacks (child)	60	4.3
Fruit drink, powdered	830	59
FSFYC	3,940	281
Grapes	20	1.4
Ham	70	5.0
Hamburger, plain	80	5.7
Honey	20	1.4
Ice cream	150	11
Infant & follow on formula	0	0
Infant weaning food, cereal based	0	0
Infant weaning food, custard/fruit dish	0	0
Infant weaning food, savoury dish	120	8.6
Jam	20	1.4
Kiwifruit	50	3.6
Kumara	30	2.1
Lamb/Mutton	40	2.9
Lambs liver	0	0
Lettuce	15	1.1
Margarine/Table Spread	35	2.5
Meat pie	90	6.4
Melon	30	2.1
Milk, flavoured	0	0

Food	Food Consumption Amount (grams per 14 days)	Food Consumption Amount (grams per day)
Milk, trim (0.5%)	0	0
Milk, whole	0	0
Muesli	15	1.1
Muffin/scone	70	5.0
Mushrooms	15	1.1
Mussels	0	0
Nectarines	30	2.1
Noodles, instant	160	11
Oats, rolled	120	8.6
Oil	35	2.5
Onion	15	1.1
Orange juice	280	20
Oranges	260	19
Oysters	0	0
Pasta, dried	150	11
Peaches, canned	50	3.6
Peanut butter	20	1.4
Peanuts	0	0
Pears	70	5.0
Peas	60	4.3
Pineapple	20	1.4
Pizza	70	5.0
Pork chop	20	1.4
Potato crisps	35	2.5
Potato, hot chips	210	15
Potatoes, peeled	240	17
Potatoes, with skin	60	4.3
Prunes	20	1.4
Pumpkin	80	5.7
Raisins/Sultanas	99	7.1
Rice, white	55	3.9
Salad dressing	0	0
Sausages, beef	150	11
Silverbeet	20	1.4
Snack bars	30	2.1
Soup	50	3.6

Food	Food Consumption Amount (grams per 14 days)	Food Consumption Amount (grams per day)
Soy, milk	100	7.1
Spaghetti in sauce (canned)	150	11
Strawberries	20	1.4
Sugar	25	1.8
Taro	0	0
Tea	0	0
Tomato	65	4.6
Tomato sauce	50	3.6
Tomatoes in juice	45	3.2
Water	3,500	250
Weetbix	210	15
Wine, still red	0	0
Wine, still white	0	0
Yeast extract	25	1.8
Yoghurt	870	62

Attachment 5

Food Technology Assessment

Summary

The food technology aspects of lutein used as a nutritive substance to be added to formulated supplementary foods for young children (aged 1-3 years) 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, so a new specification is not required to be written for the Code.

The commercial lutein preparation that is subsequently added to food is produced in vegetable oil with approved food additives; antioxidants and emulsifiers. Stability results for powdered products, such as formulated supplementary foods for young children (1-3 years) being the products of interest for this Application indicated reasonably good stability. Losses after 12 months at ambient temperature (27°C and 70% relative humidity (RH)) were determined to be up to a maximum of 35%. Stability results also indicated that most of the losses occurred early during storage. Stability results under more extreme conditions (37°C and 75% RH) indicated the worst losses to be 44% after 6 months storage.

Manufacturers will need to be aware of losses of lutein that occur for their products with storage conditions and could apply a suitable over dosing to account for such losses. However, manufacturers also need to be aware that there are regulatory limits for lutein in formulated supplementary foods for young children prescribed in the Code (i.e. not more than 500 µg/L), so they need to ensure that products commercially available for sale meet the requirements of the Code.

Introduction

FSANZ has received an Application from Wyeth Pty Ltd seeking permission to add lutein as a nutritive substance to formulated supplementary foods for young children.

