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

**20 March 2009**
**[4-09]**

# FINAL ASSESSMENT REPORT

# APPLICATION A597

# ADDITION OF LUTEIN TO FORMULATED SUPPLEMENTARY FOODS FOR YOUNG CHILDREN

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

## Executive Summary

Food Standards Australia New Zealand (FSANZ) received a paid Application from Wyeth Australia Pty Ltd (the Applicant) on 2 January 2007 seeking to amend Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods of the *Australia New Zealand Food Standards Code* (the Code), to permit the voluntary addition of lutein as a nutritive substance to formulated supplementary foods for young children (FSFYC).

FSFYC are special purpose foods for children aged one to three years that are specifically designed to supplement a normal diet to address situations where intakes of energy and nutrients may not be adequate to meet an individual's requirements. The majority of FSFYC available in Australia and New Zealand are milk-based drinks known as 'toddler formula' or 'toddler milk'.

The Applicant has requested permission to add lutein from marigold (*Tagetes erecta L.*) to FSFYC at a maximum concentration of 500 µg/L, to provide a modest yet significant amount of lutein in the diet of young children. The material proposed by the Applicant for addition to FSFYC is a purified extract which contains both lutein and its isomer zeaxanthin (a structurally similar molecule) in a ratio of approximately 10:1. While marigold flowers are not normally consumed in the Australian and New Zealand diet, the chemical structure of lutein and zeaxanthin in the purified extract from marigold flowers is the same as the two carotenoids found in other edible plant sources which are found in the Australian and New Zealand diet (see Figure 1). Also, the ratio of lutein to zeaxanthin is within the range of ratios found in other edible plant sources.

Lutein is a plant pigment; it is a non-vitamin A carotenoid that cannot be synthesised by humans. Plant foods rich in lutein include dark green leafy vegetables, green 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. One 200 mL serving of FSFYC at the maximum concentration of 500 µg/L requested by the Applicant would provide the same amount of lutein and zeaxanthin that would be provided in a child sized serving of some fruits and vegetables.

This Final Assessment Report discusses issues, including those raised in submissions, on permitting the voluntary addition of lutein to FSFYC. This Application and a previous separate Application A594 – Addition of Lutein as a Nutritive Substance to Infant Formula, both raised a number of complex issues and generated significant concern amongst some submitters. These issues and concerns were discussed at length by the FSANZ Board in arriving at its decisions.

- Issues raised included: concerns regarding the role of FSFYC in the diet of young children and their potential impacts on children's eating practices; whether a higher level health benefit/efficacy should be demonstrated in order to permit the addition of substances to these products; and views around the nature and extent of evidence required to support permissions.

- Some of the issues raised are outside the scope of the Board's capacity to consider in relation to individual Applications or are outside the scope of the Board's functions. For example, the question of whether 'toddler formula' are desirable in the food supply is a policy issue rather than a standards development issue.

- In addition, in the absence of policy guidance, the question of benefit has been considered in the context of whether lutein performs a physiological function, is present in the normal diet of young children, and would make a reasonable contribution to the lutein intake of young children who consume FSFYC.

A separate Application, Application A594 – Addition of Lutein as a Nutritive Substance to Infant Formula, has previously considered permitting the voluntary addition of lutein to infant formula products. A draft variation to the Code arising from Application A594 was approved by the FSANZ Board in July 2008 and the decision notified to the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council). The Ministerial Council requested a First Review of this decision. The Review has been completed and recently notified to the Ministerial Council for its consideration.

## Regulatory Approach

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

The assessment of whether lutein should be permitted as an optional nutritive substance in FSFYC has considered:

- the safety of lutein from marigold flowers (*Tagetes erecta L.*);
- if lutein is found naturally in foods commonly eaten by young children;
- whether the lutein from marigold flowers is the same as the lutein found in other edible plant sources in the Australia and New Zealand diet;
- whether the maximum requested level of lutein in FSFYC (500 µg/L), and the minimum level prescribed for the purposes of making a claim (150 µg/L, equivalent to 30 µg/serve assuming a 200 mL serve) can make a reasonable contribution to the lutein intake (accounting for bioavailability), of young children who consume FSFYC;
- the nutritional purpose or physiological function(s) of lutein; and
- the potential for a health benefit for young children who consume FSFYC with added lutein.

## Risk Assessment

At Final Assessment, the key risk assessment findings are:

- lutein cannot be synthesised by the body but is present naturally in foods commonly eaten by young children;
- the ratio of lutein to zeaxanthin found in marigold flowers is within the range of ratios of lutein to zeaxanthin found naturally in foods that are commonly eaten by young children in Australia and New Zealand;

- supplemental sources of lutein, such as lutein from marigold flowers, appear to have comparable bioavailability to plant sources of lutein, but lower than animal sources;

- lutein from marigold flowers added to FSFYC is unlikely to pose any public health and safety concerns for young children at the requested maximum concentration of 500 µg/L;

- the requested concentration of lutein in FSFYC has the potential to make a reasonable contribution to the lutein intake of young children who consume these foods, i.e. 15-38% of their daily lutein intake;

- lutein is concentrated in parts of the eye, particularly the macula lutea where it is a key functional component of the macular pigment acting as site specific antioxidant and filter of harmful blue light;

- increased lutein intake leads to increased macular pigment density in some people;

- lutein has general antioxidant activity beyond the eye; and

- there is insufficient evidence to make firm conclusions about the potential long-term benefit to eye health for young children consuming FSFYC with added lutein.

The key risk assessment issues are discussed in Section 8 of this Report. Full details of the risk assessment are found at Attachment 4 – Nutrition Assessment, Attachment 5 – Dietary Intake Assessment and Attachment 6 – Hazard Assessment.

## Food Technology

The food technology aspects of adding lutein as a nutritive substance to FSFYC have also been assessed, including the stability of lutein in powdered FSFYC over the shelf life of the product. The key food technology issues are discussed in Section 10 of this Report and the full Food Technology Assessment is provided at Attachment 7.

## Risk Management

This Final Assessment Report considers, in the context of the risk assessment findings, a number of points relevant to permitting the addition of lutein to FSFYC including:

- the appropriateness of the requested maximum concentration of lutein to be added to FSFYC (500 µg/L) in relation to its safety and ability to make a reasonable contribution to the lutein content of diets of young children;

- a prescribed minimum claimable amount for lutein in FSFYC and the ability for this amount to make a contribution to the lutein content of diets of young children;

- the immediate and potential impacts of the proposed regulatory options on affected parties.

## Decision

**To amend Standard 2.9.3 to permit the voluntary addition of lutein as a nutritive substance to formulated supplementary foods for young children up to a maximum concentration of 100 µg/serve (500 µg/L) with a minimum claimable amount of 30 µg/serve (150 µg/L) for labelling purposes.**

## Reasons for Decision

FSANZ has undertaken an assessment using the best available evidence, and recommends amending the Code to permit the voluntary addition of lutein to FSFYC, as at Attachment 1 for the following reasons:

- Lutein from marigold flowers added to FSFYC at a maximum concentration of 500 µg/L is unlikely to pose any public health and safety concerns for young children who consume these products.

- Lutein-fortified FSFYC have the potential to make a reasonable contribution to the lutein intake of young children who consume these products.

- FSFYC containing lutein provides an alternative dietary source of lutein for young children who consume FSFYC as a supplement to a normal diet when energy and nutrient intakes may not be adequate.

- The prescribed minimum claimable amount ensures that one serving (approximately 200 mL) of a lutein-fortified FSFYC will provide at least 30 µg which is about 10% of a young child's estimated mean daily lutein intake from foods other than FSFYC. This amount also exceeds the innate amounts of lutein found in the most common milk based FSFYC known as toddler formulas.

- Lutein performs a physiological function in the eye.

- Overall, permitting the addition of lutein to FSFYC provides a net benefit to all affected parties.

## Consultation

FSANZ received 12 submissions in response to the Draft Assessment Report. A summary of submissions to the Draft Assessment Report is at Attachment 2.

Key points raised by submitters at Draft Assessment have been considered by FSANZ and are addressed in this Report, either in the main report and/or in Attachment 3 – Response to Key Points Raised by Submitters at Draft Assessment.

## FSANZ's Response to Key Issues

The key issues raised in submissions to the Draft Assessment Report were related to the need to demonstrate both the benefit and safety of lutein for young children, the proposed level of addition, the minimum claimable amount, and labelling and claims.

**Health benefit and efficacy in infants**

Many submitters considered that from a public health perspective, both the benefit and safety of lutein should be demonstrated for vulnerable populations such as young children. Similarly, submitters considered that if a substance is added to achieve a nutritional purpose, such as a nutritive substance, then the nutritional benefit of that substance should be demonstrated. Many submitters stated that there is no established health benefit(s) of lutein for young children, including for the purpose of eye health.

As noted under the 'regulatory approach', in the absence of Ministerial policy guidelines, the approach to the assessment of this Application primarily focussed on the safety of lutein. However, in response to the concerns raised by submitters the nutritional purpose or physiological function, and the presence or absence of a health benefit from adding lutein to the diet of young children who consume lutein-fortified FSFYC has also been assessed. After reviewing the available evidence, FSANZ concludes that lutein is both a structural and functional component of the eye, acting as a site specific antioxidant and filter of harmful blue light. However, there is insufficient evidence to demonstrate any additional long-term benefit to eye health for infants from consuming lutein, including from FSFYC with added lutein.

The intent of FSFYC is to supplement a normal diet when energy and nutrient intakes may not be adequate, rather than to provide any additional health benefit. Therefore, the assessment has also considered whether the requested level of lutein in FSFYC (up to 500 µg/L), and the minimum level prescribed (150 µg/L) can make a reasonable contribution to the lutein intakes of young children who consume these products.

**Level of addition**

Some submitters considered that the proposed maximum concentration of 500 µg lutein/L appeared excessive, while others supported the proposed level.

There is no relevant nutrient reference value against which to compare the estimated mean intake of lutein from both natural sources and fortified FSFYC in order to determine if dietary intakes meet nutritional needs. However, one serve of fortified FSFYC (at a concentration of 500 µg/L) compares with the level of lutein found naturally in one tablespoon of broccoli, two teaspoons of corn or various other household measures of foods that can be expected to be consumed by children aged 1-3 years. Also, from a safety perspective, the estimated mean dietary intake of lutein by young children was shown to be well below the Acceptable Daily Intake (ADI) of 2 mg/kg body weight.[1, 2]

[1] Group ADI for lutein from *Tagetes erecta* and synthetic zeaxanthin, established by the Joint FAO WHO Expert Committee on Food Additives (JECFA) in 2004.

[2] For Australian and New Zealand children aged 1-3 years, the estimated mean and 90$^{th}$ percentile intakes to lutein and zeaxanthin were all below the ADI. For the lower and upper concentrations of lutein in FSFYC (150 µg/L and 500 µg/L, respectively) the 90$^{th}$ percentile intakes were estimated at 5-8% ADI and 6-9% ADI; these ranges are attributed to the different age groups assessed for Australian and New Zealand children (refer to Tables 4 and 5 in Attachment 3).

In addition, when compared to levels permitted internationally for similar products, the proposed maximum concentration is one-tenth of the level granted 'generally recognised as safe' status by the United States Food and Drug Administration for use in specified categories of foods including infant and toddler foods. The proposed maximum concentration is also similar to the level permitted in products sold in China.

**Minimum claimable amount**

Submitters generally supported prescribing a minimum claimable amount for lutein. However, some submitters considered the minimum level should reflect the purpose of the added lutein (e.g. 10% of the level required to reasonably achieve the nutritional purpose or the minimum effective level). Some submitters were unclear whether a minimum level of 30 µg/serve is meaningful, in the absence of a reference value for lutein.

- Setting a minimum claimable level that reflects the nutritional purpose or minimum effective level of lutein, as recommended by some submitters, could be considered inconsistent with the intended purpose of a FSFYC, which is to supplement a normal diet rather than to provide an additional health benefit.

- For compounds known to be nutrients but for which there is inadequate information to determine the average requirement (and therefore a Recommended Dietary Intake), the average intake in a population with no apparent deficiency is one method used to set an Adequate Intake.

- A value of 10% of the Recommended Dietary Intake/serve is commonly used in the Code to set a claimable level for a nutrient. Using an analogous approach, the minimum claimable amount of lutein would be approximately 10% mean intake of the 1 year old age group

- i.e. 30 µg lutein/serve of FSFYC. This means that the minimum permitted concentration would be 150 µg/L, assuming that one serve is 200 mL.

- The recommended minimum also exceeds the innate amounts of lutein found in unfortified toddler formula and therefore a claim about lutein is only likely to be made when lutein is added to a FSFYC.

**Labelling and claims**

Some submitters considered that all foods regulated by Standard 2.9.3 should be ineligible to carry nutrition and health related claims. Others considered claims for lutein on FSFYC should not be permitted as there is insufficient evidence to establish a minimum effective level and to support a benefit.

At present in the Code, nutrition claims are permitted on FSFYC. Clause 7 of Standard 2.9.3 prescribes the requirements for making nutrition claims about vitamins or minerals, while nutrition claims about other nutrients or biologically active substances would default to generic conditions prescribed under Standard 1.2.8. In addition, FSFYC must also comply with any requirements of Standard 1.1A.2 – Transitional Standard for Health Claims.

FSANZ is currently considering a new regulation around nutrition and health claims under Proposal P293. Under the proposed new regulation for nutrition content claims, where there is no established reference value for the substance in the Code only those nutrition content claims that refer to the presence of the 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. It is currently proposed that nutrition content claims and general level health claims on FSFYC would require substantiation in accordance with the requirements in the draft Standard. In addition, it is proposed that a high level health claim about lutein could only be made if a food-disease relationship about lutein is pre-approved in the future.

Conditions for making nutrition content claims and health claims under the proposed regime would therefore be more stringent than current requirements.

## Implementation and Review

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

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# INTRODUCTION

Food Standards Australia New Zealand (FSANZ) received a paid Application from Wyeth Australia Pty Ltd (the Applicant) on 2 January 2007 seeking to amend Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods of the *Australia New Zealand Food Standards Code* (the Code), to permit the voluntary addition of lutein as a nutritive substance to formulated supplementary foods for young children (FSFYC).

## 1. Nature of the Application

### 1.1 Basis of the Application

The Applicant has requested that lutein from marigold (*Tagetes erecta L.)* be permitted as an optional nutritive substance in FSFYC, for inclusion in Division 4 of Standard 2.9.3, at a maximum concentration of 500 µg/L.

The Applicant has advised that lutein is found naturally in some foods, most commonly in many yellow and dark green vegetables (e.g. maize, spinach and green peas) and that current formulations of milk based FSFYC (e.g. toddler formula) contain little or no lutein. The Applicant considers lutein has potential eye health benefits for young children.

The Applicant requests permission to add lutein to FSFYC, namely toddler formula, in an amount that would provide a modest yet significant amount of lutein in the diet of young children, whose diets may not reliably contain lutein. The Applicant contends that at a 600 mL intake of FSFYC with lutein added at the requested concentration of 500 µg/L, 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 of a FSFYC per day represents three 200 mL serves per day.

### 1.2 Scope of the Application

This Application relates to the voluntary addition of lutein to FSFYC. FSFYC and formulated supplementary food are defined in clause 1 of Standard 2.9.3 as follows:

> ***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 individual's requirements.*

Other product categories mentioned in Standard 2.9.3, such as formulated meal replacements or formulated supplementary foods other than for young children, would not be affected by the amendments proposed in this Application, and therefore would not be permitted to contain added lutein as a nutritive substance.

### *1.2.1 Application A594 – Addition of Lutein as a Nutritive Substance to Infant Formula*

This Application does not apply to 'infant formula products'3, as regulated in Standard 2.9.1 – Infant Formula Products. A separate Application, Application A594, has been made that seeks to permit the voluntary addition of lutein to infant formula products.

In June 2008, the FSANZ Board approved the draft variation to Standard 2.9.1 to permit the voluntary addition of lutein as a nutritive substance in infant formula products at a maximum concentration of 9 µg/100 kJ (250 µg/L) with a minimum declaration of 2 µg/100 kJ required for labelling purposes. The primary reason for this decision was that lutein added to infant formula at the maximum concentration is unlikely to pose any safety concerns for formula-fed infants and would achieve a nutritionally equivalent effect, in relation to serum lutein concentrations, to the amounts of lutein found naturally in breast milk.

The FSANZ Board's decision was notified to the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council). The Ministerial Council requested a Review of the Board's decision. The Review has been completed and notified to the Ministerial Council for its consideration.

## 1.3 Identity of source

The source of lutein proposed for addition to the Applicant's FSFYC is FloraGLO® Lutein 20% Liquid in safflower oil obtained from Kemin Health, L.C (Des Moines, Iowa). This product also contains zeaxanthin in a ratio of lutein:zeaxanthin of approximately 10:1.

Lutein and its isomer, zeaxanthin, are xanthophyll carotenoids obtained from the petals of marigold flowers (*Tagetes erecta L.*). An oleoresin rich in these carotenoids is extracted from marigold flowers 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.

## 1.4 Lutein as a nutritive substance

The Applicant has requested permission for the 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 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:

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

| Definitional elements | Rationale |
|---|---|
| A substance not normally consumed as a food in itself | Lutein is not available for retail sale as a food in Australia and New Zealand. |
| A substance not normally used as an ingredient in food | Lutein is permitted as a food additive (colour) in some food categories but it is not normally used as an ingredient. |
| A substance that is extracted, refined or synthesised | Lutein is extracted from marigold flowers and highly refined. |
| A substance intended to achieve a nutritional purpose | Consistent with other carotenoids, lutein has specific antioxidant properties. Additionally, unlike other carotenoids lutein and its isomer zeaxanthin are structural components of the eye, most notably the macula lutea. The two confirmed functions of lutein in the eye are as an antioxidant and filter of blue light. Further, animal models also indicate lutein plays a role in the structural development of the eye. Lutein is not synthesised in the human body. |

### 1.5 Novel foods and the status of lutein

As this Application seeks to permit the addition of lutein to FSFYC as a nutritive substance, the issue of whether or not lutein is a novel food has not been specifically addressed. However, if consideration was given to whether lutein meets the definition of 'novel food' in Standard 1.5.1 – Novel Foods, consideration would firstly need to be given to whether or not lutein is a 'non-traditional food' for the purposes of that Standard. As lutein is present in breast milk and some foods commonly eaten by young children such as peas, broccoli and eggs, it is likely that it would not meet the definition of 'non-traditional food', and if that were the case, would therefore not meet the definition of 'novel food'.

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

## 2. Background

Carotenoids are red and yellow pigments contained in animal fat and some plants. Carotenoids are divided into two classes: carotenes (which contain only hydrogen and carbon) and xanthophylls (which contain hydrogen, carbon and oxygen). Lutein and zeaxanthin belong to the class of xanthophylls.

Although several hundred carotenoids have been identified, the most prevalent dietary carotenoids are α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin. Three of these, α-carotene, β-carotene and β-cryptoxanthin, are precursors of vitamin A, whereas lutein, zeaxanthin and lycopene cannot be converted to vitamin A. Humans cannot synthesise these carotenoids and must obtain all of them, including lutein, from dietary sources.

Despite having specific functions in the eye and general antioxidant properties common to many carotenoids, there is no evidence to indicate lutein is essential to sustain life.

Lutein was not considered for the review of, and has not been included in the *Nutrient Reference Values for Australia and New Zealand*[4] or other dietary recommendations.

Good sources of lutein include eggs, carrots, corn, citrus fruits, avocado, broccoli, green peas 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.

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

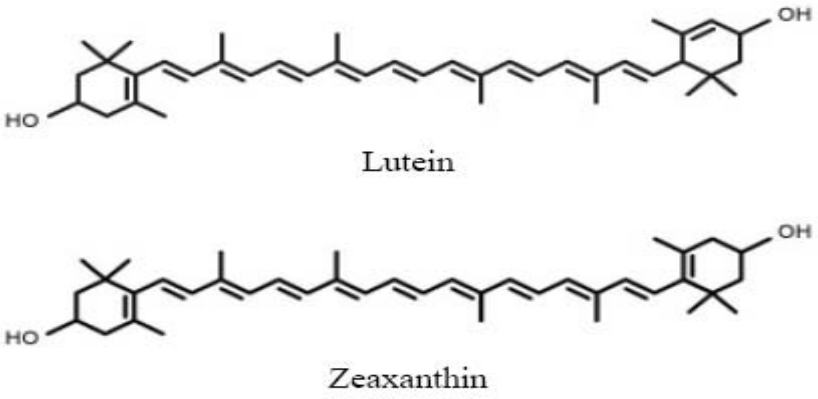


*Figure 1: Chemical structures of lutein and zeaxanthin*

Lutein has been shown to function in the eye as an antioxidant (Kim *et al*., 2006), and a blue light filter (Junghans *et al*., 2001). Dietary lutein and zeaxanthin are absorbed and subsequently accumulate in the retina, a layer of light-sensitive cells at the back of the eyeball (Alves-Rodrigues and Shao, 2004). In particular, lutein and zeaxanthin are concentrated in an area centred on the fovea, referred to as the macula lutea (macula) or 'yellow spot' (Alves-Rodrigues and Shao, 2004). 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 (Bone *et al.,* 1997). Collectively, lutein, zeaxanthin and *meso*-zeaxanthin are referred to as 'macular pigment' (Landrum and Bone 2001). A major cause of irreversible vision loss is an age-related degenerative disease of the macula (Taylor et al., 2005). The presence of lutein and zeaxanthin in the macula has led to hypotheses and research into possible protective and palliative roles of these pigments against age-related macular degeneration (Chong *et al.*, 2007).

[4] This document is available online at: http://www.nhmrc.gov.au/publications/synopses/n35syn.htm. Accessed 7 July 2008.

# 3. Current Situation

## 3.1 Domestic regulations

### *3.1.1 Australia New Zealand Food Standards Code*

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

- Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods regulates FSFYC, with clauses 6 and 7 providing the compositional and labelling requirements respectively. However, clause 6 details compositional provisions on energy, protein and vitamins and minerals only.

- Standard 1.3.1 – Food Additives, clause 3, permits the addition of lutein as a food colour (INS 161b) under Schedule 3 in processed foods specified in Schedule 1, including formulated supplementary foods.

### *3.1.2 Therapeutic Goods Administration, Australia*

Lutein is eligible for use in listed medicines on the Australian Register of Therapeutic Goods for supply in Australia, with no substance specific restrictions noted[5].

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

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

Lutein is not a scheduled medicine in New Zealand and is not contained in any medicines currently registered in New Zealand[7].

### *3.1.4 Dietary Supplement Regulations, New Zealand*

The New Zealand *Dietary Supplement Regulations 1985* (Dietary Supplement Regulations) currently regulate food-type and therapeutic-type dietary supplements in New Zealand. Dietary supplements are intended to supplement the intake of those substances normally derived from food. As a substance normally derived from food, lutein products are permitted to be sold as dietary supplements under the current Dietary Supplement Regulations, with products currently available on the market (e.g. lutein in capsules).

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

[5] Substances that may be used in listed medicines in Australia, found at: www.tga.gov.au/cm/listsubs.htm. Accessed 7 July 2008.
[6] Personal communication, Therapeutic Goods Administration, Australia, 14 March 2007
[7] Personal communication, Medsafe, Ministry of Health, New Zealand, 15 March 2007.

FSANZ was advised by NZFSA that FSFYC with added substances are not intended to be regulated as food-type dietary supplements but will remain under the Code.

A further discussion paper was released in July 2008 along with the Draft New Zealand Food (Supplemented Food) Standard 2008. The discussion paper indicates that Part 2.9 of the Code is excluded from the draft Standard as it is outside the policy intention and scope of the Standard. In addition, clause 7 of the draft Standard lists those standards in the Code that would apply to supplemented foods manufactured, sold or prepared for sale in New Zealand and or imported into New Zealand. Standard 2.9.3 is not included in this list.

## 3.2 Overseas and international regulations

### *3.2.1 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 when adopting the guidelines to meet the unique conditions of the local environment.

### *3.2.2 United States of America*

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

The first relates to the use of crystalline lutein in a range of foods including infant and toddler foods. The US 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 4 to 6 months up to 12 months, excluding infant formula) and toddler foods (for children over 12 months of age), at levels up to 1 mg per serve[8]. The crystalline lutein preparation is the same as that used in FloraGLO® Lutein 20% Liquid in Safflower Oil.

Although not directly relevant to this Application, the second notification was submitted to the US FDA for GRAS status for crystalline lutein suspended in safflower oil (FloraGLO® Lutein 20% Liquid in Safflower Oil) in infant formula (intended from birth up to 12 months of age) to a maximum level of 250 μg/L[9]. The US FDA responded on 23 October 2007 that it had no questions about this notification.

### *3.2.3 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.

[8] FDA decision for GRAS Notice: GRN No. 140. Available at: http://www.cfsan.fda.gov/~rdb/opa-g140.html
[9] FDA decision for GRAS Notice: GRN No. 221. Available at: http://www.cfsan.fda.gov/~rdb/opa-g221.html

The European Food Safety Authority[10] (EFSA) has recently released a scientific opinion on the suitability of lutein in infant formula and follow-on formula. The EFSA opinion raised no safety concerns for lutein at the concentration of 250 µg/L proposed by the Applicant for addition to infant formula products.

### *3.2.4 Other countries*

In China, lutein is permitted to be added as a 'nutrition fortifier' to formula for young children and preschoolers, as well as to infant formula and follow-on formula. The maximum permitted levels of lutein in formula for young children and preschoolers are 4230 µg/kg and 2700 µg/kg of powdered product respectively (equates to approximately 570 µg/L in formula for young children and 360 µg/L in formula for preschoolers).

Currently Wyeth has gained relevant government and/or product registration approvals for lutein-containing third age products (i.e. formula products for children aged over 12 months of age) in Indonesia (permitted only until July 2009), Philippines, Peru, Colombia, Costa Rica, El Salvador, Honduras, Nicaragua, Panama, Thailand, Kuwait, Oman, Guatemala, Hong Kong, United Arab Emirates, Jordan, Malaysia and Ecuador.