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

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

Chemistry of lutein

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

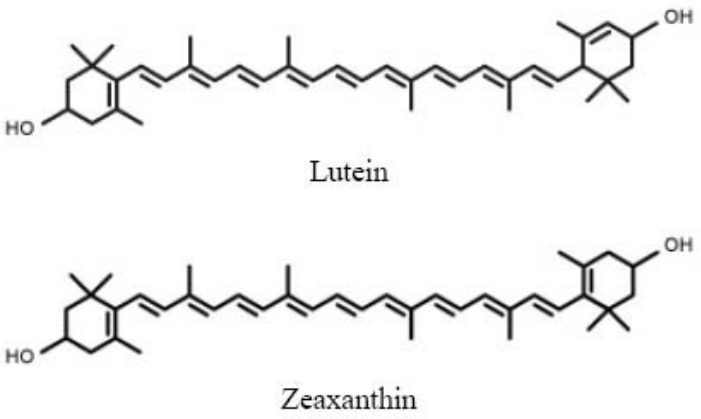

Figure 1: Chemical structures of lutein and zeaxanthin

Lutein has the molecular formula of $C_{40}H_{65}O_2$, with the molecular weight of 578.87 g/mol. Under IUPAC nomenclature rules, lutein has the chemical name 4-[18-(4-hydroxy-2,6,6-trimethyl-1-cyclohex-2-enyl)-3,7,12,16-tetramethyl-octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-3-en-1-ol. It has the Chemical Abstracts System (CAS) number 127-40-2. Lutein also has the food additive number INS No. 161b when it is used as a colouring. Lutein is listed in Schedule 3 of Standard 1.3.1 – Food Additives as a colour that can be added to many processed foods to levels determined by Good Manufacturing Practice where permitted by Schedule 1. However, lutein is not permitted as a colour for food category 13.1 – Infant formula products or 13.2 – Foods for infants in Schedule 1 of Standard 1.3.1.

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

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

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

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

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.

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.