## 3.3 Ministerial Policy Guidelines

FSANZ must have regard to any written policy guidelines formulated by the Ministerial Council when developing and varying food standards.

The Ministerial Council recently endorsed a Policy Guideline on the *Addition to Food of Substances other than Vitamins and Minerals.* However, this Policy Guideline does not apply to special purpose foods such as FSFYC.

The Ministerial Council is currently developing policy guidance on the intent of Part 2.9 – Special Purpose Foods of the Code. A Consultation Paper[11] was released for public comment in January 2009, with submissions due in early March 2009.

In the absence of policy guidance, FSANZ's assessment has primarily focussed on the safety of lutein and whether a lutein-containing FSFYC would act as an alternative source and be a reasonable contributor to the lutein intake of young children who consume the product. However, the potential health benefits have also been assessed.

The regulatory approach taken to assess this Application is discussed further in Section 6 – Regulatory Approach.

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

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

### 3.4 Current market

*3.4.1 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 'ready-to-drink' and 'fresh' varieties of toddler formulas are being marketed in Australia and New Zealand.

FSANZ is aware of only a small number of manufacturers/importers of FSFYC in Australia and New Zealand. Generally, the manufacturers of FSFYC are also manufacturers of infant formula products. Total annual third age (i.e. toddler formula) sales are worth approximately $AUD30 million in Australia and $NZ10 million in New Zealand[12].

*3.4.2 International Market*

Given the global nature of toddler formula manufacture, similar to infant formula product manufacture, there is a cost advantage for companies to manufacture one formulation for worldwide distribution.

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

## 4. The Issue

The Applicant is seeking permission for the voluntary addition of lutein as a nutritive substance to FSFYC. The Applicant considers this would provide a modest yet significant alternative source of lutein in the diets of young children who consume FSFYC as a supplement to a normal diet when energy and nutrient intakes may not be adequate.

Nutritive substances must not be added to food unless expressly permitted in the Code. Currently, Standard 2.9.3 does not permit the addition of lutein as a nutritive substance to FSFYC.

Lutein is naturally present in some foods such as pumpkin, green peas, carrots and eggs. Lutein is also approved as a food colour and may be used as a colour in some foods eaten by young children.

The issue is whether the addition of lutein as a nutritive substance to FSFYC, at the requested level, is safe and would act as a reasonable contributor to the lutein intake of young children.

[12] Synovate AZTEC data: moving annual total figures for Australia (to 30/04/08) and New Zealand (to 11/05/08).

Whether these products would provide an alternative source of lutein for young children who consume FSFYC, in addition to other food sources also requires consideration.

## 5. Objectives

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

## 6. Regulatory Approach

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

The assessment of whether lutein should be permitted as an optional nutritive substance in FSFYC has considered:

- the safety of lutein;
- whether lutein is found naturally in foods commonly eaten by young children;
- whether the requested level of lutein in FSFYC (500 µg/L), and the minimum level proposed for purposes of making a claim on FSFYC (150 µg/L) can make a reasonable contribution to the lutein intake (accounting for bioavailability), of young children who consume FSFYC;
- the nutritional purpose or physiological function(s) of lutein; and

- the potential for a health benefit for young children who consume FSFYC with added lutein.

The regulatory approach for lutein in FSFYC is different to that taken for lutein in infant formula products, as assessed under Application A594. As the purpose of FSFYC is as a supplement to a normal diet for young children when energy and nutrient intakes may not be adequate, the approach considers whether lutein-containing FSFYC can provide an alternative source of lutein and make a reasonable contribution to the lutein intake of young children who consume FSFYC. By contrast, the approach for infant formula products considered nutritional equivalence with breast milk, as these products are used as a substitute for breast milk and in some instances as the sole source of nutrition for formula-fed infants. Both approaches require the safety of lutein for the target population to be demonstrated.

# RISK ASSESSMENT

## 7. Risk Assessment Questions

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

1. Is lutein found naturally in foods, and if so, how do the concentrations in foods compare with that proposed to be added to FSFYC?

2. What is the concentration of lutein in FSFYC without added lutein?

3. Does lutein have a nutritional purpose or physiological function?

4. Is there a health benefit for young children who consume FSFYC with added lutein?

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

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

7. What is the estimated impact on the lutein intakes of young children who consume FSFYC containing lutein at a minimum concentration of 150µg/L and a maximum concentration of 500 µg/L?

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

## 8. Risk Assessment Issues

The following section summarises the response to the risk assessment questions. A more detailed assessment of these issues is contained in the attachments to this Report. The Nutrition Assessment (Attachment 4) contains information related to questions 1, 2, 3 and 4. Questions 4 and 5 are addressed by the Dietary Intake Assessment (Attachment 5). The Hazard Assessment (Attachment 6) contains detailed discussion relating to question 6.

## 8.1 Lutein content of foods

### *8.1.1 Is lutein found naturally in foods?*

Lutein is a plant pigment; a substance responsible for many of the bright natural colours in plants. Plant foods rich in lutein include dark green leafy vegetables such as spinach and kale. Other coloured vegetables high in lutein include green peas, broccoli, carrots, and corn. Citrus fruits, tomatoes, peaches and other fruit also contain lutein. Lutein is also present in egg yolks, the fat of animals whose diets include lutein-rich plants and in human breast milk (United States Department of Agriculture, 2008).

Lutein and its isomer zeaxanthin (a structurally similar molecule shown in Figure 1 above) occur together in nature. Because most food composition analyses are unable to separate them, lutein and zeaxanthin are often reported together as a combined concentration. Lutein is more abundant than zeaxanthin in greens but the concentration of zeaxanthin is more equal to the concentration of lutein in most yellow-orange fruits and vegetables. Chitchumroonchokchai *et al*. (2004) reported the ratio of lutein:zeaxanthin in foods as high as 40:1.

Another study determined the separate concentrations of lutein and zeaxanthin in several fruits, vegetables, and pasta products. The ratio of lutein to zeaxanthin in green vegetables ranged from 12:1 to 63:1 (Humphries and Khachik, 2003). The authors attributed to the dominant role of lutein in photosynthesis. In most yellow-orange fruits and vegetables the ratio was found to be nearly 1:1; with the exception of butternut squash which had a ratio of 9:1. Corn and nectarine were also found to be exceptions in this study as they contained a higher concentration of zeaxanthin relative to lutein. In the wheat and pasta products tested in this study, the ratio of lutein to zeaxanthin ranged from 2.5 to 12:1.

The source of lutein in this Application is from the petals of marigold flowers (*T. erecta L*) which also contain zeaxanthin. The material proposed by the Applicant for addition to FSFYC is a purified extract of lutein from marigold oleoresin which contains both lutein and zeaxanthin in a ratio of approximately 10:1. Thus, while marigold flowers are not normally consumed in the Australian and New Zealand diet, the chemical structure of lutein and zeaxanthin in the purified extract from marigold flowers is the same as the two carotenoids found in other edible plant sources (see Figure 1), and the ratio of lutein to zeaxanthin is within the range of ratios found in other edible plant sources.

### *8.1.2 How does the concentration of lutein in foods compare with the concentration proposed to be added to FSFYC?*

The Applicant has sought a maximum concentration of 500 µg/L of lutein in FSFYC. This would provide at most 100 µg of lutein in a recommended serving of 200 mL.

The concentration of lutein and zeaxanthin in foods is variable. The content tends to be higher in brightly coloured plant foods. For example, one tablespoon of shredded green cos lettuce provides roughly the same amount of lutein and zeaxanthin as six tablespoons of the less brightly coloured lettuce variety known as iceberg or crisp head lettuce. Table 1 compares the lutein and zeaxanthin content of different foods that could be expected to be consumed by children aged 1-3 years.

For example, the same amount of lutein and zeaxanthin that would be provided in one 200 mL serving of FSFYC at the maximum concentration of 500 µg/L could be obtained from eating ¼ teaspoon of spinach; or one teaspoon of peas; or two teaspoons of corn; or one tablespoon of sliced carrot; or ½ of a large egg; or 1/3 cup of orange juice.

Lutein is also a food colouring agent (INS 161b) that is permitted to be added to a variety of foods under Schedule 1 of Standard 1.3.1. FSANZ examined its food additive database to determine the types of products that contain the additive 161b. While this database is not necessarily representative of the Australian and New Zealand food supplies, it is often used for indicative purposes. Very few products were found to have lutein listed as an ingredient: one sweet biscuit, one dry sauce mix, one mayonnaise, and one carbohydrate modified confectionery. Consequently, it was considered that lutein added as a food colouring agent was unlikely to contribute greatly to the lutein intakes of children aged 1-3 years.

**Table 1: Comparison of the lutein and zeaxanthin concentrations in selected foods with the maximum concentration of lutein and zeaxanthin proposed to be added to FSFYC by the Applicant**

| Food item | Lutein and zeaxanthin (µg/100g) | Serve size (grams) which provides 100 µg lutein and zeaxanthin | Approximate estimate of household measure which provides 100 µg lutein and zeaxanthin[1] |
|---|---|---|---|
| **FSFYC [2]** | NA | 200 mL | 4/5 cup |
| **Kale** | 18,246 | 0.5 | 1/6 teaspoon |
| **Spinach** | 11,308 | 0.9 | ¼ teaspoon |
| **Green Peas** | 2,400 | 4 | 1 teaspoon or 3 peas |
| **Lettuce, cos or romaine** | 2,313 | 4 | ½ of one inner leaf or 1 tablespoon shredded |
| **Broccoli** | 1,403 | 7 | 1 tablespoon |
| **Brussels Sprouts** | 1,290 | 8 | 1/3 of one sprout |
| **Breakfast cereal** | 977 | 10 | 1/3 cup |
| **Corn** | 949 | 11 | 2 teaspoons |
| **Carrots** | 687 | 14 | 1 tablespoon of slices |
| **Beans** | 564 | 18 | 1 ½ tablespoons |
| **Egg, cooked** | 354 | 28 | ½ large egg or 1/5 cup chopped egg |
| **Celery** | 283 | 35 | 2 small stalks or 1/3 cup chopped celery |
| **Lettuce, iceberg** | 277 | 36 | 2 and ½ large leaves or 6 tablespoons shredded |
| **Nectarines** | 130 | 77 | ½ medium nectarine or ½ cup slices |
| **Oranges** | 129 | 78 | ¾ of one small orange or 2/5 cup of orange sections |
| **Tomatoes** | 123 | 81 | 3 thick slices or ½ cup of cherry tomatoes |
| **Orange juice** | 115 | 87 | 1/3 cup |
| **Peaches** | 91 | 110 | ¾ cup slices |
| **Bread** | 48 | 208 | 6-7 slices (25-30 g per slice) |

| Food item | Lutein and zeaxanthin (µg/100g) | Serve size (grams) which provides 100 µg lutein and zeaxanthin | Approximate estimate of household measure which provides 100 µg lutein and zeaxanthin[1] |
|---|---|---|---|
| **Pears** | 34 | 294 | 1 and 1/5 cup of pear halves |
| **Cucumber** | 23 | 435 | 4 and 1/5 cup of slices |

Source: United States Department of Agriculture 2008.
[1] One level metric cup = 250 mL. One level metric tablespoon = 20 mL. One level metric teaspoon = 5 mL.
[2] With added lutein from *Tagetes erecta L*, to provide a maximum concentration of 500 µg/L when reconstituted as directed.

### *8.1.3 What is the concentration of lutein in FSFYC without added lutein?*

Information from the Applicant indicates that the ingredients of milk-based FSFYC contain some natural level of lutein and zeaxanthin. According to the Applicant, this innate source contributes approximately 4-6 µg lutein per 200 mL serve of FSFYC.

### *8.1.4 What are the functions of lutein?*

Lutein and zeaxanthin must be acquired from the diet; they cannot be synthesized in the body. Their presence has been detected in many tissues, but they are particularly prevalent in the eye where their respective concentrations can exceed those in serum by up to several thousand-fold (Handelman *et al.*, 1988; Schmitz *et al*., 1993). They are the only carotenoids present in the lens (Yeum *et al.*, 1995), where they, along with *meso*-zeaxanthin, a non-dietary carotenoid thought to derive from lutein, comprise the 'macular pigment' (Beatty *et al.*, 1999; Bone *et al.*, 1997; Landrum and Bone 2001). Their presence in the lens gives it its characteristic yellow color (Bernstein *et al*., 2001; Bone *et al*., 1988; Rapp *et al*., 2000).

Other carotenoids have not been found to be concentrated in tissue this way, suggesting that lutein and zeaxanthin are unique in this respect (Alves-Rodrigues and Shao, 2004). Further, lutein and zeaxanthin levels in the eye are preferentially preserved over serum concentration following a decreased intake (Johnson *et al*., 2000; Zeimer *et al.*, 2009). It is therefore clear that there is a strong biological drive to ensure the presence of lutein and zeaxanthin in the eye.

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

The human eye is naturally exposed to considerable oxidative stress through light, with particular sensitivity to blue light (Snodderly, 1995). Lutein has been shown to act as a filter of blue light in the eye (Junghans *et al*., 2001). Lutein and zeaxanthin have also been shown to act as antioxidants in the eye (Kim *et al*., 2006), and, much like other carotenoids, more generally in the body (Lim *et* al., 1992; Tomey *et al.*, 2007; Trevithick-Sutton *et al*., 2006, Zhang *et al*., 1991).