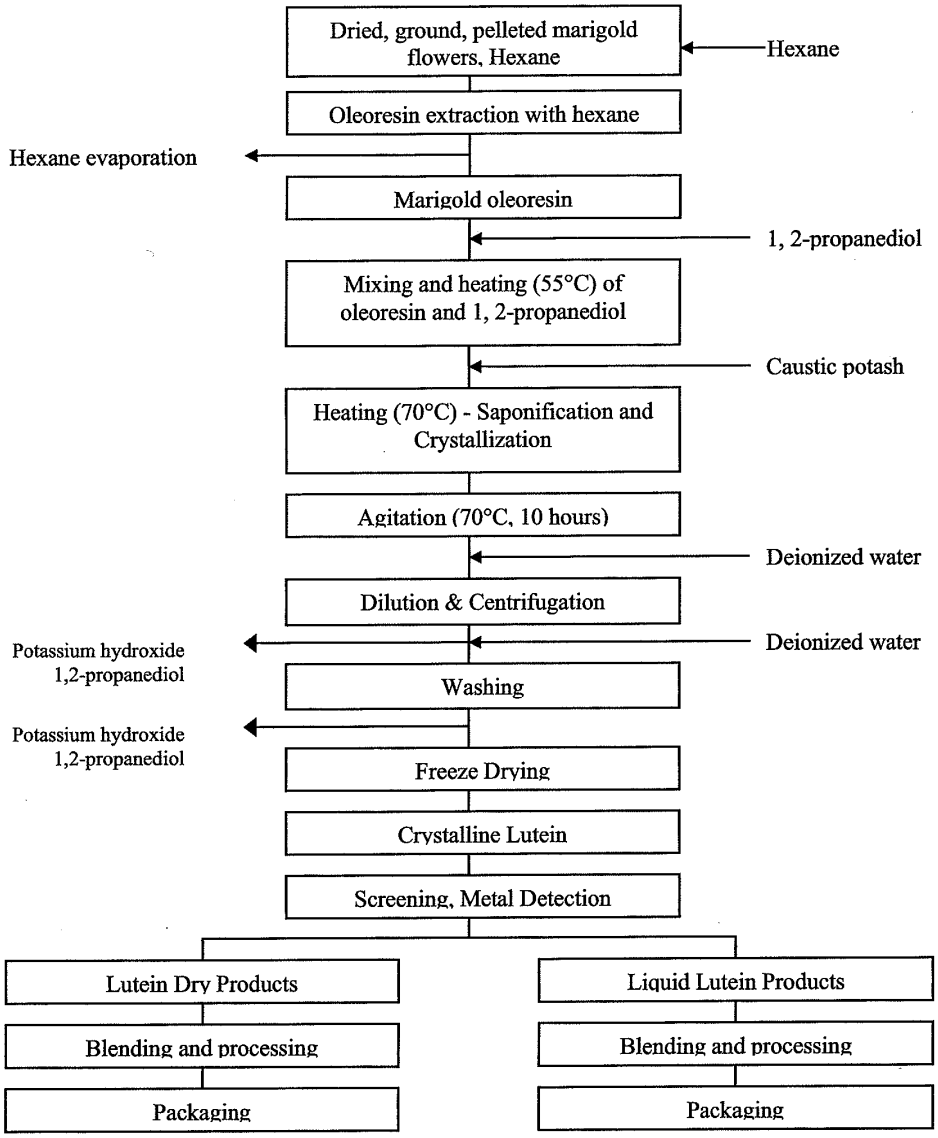

Figure 2: Schematic of the lutein preparation manufacturing process

Specification of lutein extract

The specification of lutein extracted from marigold (*Tagetes erecta* L.) flowers of the Application is consistent with the recent specification prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004 (JECFA Compendium of Food Additive Specifications, 2004) titled Lutein from *Tagetes Erecta*. The JECFA specifications are a primary source of specifications, being reference (a) in clause 2 of Standard 1.3.4. This means the specification of the lutein 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/10 g
Listeria monocytogenes	Negative/25 g
Salmonella	Negative/10 g
Staph enrichment	Negative/10 g
Coliform enrichment	Negative/25 g
Yeast count	Max. 100 cfu/g
Mould count	Max. 100 cfu/g

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 solid (powders) infant formula type products. Although limited liquid ready-to-feed products are commercially available, FSFYC are mainly available as powders, therefore stability results have been given for powders.

The Applicant performed stability trials on lutein concentration in commercially prepared products specific for the Application and the results are reported in the Application, and in later stability data provided by the Applicant. The important results are summarised below.

For powdered product stability trials were performed at 27°C and 70% RH, and 37°C and 75% RH for 3 month periods for follow-on formula and what they refer to as international formula for children both 1-3 years and 3-7 years, with targeted levels of lutein being 200 µg/L After 12 months at 27°C and 70% RH, the largest losses were 35%. The results also indicated that largest losses occurred earlier during storage and then the losses stabilised. Separately, the highest losses for storage at more extreme conditions (37°C and 75% RH) were 44% after 6 months storage. This Application is seeking approval for higher levels of lutein, at a maximum of 500 µg/L. The stability results and losses found indicated to the Applicant that they needed to overdose with extra lutein to account for losses during storage.

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

However, manufacturers also need to be aware that there are regulatory limits for lutein in formulated supplementary foods for young children proposed in the Code (i.e. not more than 500 µg/L), so they need to ensure that products commercially available for sale meet the requirements of the Code.

Conclusion

This review of the food technology aspects of addition of lutein to FSFYC indicates that there are no technological concerns. The Application states that the lutein preparation uses approved the food additives: antioxidants and emulsifiers. The specification of lutein extracted from *Tagetes erecta L.* meets the JECFA specification. This specification is referenced in the Code so no new specification needs to be written if the Application is approved. Lutein has reasonable stability in the commercial powdered products, with the largest losses being 35% after storage of 12 months at ambient temperature (27°C). Manufacturers can take account of such losses by overdosing with lutein, provided levels of product for commercial sale meet the requirements proposed for lutein in formulated supplementary foods for young children.

References

1. 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.

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

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

Attachment 6

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

FSANZ received 10 submissions in response to the release of the Initial Assessment Report for Applications A594 and A597, during the 6-week public consultation period of 4 April to 16 May 2007. A summary of submitter comments is provided in the table below.

The Initial Assessment Report sought input on the likely regulatory impact of both Applications A574 and A597 together. 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. Only comments specific to Application A597 have been considered in the body of this Draft Assessment Report.

Two regulatory options for Application A597 were presented at Initial Assessment, namely:

- *Option 1* – Maintain the status quo by not amending the Code to permit the addition of lutein as a nutritive substance in formulated supplementary food for young children (FSFYC); or
- *Option 2* – Amend Standard 2.9.3 to permit the addition of lutein as a nutritive substance at a maximum concentration of 500 µg/L in FSFYC.

No.	Submitter	Submission Comments
Industry		
1.	**Food Technology Association of Victoria Inc.** *David Gill*	**Supports Option 2 (Application A594 only)** No supporting information provided. No reference to Application A597.
2.	**Nestlé Australia Ltd** *Kirsten Grinter*	**Supports Option 1 (Applications A594 & A597)** ***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.

No.	Submitter	Submission Comments
		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 bioavailable 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. ***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/zeaxanthin in breast milk varies amongst populations. Provides figures of a median combined lutein/zeaxanthin content of breast milk of 20µg/L (range 15-44). Refers to a recent study reporting a lutein content of 50µg/L in a breast milk sample collected 19 days post partum and a zeaxanthin level of 11µg/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/g fat (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 2-33µg/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.

No.	Submitter	Submission Comments
3.	**Australian Food and Grocery Council (AFGC)** *Kim Leighton*	**Supports Option 2 (Applications A594 & A597)** Support for Option 2 is provided if 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. 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 zeaxanthin 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.

No.	Submitter	Submission Comments
4.	**Wyeth Australia Pty Ltd** *Jeanette Fielding*	**Supports Option 2 (Applications A594 & A597)** 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 µg/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. ***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 the Peoples Republic of 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 µg/day and 1194 µg/day respectively.

No.	Submitter	Submission Comments
		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 95µg/serve for toddlers. The maximum lutein concentration for toddler milk proposed in Application A597 in a 200 mL serve would equal 100 µg, 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.
Government		
5.	**Dept Health South Australia** *Elena Anear*	**Supports Option 1 (Applications A594 & A597)** 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.

No.	Submitter	Submission Comments
		Claims Concerned about potential for health claims to be permitted on foods regulated by Standards 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 Proposal 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.*
6.	**New Zealand Food Safety Authority (NZFSA)** *Carole Inkster*	**Preferred option not stated (Applications A594 & A597)** **<u>Application A594:</u>** ***Scope and intent of Standard 2.9.1*** Prefers a conservative approach when considering infant formula. Strongly supports Ministry of Health nutrition policy including promotion of breastfeeding. ***Safety / benefits*** Believes the composition of infant formula should not exceed or provide additional benefits over breast milk. 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.

No.	Submitter	Submission Comments
		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. **Application A597:** ***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. NZFSA supports further discussion on the merits of specific labelling requirements for FSFYC with added nutritive substances or substances added for physiological benefit.
7.	**Victorian Dept Human Services** *Fiona Jones*	**Recommends delaying work (Applications A594 and A597)** ***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 Ministerial Council. ***Safety***

No.	Submitter	Submission Comments
		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.
8.	**NSW Food Authority** *David Cusack*	**Preferred option not stated (Applications A594 & A597)** 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); • 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.
9.	**Queensland Health** *Tenille Fort*	**Preferred option not stated (Applications A594 & A597)** Has not yet established a position in relation to Application A594. Will review the Draft Assessment Report and provide comment at that time. No comments provided on Application A597.

No.	Submitter	Submission Comments
Health Professionals		
10.	**Dietitians Association of Australia (DAA)** *Kate Poyner*	**Preferred option not stated (Applications A594 & A597)** Supports FSANZ decision to accept Applications A594 and A597 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.