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

However, a diet devoid of lutein and zeaxanthin is highly unlikely in young children, and this research does not indicate at what intake these structural changes would be prevented.

The published data clearly show that lutein and zeaxanthin are functional components of the eye; no other carotenoid has been shown to be able to take their place. Further, increased intakes of lutein, either from food or supplement use, have been shown to increase the density of the macular pigment in some but not all individuals (Aleman *et al.*, 2007, Berenschot *et al.*, 2000; Bone *et al.*, 2007; Hammond *et al.*, 1997; Nolan *et al.*, 2007, Zeimer *et al.*, 2009).

### *8.1.5 Is there a health benefit to young children of consuming FSFYC with added lutein?*

The ability of increased lutein intake to increase macular pigment density; observations that higher intakes of lutein are sometimes associated with lower risk of age-related macular degeneration; and the ability of lutein to reduce oxidative stress in the eye, have led to speculation that increasing lutein intakes may reduce the risk of conditions such as age-related macular degeneration (Alves-Rodrigues and Shao, 2004; Beatty *et al.*, 1999; Snodderly, 1995).

As age-related macular degeneration is generally experienced late in life, demonstrating a preventative role of dietary lutein in early childhood with any certainty would require a large group to be followed up for many decades. Even then it might not be possible to differentiate the benefit of intakes early in life with those from intakes in subsequent life stages.

In the absence of longitudinal data with follow-up starting in early childhood, results from studies in adults constitute the best available evidence. A recent systematic review and meta-analysis examining the role of lutein, among other antioxidants, in the primary prevention of age-related macular degeneration reported that *high antioxidant levels in the healthy retina did little to prevent the development of early AMD* [age-related macular degeneration] (Chong *et al.*, 2007). As none of the studies included young children, they could not investigate the question of possible benefit from lutein consumption early in life. Therefore, the negative finding in adults does not rule out the possibility of benefit over a longer period.

Studies of secondary prevention are not relevant to this assessment, as young children do not suffer from age-related macular degeneration.

At this stage, although it is biologically plausible for lutein to provide a benefit to long-term eye health, there is insufficient evidence to make such a conclusion with any certainty.

## 8.2 Bioavailability

### *8.2.1 Is lutein derived from marigold flowers bioavailable for young children?*

The bioavailability of lutein has been assessed by measuring changes in concentration of lutein in blood. Three unpublished studies provided by Wyeth comparing the bioavailability of lutein in breast milk with that in infant formula clearly demonstrate lutein from the proposed source, *Tagetes erecta*, added to infant formula increase blood lutein concentrations in infants (Wyeth, 2006a; Wyeth, 2006b; Wyeth, 2007). The studies did not compare the bioavailability of lutein in formula with that of foods such as young children are likely to be consuming.

Further, in response to the first review request for Application A594 – Addition of Lutein as Nutritive Substance Infant Formula Products, FSANZ requested additional information from Wyeth about these studies including further information on sample handling and preparation, and analysis. Several aspects of the Wyeth studies indicated their results were not likely to be accurate enough to establish the quantitative bioavailability of lutein in breast milk relative to lutein in infant formula with confidence. Despite some deficiencies, the studies do confirm that lutein from *T. erecta* is qualitatively bioavailable in an infant formula like matrix. The comparison of quantitative bioavailability between breast milk and infant formula is not a pivotal issue in this assessment as FSFYC is not intended to be a substitute for breast milk.

Studies in adult subjects indicate that lutein from *T. erecta* given as supplements is more bioavailable than that in yellow carrots (Molldrem *et al*., 2004), similarly bioavailable to that in spinach (Chung *et al.*, 2004), and less bioavailable than that from eggs (Chung *et al*., 2004).

*8.2.2 Is the bioavailability of lutein derived from marigold flowers comparable to the bioavailability of lutein from natural food sources?*

Lutein is a fat soluble substance. Like other carotenoids, its absorption is influenced by fat intake. In particular, the concurrent presence of fats and oils in the gut is likely to improve lutein bioavailability. Roodenburg *et al.* (2000) compared the effects on the serum concentration of lutein in healthy adults with different levels of concurrent fat intake. The serum concentration of lutein was increased by 88% and 207% when consumed with a low-fat and a high fat meal, respectively.

Results from investigations of interactions between lutein and other carotenoids during digestion and absorption are variable. Some (Micozzi *et al*., 1992; Kostic *et al*., 1995; van den Berg and van Vliet, 1998), but not all studies reported an interaction (Riso *et al*., 2004).

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 infant formula.

## 8.3 Dietary intake of lutein by young children

There are no national nutrition survey data for Australian children aged less than 2 years, and New Zealand children aged less than 5 years. In this situation, international best practice is to construct a theoretical diet.

FSANZ has previously developed such a diet to permit estimation of mean dietary intakes for Australian children aged 1 year and New Zealand children aged 1-3 years. The 1995 National Nutrition Survey data 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 information provided by the Applicant with regard to FSFYC, and from the U.S. Department of Agriculture nutrient database.

Results of the Dietary Intake Assessment are presented in more detail in Section 6 of Attachment 5.

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

There is no estimate of the intake of lutein alone because food composition databases report a level for lutein and zeaxanthin combined. The ratio of naturally occurring lutein:zeaxanthin varies with each food (Section 8.1). The estimated mean intake of lutein and zeaxanthin from non-FSFYC foods was 385 µg/day and 740 µg/day in Australian children aged one year and 2-3 years respectively, and 680 µg/day in New Zealand 1-3 year olds (refer Tables 2 and 3 of 5).

The major contributors (≥ 5%)[13] to combined lutein and zeaxanthin intakes were:

- Australian children aged one year: fruit and vegetables juices (20%), fruits (10%), grain/cereal based foods (8%), green peas (8%), carrots (7%), leafy vegetables (7%), onions (7%), sweet corn (6%), broccoli/cauliflower (5%), and all other vegetables (14%).

- Australian children aged 2-3 years: oranges (19%), green peas (14%), fruits except oranges (12%), grains (9%), pumpkin (9%), leafy vegetables (8%), sweet corn (6%), broccoli (5%) and all other vegetables (13%).

- New Zealand children aged 1-3 years: silverbeet (23%), fruits including juices (12%), grain/cereal foods (11%), green peas (10%), pumpkin (9%), carrots (8%), and all other vegetables (15%).

### *8.3.2 What is the estimated impact on lutein intakes of young children who consume FSFYC containing lutein at a minimum concentration of 150 µg/L and a maximum concentration of 500 µg/L?*

To provide an indication of the likely impact on lutein intakes among young children aged 1-3 years who consume FSFYC, two fortification scenarios were used.

The first scenario considered a minimum concentration of 150 µg/L lutein in FSFYC (or 165 µg/L lutein and zeaxanthin combined) based on the prescribed minimum claimable amount of 30 µg/serve and assuming a 200 mL serve size (see Section 22).

The second scenario considers the maximum concentration requested by the Applicant of 500 µg/L lutein in FSFYC (or 550 µg/L lutein and zeaxanthin combined). These two levels represent the range of lutein concentrations that might be added to FSFYC.

Addition of lutein to FSFYC was estimated to increase mean intakes of lutein and zeaxanthin by 18-61% for Australian children aged one year, by 8-28% for Australian children aged 2-3 years and by 6-23% for New Zealand children aged 1-3 years, assuming 165 µg/L and 550 µg/L lutein and zeaxanthin combined respectively.

[13] Single foods or food groups contributing ≥ 5% to total dietary exposure to a given food chemical for a specified population group are generally termed 'major contributors' by international convention.

The estimates were based on FSFYC consumption of 423 g/day for Australian children aged one year, and 281 g/day for New Zealand children aged 1-3 years, assuming all milk, infant formula and follow-on formula was replaced by FSYC[14]. The average consumption of FSFYC by Australian children aged 2-3 years was estimated to be 403 g/day. These amounts approximate one to two 200 mL serves of FSFYC per day.

The major contributors (≥ 5%) to lutein and zeaxanthin (combined) intakes for the *150 µg/L lutein in FSFYC scenario* were:

- Australian children aged one year: fruit and vegetables juices (17%), FSFYC (15%), fruits (8%), grain/cereal based foods (7%), green peas (6%), carrots (6%), leafy vegetables (6%), onions (6%), sweet corn (5%) and all other vegetables (16%).

- Australian children aged two to three years: oranges (18%), green peas (13%), fruits except oranges (11%), grains (9%), pumpkin (8%), FSFYC (8%), leafy vegetables (7%) sweet corn (5%), and all other vegetables (17%).

- New Zealand children aged one to three years: silverbeet (22%), fruits including juices (12%), grain/cereal foods (10%), peas (10%), pumpkin (8%), carrot (8%), FSFYC (5%), and all other vegetables (14%).
-

The major contributors (≥ 5%) to lutein and zeaxanthin (combined) intakes for the *500 µg/L lutein in FSFYC scenario* were:

- For Australian children aged one year: FSFYC (38%), vegetables (34%), fruit and vegetables juices (13%), and fruits (6%).

- For Australian children aged two to three years: FSFYC (22%), oranges (15%), green peas (11%), fruits except oranges (9%), grains (7%), pumpkin (7%), leafy vegetables (6%) and all other vegetables (19%).

- For New Zealand children aged one to three years: silverbeet (19%), FSFYC (15%), fruits including juices (10%), grain/cereal foods (9%), green peas (9%), pumpkin (7%), carrots (7%), and all other vegetables (13%).

- These results indicate that at both the upper and lower levels of fortification, FSFYC could become a major contributor (≥ 5%) to the lutein and zeaxanthin intakes of Australian and New Zealand children aged 1-3 years.

- As the scenarios are based on complete replacement of all liquid milk, infant formula and follow-on-formula they may overestimate the contribution of FSFYC to lutein intake in this age group, but at the upper concentration level FSFYC are still likely to be major (≥ 5%) contributors to lutein intake even if 100% replacement of all liquid milk and formulas does not occur.

[14] The differences between the Australian and New Zealand estimates of milk consumed are due in part to different methods used to determine the theoretical diets for Australian one year olds and New Zealand 1-3 year olds (see Section 3.7, Attachment 3 for further information about the construction of theoretical diets in these age groups).

### 8.4 Safety of lutein in FSFYC

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

The Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) evaluated lutein and zeaxanthin from marigold flowers (*Tagetes erecta L*) at its 63rd meeting (in 2004) and established an ADI of 2 mg/kg body weight per day. This was based on the highest dose tested in a ninety-day repeat-dose toxicity study in rats and includes a safety factor of 100. The ADI is an estimate of the amount of a substance in food, expressed on a body weight basis (usually mg/kg body weight per day), which can be ingested daily over a lifetime, from 12 weeks of age onwards, without appreciable health risk. Therefore, if the total intake of lutein and zeaxanthin (from natural sources and from FSFYC) by young children is at or below the ADI, there is very low risk to public health and safety. FSANZ has adopted the JECFA ADI of 2 mg/kg body weight per day. This ADI applies only to lutein preparations which meet the JECFA specifications.

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 products at a maximum level of 250 µg/L is unlikely to pose any public health and safety risk to formula-fed infants. The data assessed included the ninety-day, repeat-dose, toxicity study in rats mentioned above, and a developmental toxicity study in rats. It also included 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) has been observed, but the dose at which it has been observed varies between individuals and between ethnicities. Carotenodermia is considered harmless and is readily reversible upon discontinuation of high intakes of lutein. Further detail is provided in the Hazard Assessment at Attachment 6.

For Australian and New Zealand children aged 1-3 years, the estimated mean and 90th percentile intakes to lutein and zeaxanthin were all below the ADI (see Tables 4 and 5 in Attachment 5). For the lower and upper concentrations of lutein in FSFYC (150 µg/L and 500 µg/L, respectively) the 90th percentile intakes were estimated at 5-8% ADI and 6-9% ADI.

Therefore, FSANZ concludes that the risks to young children from consuming FSFYC containing lutein derived from marigold flowers (*T. erecta L.*) up to the maximum concentration of 500 µg/L is very low.

## 9. Risk Assessment Summary

Lutein (and its isomer zeaxanthin) occurs naturally in many foods commonly eaten by young children in Australia and New Zealand, such as pumpkin, green peas, carrots and eggs. Lutein is also found in breast milk.

Lutein is absorbed from food and, along with zeaxanthin, is concentrated in parts of the eye, particularly the macula lutea where it is a key functional component of the macular pigment acting as site specific antioxidant and filter of harmful blue light. Increasing lutein intake has been shown to increase the density of the macular pigment.

Although it is biologically plausible for lutein to promote eye health, there is insufficient evidence to make firm conclusions in relation to any additional long-term benefit to eye health for infants from consuming lutein, including FSFYC containing added lutein.

Lutein in infant formula is bioavailable. The form of lutein proposed for addition to FSFYC appears to be more bioavailable than that in yellow carrots, similarly bioavailable to that in spinach, and less bioavailable than that in eggs. Consistent with findings for other carotenoids: consuming lutein-rich food along with a source of dietary fat is likely to enhance its bioavailability.

Estimated mean intakes of lutein in children aged 1-3 years in Australia and New Zealand were between 385-740 µg/day. One 200 mL serve of FSFYC (with a lutein concentration of 150 µg/L or 500 µg/L) will add a further 30 or 100 µg/day, respectively, to the lutein intake in this age group. These increases, based on either the lower or upper concentrations of lutein, could result in FSFYC becoming one of the major contributors (≥ 5%) to the lutein and zeaxanthin intakes of Australian and New Zealand children aged 1-3 years, this being more likely if 100% milk was replaced by FSFYC.

Taking into account this additional intake, the estimated 90$^{th}$ percentile of lutein intake among 1-3 year olds based on the maximum concentration of 500 µg/L lutein in FSFYC would be only 6-9% of the safety standard (i.e. the ADI).

Therefore, FSANZ concludes that there is unlikely to be any public health and safety concerns from lutein added as a nutritive substance to FSFYC at the maximum levels proposed by the Applicant. Also, lutein-fortified FSFYC has the potential to make a reasonable contribution to the lutein intake of 1-3 year old consumers of these foods.

# FOOD TECHNOLOGY

## 10. Food Technology Issues

The food technology aspects of lutein used as a nutritive substance to be added to FSFYC 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 in FSFYC, since its proposed use in this Application is not for this purpose.

Lutein is a natural carotenoid with the commercial lutein extract prepared from marigold (*T. 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 JECFA in 2004. The preparation is from a natural extract, not a synthetically synthesised chemical.

One submitter recommended that the proposed permission should be extended to include lutein esters, rather than free lutein alone. However, the JECFA specification is for the free lutein, not the lutein esters. Also, Application A597 relates to free lutein only, not lutein esters. Hence the scope of this Application, and any subsequent permission, relates to free lutein.

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 (further detail is provided in Attachments 7 and 3).

The commercial lutein preparation that is subsequently added to food is carried in vegetable oil with approved food additives being antioxidants and emulsifiers. These food additives would not be expected to have any technological additive function in the final FSFYC. Stability results for powdered products, as in the most common FSFYC, indicated some losses of lutein occurred during storage. 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 are aware of losses of lutein that occur for their products during storage and therefore apply a suitable over dosing to account for such losses (commonly referred to an overage). The Applicant has requested a maximum level of 500 µg/L to ensure they always achieve a level of 200 µg/L when the solution is made up.

For their commercial operations, the Applicant aims for an overage of 180% to account for losses during storage and distribution to ensure the product meets their label concentration up until the end of the product's shelf life. The extra allowance above 180% is to ensure their product will always meet the requirements of the Code, being within the minimum and maximum limits. The Applicant's request for higher levels of lutein to account for losses is comparable to that commonly used for the addition of sensitive vitamins to food that are prone to losses during storage.

The addition of lutein as a nutritive substance up to a level of 500 µg/L will not impact on other ingredients in FSFYC.

The full Food Technology Assessment is found at Attachment 7.

# RISK MANAGEMENT

## 11. Risk Management Issues

On the basis of FSANZ's risk assessment the following sections discuss the management of any identified health and safety risks, other broader issues relevant to permitting the voluntary addition of lutein in FSFYC, and responds to key points raised in submissions.

### 11.1 Protection of public health and safety

The protection of the public health and safety of young children who consume FSFYC is the primary objective in consideration of this Application.

FSANZ's risk assessment has examined substantial evidence from the Applicant and other sources.

The findings of the risk assessment align the regulatory approach taken to the assessment of this Application, in the absence of Ministerial policy guidance.

Firstly, the regulatory approach requires that lutein is found naturally in foods commonly eaten by young children. As reported in the risk assessment, lutein is found naturally in plant foods including spinach, green peas, carrots, corn and citrus fruits, in egg yolks, and in the fat of animals whose diets include lutein-rich plants. These lutein-rich foods will often form part of a young child's diet as it increases in quantity and becomes more diverse to meet their energy and nutrient requirements. As shown in the risk assessment, the major dietary contributors of lutein and zeaxanthin for Australian and New Zealand children aged 1-3 years included fruit and vegetable juices, peas, oranges, pumpkin and silverbeet.

Lutein in FSFYC must also be assessed as safe for young children. The risk assessment concluded that the risk to young children from consuming FSFYC containing lutein derived from marigold at a maximum concentration of 500 µg/L is very low. Specifically, it showed that intakes of lutein for young children from both natural food sources and lutein-fortified FSFYC were all well below the ADI.

The regulatory approach also requires consideration of whether the requested level of lutein in FSFYC (up to 500 µg/L) is likely to make a reasonable contribution to the lutein intake of young children, accounting for bioavailability. The risk assessment showed that lutein added to FSFYC is no less bioavailable than that naturally occurring in plant sources and concludes that lutein-fortified FSFYC could make a reasonable contribution to the lutein intake of 1-3 year old children who consume these foods. The risk assessment also showed that lutein-fortified FSFYC at both the minimum and the maximum concentration have the potential to become one of the a major contributors (≥ 5%) to lutein intakes of young children (aged 1 -3 years) who consume FSFYC – 5-15% and 15-38% of their dietary lutein intake respectively will be from FSFYC. At the maximum requested level of lutein in FSFYC, the increase in mean daily lutein intake from lutein-fortified FSFYC is comparable to the amount of lutein found in a child size serving of some fruits and vegetables. With the minimum concentration of lutein FSFYC could potentially become one of the major contributors (≥ 5%) to the lutein intake of young children, if there was complete replacement of milk and / or infant formula as in the theoretical diets used in dietary intake assessments.

Also, New Zealand research (Attachment 5 Section 3.7.1) indicated the average consumption of FSFYC was 460 mL per day which would result in a greater daily intake of lutein than the theoretical diets used in the above estimations for New Zealand children.

As demonstrated above, the request to permit the addition of lutein to FSFYC is consistent with the approach to the assessment of this Application. Furthermore, lutein-fortified FSFYC would provide an alternative source of lutein to those food sources noted in Section 8.1.1 and would have the potential to make a reasonable contribution to lutein in the diets of young children who consume them. This is consistent with the purpose of FSFYC as a supplement to the normal diet when a young child's energy and nutrient intakes may not be adequate.

## 11.2 Level of addition

The Applicant has requested the addition of lutein to FSFYC at a maximum concentration of 500 µg/L to provide a modest yet significant amount of lutein in the diet of young children. This includes the overage to allow for losses over time during storage.

Some submitters to the Draft Assessment Report expressed concern that the proposed maximum level appeared excessive when compared to levels used in a study of adult subjects that showed a potential health benefit, particularly as young children are only approximately a fifth of an adults' body weight.

The proposed maximum lutein concentration of 500 µg/L equates to 100 µg per 200 mL serve of FSFYC[15], which is comparable to the lutein content of one teaspoon of green peas, or one tablespoon of sliced carrot, or half of a large egg.

When compared with levels of lutein permitted in FSFYC-like products internationally, the proposed level is one-tenth of the level granted GRAS status by the US FDA (1 mg per serve) and is similar to the level permitted in products sold in China.

The proposed maximum concentration of 500 µg/L accounts for losses of lutein during storage (as discussed in Section 10). The maximum expected loss after 12 months for powdered products, such as FSFYC is 35%. While the product might contain close to the maximum permitted level at the start of the shelf-life, lutein will most likely be present in FSFYC at levels less than the maximum concentration of 500µg/L when consumed. If the concentration is greater than the maximum at any time during the product's shelf life it will be considered non-compliant with the Code. However as noted above, levels of lutein at the minimum concentration of 150 µg/L FSFYC could still potentially make a reasonable contribution to lutein intakes of young children who consume these products.

### *11.2.1 Unit for lutein concentration in draft Standard*

In the draft Standard, the minimum and maximum concentrations of lutein are expressed per serving, consistent with permissions for vitamin and minerals in FSFYC in Division 4 of Standard 2.9.3.

The proposed levels assume a serving size of 200 mL, which is a size commonly attributed to FSFYC by manufacturers of toddler formula. The maximum concentration of 100 µg/serve represents the Applicant's original request for 500 µg/L.

## 11.3 Labelling requirements

The label on a package of a FSFYC must comply with general labelling provisions contained in Part 1.2 of the Code, which requires consideration of both ingredient labelling and nutrition information labelling. In addition, Standard 2.9.3 prescribes labelling requirements specific to FSFYC.

[15] 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.

### *11.3.1 Ingredient labelling*

General labelling provisions contained within Standard 1.2.4 – Labelling of Ingredients apply to nutritive substances permitted for addition to FSFYC. Therefore, if lutein is added to a FSFYC, declaration of lutein in the statement of ingredients will be required.

### *11.3.2 Nutrition information labelling and claims*

Standard 1.2.8 – Nutrition Information Requirements requires a nutrition information panel on all foods, including FSFYC. However, there is no requirement for lutein to be listed in the nutrition information panel unless a nutrition claim is made. A nutrition claim could include a reference to the presence or average quantity of a particular nutrient or biologically active substance[16]. Lutein would be considered a biologically active substance for the purposes of making a claim.

At Draft Assessment, FSANZ proposed that a claim about lutein on a FSFYC could only be made if the product contained a minimum of 30 µg/serve of lutein. Most submitters to the Draft Assessment Report commented on the minimum claimable amount prescribed for lutein. Some submitters were concerned that the minimum amount had been based on data extrapolated from theoretical diets that used outdated dietary intake data. Other submitters considered that the minimum amount should reflect purpose; for example, it should comprise of 10% of the level required to reasonably achieve the nutritional purpose or indicate the minimum effective level. One submitter commented that it was unclear whether the proposed minimum amount was meaningful, given that there is no reference value for lutein.

- Setting a minimum claimable level that reflects the nutritional purpose or minimum effective level of lutein, as recommended by some submitters could be considered inconsistent with the intended purpose of a FSFYC.

- A minimum claimable amount of 30 µg/serve of lutein is recommended as consumption of one 200 mL serve at this concentration would provide approximately 10% of the lowest estimated mean dietary intake of one year old children from foods other than FSFYC (Section 6, Attachment 5). The mean intake is used to set an AI, when there is no evidence of deficiency in the population and not enough information to define the requirement.

- As there is no evidence of deficiency or inadequate intakes of lutein in this age group in Australia and New Zealand, FSANZ has adopted an approach analogous to defining AIs, and selected the mean intake as the basis for determining the claimable amount for lutein in FSFYC.

- This approach is also consistent with the purpose of a FSFYC which is to supplement a normal diet rather than to provide additional potential health benefit.

The recommended minimum also exceeds the innate amounts of lutein found in unfortified toddler formula and therefore a claim about lutein is only likely to be made when lutein is added to a FSFYC.

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

Therefore, at Final Assessment, it is recommended that a minimum claimable amount of 30 µg/serve of lutein is required before a claim about lutein can be made on a FSFYC.

The recommended minimum claimable amount for lutein does not constitute a 'reference value', unlike the reference values listed in the Table to subclause 7(3) of Standard 1.2.8, and the RDI or ESADDI values of vitamins and minerals referenced elsewhere in the Code.

Therefore, in the absence of a reference value in the Code, the recommended minimum claimable amount for lutein cannot be used to calculate percentage daily intake in nutrition information panel.

### *11.3.3 Nutrition and health claims*

#### 11.3.3.1 Current

At present in the Code, nutrition claims are permitted on FSFYC. Clause 7 of Standard 2.9.3 prescribes the requirements for making nutrition claims about vitamins or minerals only. Generic conditions prescribed under Standard 1.2.8 apply to nutrition claims about other nutrients or biologically active substances. In addition FSFYC must also comply with any requirements of Standard 1.1A.2 - Transitional Standard - Health Claims.

#### 11.3.3.2 Proposed

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

The proposed new regulations for nutrition content claims and health claims retain the existing requirement that a claimed nutrient or biologically active substance, including the average quantity, must be declared in the nutrition information panel.

For nutrition content claims, it is proposed that, where there is no established reference value for the substance in the Code, only those claims that refer to the presence of the 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.

For health claims, it is currently proposed that general level health claims will be permitted including for biologically active substances, where the amount required to qualify for a claim must be based on the relevant substantiation process.

If lutein is permitted to be added to FSFYC, the prescribed minimum claimable amount could be exceeded if substantiation revealed that a greater amount is required to achieve a specific health effect (provided the total of the naturally occurring and added amounts of lutein is no more than 100 µg/serve in FSFYC).

Submitters to the Draft Assessment Report for this Application raised some concerns in relation to nutrition and health claims under Proposal P293, particularly with regard to substantiation of claims.
Some submitters considered that foods regulated by Standard 2.9.3 should be ineligible to carry nutrition content claims and health claims.

In relation to lutein in FSFYC, submitters considered a claim could not be permitted as there is a lack of sufficient data to establish a minimum effective level of lutein or to support a benefit for eye health. Several submitters noted that any claims would need to be substantiated. One submitter believed that nutrition content claims for lutein should be permitted, as these would enable consumers to make informed choices.

Currently under Proposal P293, the approach for nutrition content claims and other relevant claims requires that the amount claimed as being present in the product must be substantiated. It is also proposed that a high level health claim about a food-disease relationship would be permitted subject to full substantiation through a pre-market approval process conducted by FSANZ.

Therefore, only substantiated nutrition content claims, general level health claims and high level health claims will be permitted on FSFYC under the proposed Standard 1.2.7.

As a result, conditions for making nutrition content claims and health claims under the proposed regime are more stringent than current requirements.

It is noted that under the proposed Standard 1.2.7, special purpose foods regulated in Part 2.9 of the Code, such as FSFYC, will be exempt from profiling requirements because their nutrition composition is already prescribed.

# 12. Options

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

- Option 1 – rejecting the Application, thus not amending the Code to permit the voluntary addition of lutein as a nutritive substance in FSFYC; and

- Option 2 – amending Standard 2.9.3 to permit the voluntary addition of lutein as a nutritive substance in FSFYC up to a maximum concentration of 100 µg/serve (500 µg/L) and to require a minimum claimable amount of 30 µg/serve.

# 13. Impact Analysis

## 13.1 Affected Parties

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

## 13.2 Benefit Cost Analysis

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

### *13.2.1 Option 1 — rejecting the Application, thus not amending the Code to permit the voluntary addition of lutein as a nutritive substance in FSFYC*

13.2.1.1 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, except potentially in the case of young children who rely on FSFYC to supplement their normal diet.

13.2.1.2 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, as the market for FSFYC is possibly growing, 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.

13.2.1.3 Government

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

### *13.2.2 Option 2 – amending Standard 2.9.3 to permit the voluntary addition of lutein as a nutritive substance in FSFYC*

13.2.2.1 Consumers

Permitting the voluntary addition of lutein to FSFYC would benefit young children by providing an alternative source of lutein in their diet should they choose to consume FSFYC. The addition of lutein to FSFYC at the proposed maximum level will provide a safe source of lutein, and would act as a reasonable contributor to the lutein intake of young children. Lutein added to FSFYC would perform the equivalent function in the eye as lutein from other foods consumed by young children. However, there is insufficient evidence to make firm conclusions regarding the long-term benefit to eye health to young children who consume these products.

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

13.2.2.2 Industry

A permission to add lutein to FSFYC 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, provided the maximum concentration of lutein in the imported FSFYC did not exceed 100 µg/serve.

13.2.2.3 Government

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

### 13.3 Comparison of Options

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

Evidence indicates that the addition of lutein in the form and at the level proposed in Option 2 is safe and suitable for young children. Lutein-fortified FSFYC would provide an alternative source of lutein for young children in addition to the dietary sources noted in Section 8.1. Also these products would act as a reasonable contributor to the lutein intake of young children who consume these products as a supplement to a normal diet when energy and nutrient intakes may not be adequate.

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

# COMMUNICATION AND CONSULTATION STRATEGY

## 14. Communication

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

## 15. Consultation

### 15.1 Public consultation

#### *15.1.1 Initial Assessment*

A joint Initial Assessment Report for both this Application and Application A594 was released for public comment from 4 April 2007 to 16 May 2007. FSANZ received ten submissions in response to the Initial Assessment Report.

Of the ten submissions received, nine provided comments specific to Application A597.

Overall, the majority of submitters (including four of the five government submitters) did not specify a preferred option, with several recommending that further assessment of safety and efficacy was required. Two submitters supported maintaining the *status quo* citing insufficient evidence and a need to demonstrate a health benefit to the target group. Three submitters supported permitting the addition of lutein to FSFYC. However, one submitter's support was contingent on a satisfactory safety assessment.

### *15.1.2 Draft Assessment*

The Draft Assessment Report for this Application was released for public comment from 21 December 2007 to 22 February 2008. FSANZ received 12 submissions in response to the Draft Assessment Report.

The majority of submitters, including all government submitters, supported maintaining the *status quo*. Key issues raised by submitters who opposed the addition of lutein to FSFYC included:

- both the benefit and safety of lutein should be demonstrated, especially for vulnerable populations such as young children and when a substance is added for a nutritional purpose;
- no evidence that lutein is a necessary component of a young child's diet and that dietary intakes of lutein in young children are inadequate;
- concern about the proposed level of addition;
- lack of confidence in the dietary modelling to provide an appropriate estimate of dietary intake;
- uncertainty about the long-term effect of a high lutein intake for young children;
- the minimum claimable amount should reflect purpose; and
- concern that claims about lutein would be permitted on lutein-fortified FSFYC.

Responses to key issues raised in submissions have been addressed in this Report as well as in Attachment 3 – Response to Key Issues Raised by Submitters at Draft Assessment.

## 15.2 World Trade Organization

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

There are relevant international standards that permit the addition of lutein to foods for infants and young children (e.g. the US FDA), and other overseas regulatory agencies are currently considering the approval of lutein in these products (e.g. the European Commission). It is expected that the recommended changes will harmonise Australian and New Zealand regulations with current and future international practices.

Therefore, amending the Code to permit the voluntary addition of lutein to FSFYC is unlikely to have a significant effect on trade. As such, WTO member nations were not notified of the proposed amendment to Standard 2.9.3 under either the Technical Barriers to Trade or Sanitary and Phytosanitary Agreements.

# CONCLUSION

## 16. Conclusion and Decision

### Decision

**To amend Standard 2.9.3 to permit the voluntary addition of lutein as a nutritive substance to formulated supplementary foods for young children up to a maximum concentration of 100 µg/serve (500 µg/L) with a minimum claimable amount of 30 µg/serve (150 µg/L) for labelling purposes.**

### 16.1 Reasons for Decision

FSANZ has undertaken an assessment using the best available evidence, and recommends amending the Code to permit the voluntary addition of lutein to FSFYC, as at Attachment 1 for the following reasons:

- Lutein added to FSFYC at a maximum concentration of 100 µg/serve (500 µg/L) is unlikely to pose any health and safety concerns for young children who consume these products.
- Lutein-fortified FSFYC have the potential to make a reasonable contribution to the lutein intake of young children who consume these products.
- FSFYC containing lutein provides an alternative dietary source of lutein for young children, who consume FSFYC as a supplement to a normal diet when energy and nutrient intakes may not be adequate.
- A minimum claimable amount of 30 µg/serve (150 µg/L) ensures at a minimum that one serving (approximately 200 mL) of a lutein-fortified FSFYC will provide about 10% of a young child's estimated mean daily lutein intake.
- This amount also exceeds the innate amounts of lutein found in the most common milk based FSFYC known as toddler formulas.
- Lutein performs a physiological function in the eye.
- Overall, permitting the addition of lutein to FSFYC provides a net benefit to all affected parties.

## 17. Implementation and Review

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

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## ATTACHMENTS

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

**Attachment 1**

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

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

**To commence: on gazettal**

**[1]** ***Standard 2.9.3*** *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 100 µg 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 30 µg per serving.

## Attachment 2

# Summary of Submissions to the Draft Assessment Report

FSANZ received 12 submissions in response to the Draft Assessment Report on Application A597 – Addition of Lutein to Formulated Supplementary Foods for Young Children, during the 9-week public consultation period of 21 December 2007 to 22 February 2008. A summary of submitter comments is provided in the table below.

Two regulatory options were presented in the Initial Assessment Report:

- Option 1 – Reject the Application thus maintaining the *status quo*; or
- 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 Formulated Supplementary Foods for Young Children (FSFYC) and to require a minimum declaration of 30 µg/serve when a nutrition claim is made.

| No. | Submitter | Submission Comments |
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| **Industry** | | |
| **1.** | **Chr Hansen Pty Ltd**<br>*Ron Cracknell* | **Supports Option 2**<br>Supports the Application, however, requests that Option 2 permit the voluntary addition of free lutein and/or lutein esters to FSFYC. |
| **2.** | **Nestlé Australia**<br>*Stephanie Rajczyk* | **Supports Option 1**<br>Does not support Option 2:<br>• insufficient peer-reviewed data relevant to the target population that substantiates the safety and efficacy of lutein from Tagetes erecta L. when added to FSFYC;<br>• inconsistent with international regulations; and<br>• insufficient evidence on lutein losses during processing and over the shelf-life of the product.<br>Comments provided in addition to comments made to the Initial Assessment Report for Applications A594 and A597.<br>***Safety***<br>Believes it is difficult to determine the risk for young children who consume FSFYC in the absence of published data.<br>Notes the Hazard Assessment was based on studies not directed at the target population.<br>***Efficacy and benefit***<br>Notes there are no peer-reviewed published studies on the benefits of formula or foods supplemented with lutein for young children.<br>Notes the uncertainty about the potential benefits of lutein in relation to eye health and later life effects of early lutein intake. |

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| | | Notes that available evidence is not based on the target population – young children.<br><br>Notes the absence of data related to bioavailability of lutein from *T. erecta L*. in the food matrix of powdered FSFYC formula.<br><br>Notes the possible antagonistic effects of other ingredients in the food matrix that may further limit the bioavailability of lutein have not been considered (e.g. fat levels).<br><br>Notes there is some evidence that demonstrates consumption of one carotenoid affects the absorption of another.<br><br>Notes there is limited knowledge on the effects of different carotenoids in the diet and added lutein from *T. erecta L.*<br><br>Notes that available evidence on bioavailability has not demonstrated equivalency between lutein added to formula compared to lutein in breast milk.<br><br>Considers Option 2 would be precedent setting, as it would permit lutein at amounts that may not generate beneficial effects similar to that of breast-fed infants.<br><br>***International regulations***<br><br>Disagrees that the addition of lutein to FSFYC is consistent with relevant international regulations as lutein is:<br><br>• not permitted for addition to FSFYC in the European Union; and<br><br>• not included in the Codex draft advisory list of nutrient compounds for use in foods for special dietary uses intended for infants and young children.<br><br>Notes the Codex criteria requires the 'presence in human milk and addition at levels comparable to human milk and generating beneficial effects similar to those observed in breast-fed infants and addition at levels generating those effects'.<br><br>***Stability of lutein***<br><br>Considers there is a lack of evidence that the lutein levels will remain between the proposed minimum and maximum at the time of consumption, and the subsequent impact on the potential benefit and safety of the substance.<br><br>Notes that degradation, and the linearity of those effects, under a worst-case temperature abuse scenario has not been demonstrated.<br><br>Considers there is incomplete data on processing losses – during manufacture/processing and preparation by the consumer.<br><br>Notes that overdosing to compensate for losses may exceed the proposed maximum level, which raises the issue of safety. |

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| **3.** | **Nutricia Australia Pty Ltd**<br>*Gregg Ward* | **Supports Option 1**<br>Supports maintaining the *status quo* until there is published evidence, relating to safety and benefit, to support the supplementation of lutein to the diets of children under three years of age.<br>***Safety***<br>Considers there is a lack of information from published studies evaluating growth and development with lutein supplementation, especially in the long term in this age group. If approved, young children may consume lutein at supplemented levels from the age of one until three years.<br>Is not aware of evidence to show if there are any side effects when long term supplementation with lutein in young children is ceased.<br>Considers evidence regarding the safety of exposure to daily lutein supplementation for greater than 12 months duration is limited.<br>Notes that lutein from *T. erecta L*. is not a usual food source of lutein.<br>Notes that in setting the JECFA specification for the lutein extract, data on infants and young children was not considered.<br>***Efficacy and benefit***<br>Notes there is no published data on the impact of lutein and zeaxanthin on visual development and function for infants and children under three years of age – no established health benefit(s).<br>Considers the statements that 'lutein has potential eye health benefits to young children' and 'there are potential later life effects of early lutein intake' are not supported by evidence.<br>Notes that optimal intakes of lutein have not been established (e.g. no NRV) and there is no evidence to indicate current lutein intakes from the diet are inadequate and pose a problem.<br>Considers there is insufficient evidence to support the need to introduce an additional source of lutein in the diet, which would become the major source of lutein in the diet of young children.<br>Is not aware of biochemical reference values for lutein and zeaxanthin for infants and young children, so there are no standards for measuring and interpreting the impact of lutein supplementation in infants and young children.<br>Recommends lutein from food sources rather than a supplement until there is sufficient evidence for the safety and benefit of lutein to infants and young children.<br>Does not agree that 'some of the richest food sources of lutein are often the least preferred foods of toddlers and young children' is a reason to permit the addition of lutein to FSFYC – the proposed fortification will not address the issue of developing healthy diet habits for life.<br>***Minimum claimable amount***<br>Does not support the establishment of a minimum claimable amount for lutein as: |

| No. | Submitter | Submission Comments |
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| | | • claiming may confuse consumers, as lutein content is not labelled on other foods or drinks that naturally contain lutein;<br>• FSFYC with lutein may be perceived by consumers as essential for children in order to obtain lutein; and<br>• marketing based on lutein content means promoting a substance where there is no scientific evidence for its supplementation, the dietary intake hasn't been shown to be inadequate, and the average consumer is unlikely to be aware of lutein.<br>Considers a minimum claimable amount would enable consumers to have some understanding that the FSFYC provided 10% of the average intake for a 1 year old.<br>Considers regulations about the type of claims that can be made is required, and any nutritional effect claims would need to be scientifically demonstrated.<br>Supports discussion on a case by case basis about minimum claimable amounts for future nutritive substances.<br>***References***<br>References provided to support some comments summarised above. |
| **4.** | **The Food Technology Association of Australia**<br>*David Gill* | **Partially supports Option 2**<br>Supports the voluntary addition of lutein to FSFYC within the proposed minimum and maximum levels, but not nutrition claims about lutein.<br>***Labelling and claims***<br>Does not support permission for nutrition claims about lutein, due to doubts about the efficacy of lutein and its bioavailability in FSFYC compared to other food sources. |
| **5.** | **Wyeth Australia Pty Ltd and Wyeth New Zealand Ltd**<br>*Yvonne Bowyer* | **Supports Option 2**<br>***Safety and efficacy/benefit***<br>The proposed addition of lutein to FSFYC protects public health and safety for the following reasons:<br>• The scientific information demonstrates no evidence of toxicity or adverse reactions at the levels proposed.<br>• The proposed maximum level of 500 µg/L is a conservative level for commercialisation and is below that of some foods commonly consumed by toddlers.<br>• The proposed maximum level of 500 µg/L is 10x lower than what is considered safe by the US FDA for similar foods.<br>• The combined lutein intake per day of a toddler would be 1076 µg, and in the worst case scenario 6% of the JECFA ADI (Wyeth Food Intake and Nutrition Status (FINS) Study). |

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| | | ***Level of addition***<br>The TGA permits the use of lutein, in unlimited quantities, in infant and children preparations.<br>Lutein is a permitted as a colour in the Code for use in a variety of foods that are commonly consumed by young children (e.g. flavoured milk, edible ices).<br>The proposed maximum level in FSFYC would not negatively impact on organoleptic properties of the product, including colour.<br>The proposed maximum level is a conservative level and is below that of some foods commonly consumed by toddlers.<br>At a maximum fortification level of 500 µg/L, a toddler would consume 300 µg/day (3x 200 mL serves), which is equivalent to 50 g green beans.<br>FSANZ dietary modelling showed that FSFYC would act as a viable contributor to the lutein intake and lutein status of children aged between 1-3 years.<br>***International Regulations***<br>There is increasing international regulatory recognition of lutein as a safe addition to food and formula, including:<br>• GRAS status for lutein in infant and toddler foods at 1 mg per eating occasion, granted by the US FDA.<br>• Codex Alimentarius – allows the addition of optional ingredients in order to provide substances ordinarily found in breast milk.<br>• The European Food Safety Authority's scientific review on lutein is ongoing.<br>• Lists a number of countries, including Mexico Philippines, China and Peru, where infant formula and toddler milk containing added lutein may be sold.<br>If the proposed fortification is not approved, this would prohibit free flow of lutein products that would otherwise be available worldwide and would potentially create a barrier to trade – Australia and New Zealand would not be harmonised with some international standards.<br>***Minimum claimable amount***<br>Agrees with the proposed minimum declaration for lutein in FSFYC of 30 µg/serve.<br>Prescribing a minimum declaration amount for lutein will permit a nutrition claim and thereby provide consumers with information to make informed choices.<br>Whether minimum claimable amounts should be established for other future nutritive substances is not relevant to this Application.<br>***Stability of lutein***<br>Wyeth undertakes preliminary stability testing of all ingredients in order to ensure the product stays within specification when in market. |

| No. | Submitter | Submission Comments |
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| | | Based on stability data, the fortification level of lutein in commercially produced formula includes an overage of 80% (i.e. 180% of label claim is added to offset stability losses).<br>***Labelling and claims***<br>Allowing a nutrition claim for lutein is important, to enable consumers to make informed choices.<br>In accordance with the Code, a nutrition claim about lutein would be permitted on the front of can, as well as being listed in the Nutrition Information Panel (NIP).<br>***Impact***<br>The approach taken for this Application supports product development, innovation and competition.<br>Wyeth is a global company and seeks consistency across its brand. Maintaining the status quo would create inconsistency among affiliates and across the brand. |
| **Public Health** | | |
| **6.** | **Dietitians Association of Australia**<br>*Annette Byron* | **Supports Option 2**<br>***Safety and efficacy/benefit***<br>Supports Option 2 as lutein is:<br>• not harmful in the amounts proposed;<br>• safe for use in small amounts in medicines in Australia;<br>• a normal constituent of the human diet;<br>• well-tolerated; and<br>• unlikely to exert adverse effects, within the wide range of consumption from natural sources.<br>Also, the range of products affected is small and the amount per serving size is small, therefore limiting the risk to young children.<br>Reservations about the small amount of evidence showing benefit for the addition to lutein to FSFYC.<br>***Minimum claimable amount***<br>Agrees that a minimum claimable amount should be established for lutein and for other future nutritive substances in FSFYC, noting the current and proposed regulations for nutrition and health claims.<br>***Claims and labelling***<br>Any claims made should be substantiated in the usual way.<br>***Consumption patterns***<br>Disagrees with the statement that 'some of the richest food sources of lutein are often the least preferred foods of toddlers and young children'. |

| No. | Submitter | Submission Comments |
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| | | Believes various foods rich in lutein are commonly consumed by young children, even if they do not consistently eat one food.<br><br>May set up false expectations for parents who may take food refusal on one occasion as permanent dislike, and therefore rely on a supplemental food for their child rather than continuing to offer a range of commonly available lutein-rich foods. |
| **Government** | | |
| **7.** | **Department of Health, South Australia**<br><br>*Elena Anear* | **Supports Option 1**<br><br>In the interest of protecting young children from exposure to substances that have no clear nutritional role and otherwise sources to varying levels from the diet, the Department takes a precautionary approach by opposing their addition to infant foods and follow-on formula.<br><br>***Efficacy and benefit***<br><br>The Draft Assessment Report does not provide sufficient evidence of assessment for nutritional purpose.<br><br>Limited evidence to show that lutein has a role in protecting eye health in young children.<br><br>The assessment of benefit is vital to the protection of public health and safety in a vulnerable population.<br><br>***Regulatory approach***<br><br>Concerned about the precedent that would be set by progressing this Application solely on the grounds that there is no safety concern.<br><br>The criteria for allowing substances to be added for a nutritional purpose should include substantiation of nutritional benefit.<br><br>***Claims and labelling***<br><br>Concerned about the proliferation and heavy marketing of so-called 'follow-on' formulae.<br><br>Foods regulated by Standards 2.9.2 and 2.9.3 should be ineligible to carry nutrition and health related claims. |
| **8.** | **Department of Health and Human Services, Tasmania**<br><br>*Jennifer Savenake* | **Supports Option 1**<br><br>***Efficacy and benefit***<br><br>If a substance is intentionally added to food to achieve a nutritional purposes, such as nutritive substances, the nutritional purpose should be demonstrated.<br><br>Currently insufficient evidence to establish an optimal intake or a minimum effective level for lutein for infants and young children.<br><br>Limited evidence for the effects of lutein on visual development and function of young children.<br><br>Need to understand the relationship between blood levels of lutein and macular levels of lutein. |

| No. | Submitter | Submission Comments |
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| | | The efficacy of adding lutein to FSFYC to achieve the nutritional purpose has not been demonstrated.<br>***Dietary modelling***<br>Food composition data, used in dietary modelling, is based on overseas concentration data.<br>While data across countries may be generally comparable, there may be omissions of generally consumed foods high in lutein.<br>Different farming and feeding practices may also have an impact.<br>Not confident that the dietary modelling provides an appropriate estimate for the risk assessment.<br>Intake data – no information available on the diet of one year olds and theoretical diet was constructed from two year olds from 1995 National Nutrition Survey data.<br>If food composition data is not available for substances with limited history of safe use and evidence of impact, the Applicant's should provide this data.<br>***Labelling and claims***<br>If approved, the minimum level should reflect the purpose – 10% of the level required to reasonably achieve the nutritional purpose, with evidence held by the manufacturer or importer.<br>***Additional information required***<br>Additional information required to consider this Application:<br>• Australian and New Zealand data on the range of lutein in a range of foods;<br>• Australian and New Zealand data on the dietary intake of lutein for young children;<br>• Australian and New Zealand data of blood lutein levels for young children; and<br>• Data on the nutritional benefits for young children of increased intake of lutein. |
| **9.** | **New South Wales Food Authority and New South Wales Health**<br>*Craig Sahlin* | **Supports Option 1**<br>Insufficient evidence in support of a nutritive benefit to the target population, where such evidence is essential due to the nature of the target population.<br>***Efficacy and benefit***<br>In the absence of Ministerial policy guidelines, the efficacy of adding substances to foods for infants and young children needs to be assessed.<br>Clinical data in support of a nutritive benefit of lutein for 1-3 year olds was not included in the Draft Assessment Report . |

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| | | No evidence provided to demonstrate that dietary intakes of lutein in children aged 1-3 years are inadequate and that lutein is a necessary component of a young child's diet – inconsistent with the definitions of formulated supplementary food and FSFYC.<br>***Additional information***<br>In the Final Assessment Report, requests evidence to suggest that:<br>• lutein is a necessary component of a young child's diet (i.e. define the nutritional purpose);<br>• a daily intake of lutein in required by young children;<br>• lutein intakes in the target population from normal diets are inadequate;<br>• a standard serve of the proposed product will address this inadequacy;<br>• the proposed form of lutein (ratio of lutein to zeaxanthin) is capable of providing similar health benefits to young children as dietary sources of lutein; and<br>• the level requested per serve is capable of providing 10% of the amount required to provide the proposed health benefit.<br>***Labelling and claims***<br>Does not support nutrient content claims on FSFYC, until evidence substantiating such claims is provided. |
| **10.** | **New Zealand Food Safety Authority**<br>*Carole Inkster* | **Supports Option 1**<br>***Regulatory approach***<br>Despite the absence of policy guidance, any substance classified as a 'nutritive substance' should be assessed for potential benefit.<br>The definition of 'nutritive substance' includes that the substance is 'intentionally added to achieve a nutritional purpose'.<br>If there is insufficient evidence to support the role of a substance in achieving this nutritional purpose, its addition as a nutritive substance should not be permitted.<br>***Efficacy and benefit***<br>Insufficient evidence to support the addition of lutein to FSFYC for the purpose of eye health – only 'postulated' and 'suggested' health benefits and no data specific to young children.<br>***Labelling and claims***<br>If a content claim is permitted, the minimum level for a claim should be based on the level required to achieve the nutritional purpose (minimum effective level).<br>Questions how realistic it is to assume that FSFYC will likely contain close to the maximum permitted level (100 µg/serve) if the claimable amount is only 30 µg/serve. |

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| | | Concerned that the minimum claimable amount 'reflects approximately 10% of the mean dietary intake of 1 year olds in Australia', as the mean intake was extrapolated from constructed theoretical diets.<br><br>In the absence of a reference value for lutein, are unable to ascertain whether 30 µg/serve is meaningful.<br><br>***Drafting***<br><br>The proposal to add section 6A Lutein to Standard 2.9.3 is confusing. If lutein in FSFYC is approved, suggests the addition of a fourth clause to section 6 of Standard 2.9.3. |
| **11.** | **Queensland Government**<br><br>*Tenille Fort* | **Supports Option 1**<br><br>Supports Option 1 due to the lack of convincing evidence to support the preferred approach.<br><br>***Regulatory approach***<br><br>Believes from a public health and safety perspective, that both safety and efficacy should be demonstrated for vulnerable populations such as infants and toddlers.<br><br>Believes they have a responsibility to ensure that any changes to foods for vulnerable population groups deliver a clear nutritional or health benefit and not simply a marketing advantage for industry.<br><br>Need to develop policy guidelines for special purpose foods for infants and young children.<br><br>Believes that a substance that is intentionally added to a food to achieve a nutritional purpose should be able to demonstrate that it can achieve that purpose.<br><br>***Efficacy and benefit***<br><br>Notes that the Draft Assessment Report did not include an analysis of the nutritional benefit proposed by the Applicant.<br><br>Limited evidence on the effects of lutein on visual development and function for young children.<br><br>Need to understand the relationship between blood levels of lutein and macular levels of lutein.<br><br>The efficacy of adding lutein to FSFYC to achieve the nutritional purpose has not been demonstrated.<br><br>Concerns about the statement 'some of the richest food sources of lutein are often the least preferred foods of toddlers and young children'. Considers this is inconsistent with the dietary guidelines which encourage children to eat plenty of vegetables, legumes, fruits and wholegrain cereals.<br><br>Notes there is no evidence to suggest that the diets of young children are deficient in lutein. |

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| | | ***International regulations***<br><br>Notes that Codex Alimentarius does not explicitly permit the addition of lutein to FSFYC, and that the EU only permits lutein as a colouring agent in FSFYC and not for any other purpose.<br><br>***Dietary modelling***<br><br>Notes the lutein content of foods in Australia and New Zealand will be different to the food composition data used, which was sourced from the USA.<br><br>Differences due to different food processing, agronomy and husbandry practices, some foods missing (e.g. silverbeet), and some foods that contain lutein were listed as containing zero amounts (e.g. cow's milk and other dairy products).<br><br>Nature of food composition data provided by the Applicant is unclear.<br><br>Appears to be incomplete information on the innate levels of lutein in FSFYC.<br><br>Concerned that the use of theoretical diets, out-of-date dietary intake data and use of overseas food composition data, may not provide an appropriate estimate of dietary intake.<br><br>***Level of addition***<br><br>Notes the dietary intake estimates for young children consuming FSFYC. Notes that without evidence of usual intake, it is not possible to say whether this level is nutritionally appropriate.<br><br>Believes the levels seem excessive when compared to those used in a study of older adults that found a positive association between dietary lutein and reduced macular degeneration (Tan *et al*, 2007).<br><br>Young children consuming FSFYC containing added lutein would be consuming higher levels than the adults in the above study despite being a fifth of their body weight.<br><br>***Labelling and claims***<br><br>Supports that a minimum claimable amount is set, as FSFYC are special purpose foods.<br><br>Supports the approach proposed under draft Standard 1.2.7 – a claim about lutein would require that a serve of the food contains at least 10% of the amount of the substance that is required to be consumed per day to achieve the specific health effect.<br><br>Believes that content claims imply a nutritional benefit and the minimum claimable amount should reflect this, though there are insufficient data to establish a minimum effective level in young children.<br><br>Therefore, considers it misleading for a content claim about lutein to be made or for a nutritional effect to be stated on the label, as there is insufficient evidence to support a relationship between lutein and eye health for young children.<br><br>Notes such claims are currently being made on the Wyeth international website. |

| No. | Submitter | Submission Comments |
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| | | Believes that a general level health claim linking lutein to eye health could not be substantiated under the proposed substantiation framework (Proposal P93 – Nutrition, Health and Related Claims).<br>***Additional information***<br>Considers the following information is required to consider this Application:<br>• data on the level of lutein in a range of foods in Australia and New Zealand;<br>• data on the dietary intake of lutein for young children in Australia and New Zealand; and<br>• data on the nutritional benefits for young children of increased intakes of lutein and what levels deliver these benefits. |
| **12.** | **Victorian Government**<br>*Victor Di Paola* | **Supports Option 1**<br>Considers that there should be a clear benefit for the addition of a new substance to foods for young children.<br>Also, the definition of 'formulated supplementary food' and the Applicant's reasons for addition lutein to toddler formula imply that there is an inadequate intake of lutein in certain children's diets and there are nutritional benefits for adding the substance. Believes the evidence for these contentions is insufficient.<br>***Regulatory approach***<br>Believes from a public health and safety perspective, that both safety and efficacy should be demonstrated for vulnerable populations such as toddlers and young children.<br>Believes they have a responsibility to ensure that any changes to foods for toddlers and young children deliver a clear benefit and not simply a marketing advantage for industry.<br>Urgent need for ministerial policy guidelines for special purpose foods for infants and young children.<br>***Efficacy and benefit***<br>Notes the definition of 'formulated supplementary food'.<br>Notes there is no known nutritional requirement for lutein, and no evidence that Australia and New Zealand children have an inadequate intake of lutein.<br>Notes there is no evidence that toddlers specifically have a low preference for lutein-containing foods.<br>Considers there is insufficient evidence to establish an adequate or optimal intake of lutein for young children.<br>Notes that the potential later life benefits of lutein have not been presented. |

| No. | Submitter | Submission Comments |
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| | | Potential eye benefits for young children are theoretical and based on studies done in test tubes and in animals, and dietary studies in older adults.<br><br>Believes that if an applicant requests to add a substance to toddler foods to achieve a nutritional purpose then they must be able to scientifically demonstrate this purpose can be met.<br><br>***Safety***<br><br>Notes that the action of supplemented nutrients cannot necessarily be predicted from dietary studies, and toxicity studies do not necessarily identify long-term risks.<br><br>Given that organ systems are still developing in toddlers, considers it imperative the addition caution is taken when adding a substance in supplemental form to their diet.<br><br>Notes that lutein also accumulates in ovaries, testes, liver, fat and skin, and there are no studies that show the effect of long-term high intake of supplemental lutein on these tissues.<br><br>***Level of addition***<br><br>Believes that if lutein is added to foods for young children for a purpose, then it should be added in levels that would reasonably achieve that purpose.<br><br>Notes that there is no evidence on the levels of lutein required to achieve adequacy or the proposed nutritional purpose.<br><br>Does not have confidence in the estimated consumption level of 300 µg/day, used to determine the minimum level, due to gaps in data, use of theoretical diets and use of overseas food composition data.<br><br>Notes the dietary intake estimates for young children consuming FSFYC. Notes that without evidence of usual intake, it is not possible to say what this level represents nutritionally.<br><br>Believes the levels seem excessive when compared to those used in a study of older adults that found a positive association between dietary lutein and reduced macular degeneration (Tan *et al*, 2007).<br><br>Young children consuming FSFYC containing added lutein would be consuming higher levels than the adults in the above study despite being a fifth of their body weight.<br><br>***References***<br><br>References provided to support some comments summarised above. |

## Attachment 3

# Response to Key Points Raised by Submitters at Draft Assessment

This Attachment provides responses to key points raised by submitters at Draft Assessment. A full summary of submitter comments to the Draft Assessment Report is at Attachment 2.

Some submitters commented that health benefit and efficacy of lutein for young children (aged 1-3 years) should be demonstrated and that there is currently insufficient evidence to do so. As discussed in Section 6 of the Final Assessment Report, the regulatory approach for assessing this Application does not require a benefit of the substance in the target population to be demonstrated.

| **Submitter issue** | **Response** |
|---|---|
| **Nutrition** | |
| *Food composition data:* | |
| Use of overseas data. | Currently, there are no published lutein data for foods available in Australia and New Zealand. While there may be differences in lutein levels between USA and Australian/New Zealand foods, lutein levels vary within foods in any case and the use of Australian/New Zealand data, if it existed, would be very unlikely to markedly change the conclusion from the dietary intake assessment. |
| Overseas data for pumpkin and silverbeet. | USA lutein and zeaxanthin concentration data were available for both pumpkin and silverbeet (also known as chard) and these data were incorporated into both the theoretical diet and DIAMOND dietary intake assessments. |
| Some foods that contain lutein contain zero amounts according to the USA data base used for the assessment (e.g. cow's milk). | In relation to the lutein content of cow's milk, a Finnish study found that lutein and zeaxanthin were one of the main carotenoid pigments in milk products, however they were only found in trace quantities (Ollilainen *et al*., 1989). A Dutch study found that the lutein content of pasteurized full fat milk was, on average, 1.0 µg/100 g and the zeaxanthin content was 0.1 µg/100 g (Hulshof *et al*., 2006). Using the lutein and zeaxanthin concentration (1.1 µg/100 g) from the Dutch study and the average consumption of milk for two to three year old children of 624 g per day from the 1995 Australian National Nutrition Survey (NNS), it would be expected that changing the lutein and zeaxanthin concentration for cow's milk would make little difference (approximately 7 µg/day or 1%) to the mean *Baseline* lutein and zeaxanthin dietary intakes estimated by FSANZ. |
| Use of data provided by the Applicant on the innate levels of lutein in FSFYC. | One submitter noted that a submission to Application A574 from another manufacturer of infant formula indicated variable levels of lutein in formulas and contended that this casts doubt on the completeness of the information provided by the Applicant in relation to the composition of FSFYC. |

| Submitter issue | Response |
|---|---|
| | There are no available data on the lutein concentrations in FSFYC currently sold in Australia and New Zealand.<br><br>The only food composition data sourced from the Applicant was that for the FSFYC. The Applicant indicated that innate sources would contribute approximately 20-30 µg/L of lutein to the total concentration of a FSFYC. This value is small compared to the proposed maximum concentration of 500 µg/L in fortified FSFYC. The level proposed by the Applicant relates to both naturally-occurring and added lutein. Under the fortification scenarios in the Dietary Intake Assessment (Attachment 5), and in the consideration of the lutein content of foods in the Nutrition Assessment (Attachment 4) naturally occurring lutein was not distinguished from added lutein.<br><br>The assumptions made in the Dietary Intake Assessment are listed under part 4 of Attachment 5. At baseline, the lutein and zeaxanthin concentration of FSFYC was assumed to be zero since the USDA report the lutein and zeaxanthin concentration in cow's milk as 0 µg/100 g (United States Department of Agriculture - Agricultural Research Service, 2008). |
| *Dietary intake data:*<br><br>Dietary intake of lutein by Australian and New Zealand children aged 1-3 years is required. | As there are no representative data on food intake in Australian children aged less than two years, and New Zealand children aged less than three years, dietary intakes were calculated using constructed theoretical diets for Australian children aged one year and New Zealand children aged one to three years.<br><br>Theoretical diets are routinely used internationally in the assessment of dietary exposures and intakes of infants. Theoretical/simulated diets have been used previously in the estimation of dietary intakes of substances such as pesticide residues and contaminants in Total Diet Studies such as the 20th Australian Total Diet Survey (Food Standards Australia New Zealand, 2002) and the New Zealand 2003/04 Total Diet Study (Vannoort and Thomson, 2005).<br><br>Although overseas food composition data was used in these theoretical diets, any differences in lutein levels between USA and Australian/New Zealand foods, if it existed, would be unlikely to markedly change the conclusion from the dietary intake assessment. |
| *Contribution of FSFYC to lutein intake:*<br><br>Comparison of estimated intakes between one to three year olds and older persons (Tan *et al*., 2008b), particularly given differences in body weight. | The paper by Tan *et al* (2008a) includes estimated intakes of lutein and zeaxanthin by Australian adults aged 49 years or older assessed using a semi-quantitative food frequency questionnaire and the United States Department of Agriculture Carotenoid Food Composition Database. |

| Submitter issue | Response |
|---|---|
| Concern that if approved, children 1-3 yrs consuming lutein at supplemented levels. | In this adult study population, the top tertile for dietary lutein and zeaxanthin intake was ≥942 µg/day and the median was 743 µg/day.<br><br>To provide an indication of the likely impact on lutein intakes among young children aged 1-3 years who consume FSFYC, two fortification scenarios have been used at the final assessment. The first considers a minimum concentration of 150 µg/L lutein in FSFYC (or 165 µg/L lutein and zeaxanthin) based on the prescribed minimum claimable amount of 30 µg/serve (see Section 22), and the second considers the maximum concentration requested by the Applicant of 500 µg/L lutein in FSFYC (or 550 µg/L lutein and zeaxanthin). These two levels represent the range of lutein concentrations that might added to FSFYC. Details are provided at Section 8.3 and Attachment 5.<br><br>Following the fortification of FSFYC with lutein and zeaxanthin at the proposed maximum level, the estimated mean intake of lutein and zeaxanthin is 618 µg/day and 936 µg/day in Australian children aged one year and 2-3 years respectively, and 835 µg/day in New Zealand 1-3 year olds (refer Table 2 and 3 of Attachment 5).<br><br>There is no New Zealand or Australian nutrient reference value against which to compare the estimated lutein intake of any population group. The proposed levels of lutein in one serve of fortified FSFYC compares with the level of lutein found naturally in one tablespoon of broccoli, two teaspoons of corn, or various other household measures of foods that can be expected to be consumed by children aged 1-3 years (refer Table 2 of Attachment 4).<br><br>The most relevant comparison to be drawn, in relation to the risk assessment questions that have been posed, is the comparison between estimated intakes of lutein and zeaxanthin for young children as a percentage of the ADI, which is expressed on a body weight basis. This is discussed below under the safety section and *long term effects of lutein intakes*.<br><br>The estimated mean intakes of lutein and zeaxanthin by children aged 1-3 years under the maximum fortification scenario as requested are presented in Tables 2 and 3 of Attachment 5. Table 2 of Attachment 4 provides comparisons of the amount of lutein in one serve of lutein-fortified FSFYC with the lutein content of various foods expected to be consumed by this age group.<br><br>At the requested concentration of lutein in FSFYC could potentially become a major contributor (≥ 5%) to the intake of lutein by young children who consume these foods – 15-38% of their daily lutein intake. |

| Submitter issue | Response |
|---|---|
| *Dietary intake estimates:*<br><br>Confidence in the dietary modelling given the use of:<br>- theoretical diets;<br>- out-of-date dietary intake data; and<br>- overseas food composition data. | The Applicant provided some dietary intake estimates as part of the Application (see Section 2 of Attachment 5). FSANZ considered it necessary to conduct its own estimates for both the Australian and New Zealand populations aged 1-3 years.<br><br>The assumptions made in FSANZ dietary intake assessment are listed under Section 4 of Attachment 5. The limitations of the dietary modelling are discussed under Section 5 of Attachment 5.<br><br>See also responses for *dietary intake data* and *food composition data*. |
| *Bioavailability:*<br><br>Bioavailability of lutein from *T. erecta L.* in FSFYC, and potential antagonistic effects of other ingredients (e.g. fat levels). | Discussion of the available data is presented in Section 8.2 of the Report and Section 4 of Attachment 4. |
| *Dietary needs:*<br><br>No evidence that lutein is a necessary component of a young child's diet? | Lutein is not covered by the *Nutrient Reference Values for Australia and New Zealand*[17] or other dietary recommendations. A range of foods that contain lutein in their natural form are consumed by children aged one-three years. This is illustrated in the data presented in Table 1 and Table 2 of Attachment 4. |
| Need evidence to demonstrate a standard serve of the proposed FSFYC with added lutein will address dietary needs. | As the purpose of FSFYC is as a supplement to a normal diet for young children when energy and nutrient intakes may not be adequate, the approach taken in this assessment considers whether lutein-containing FSFYC can make a reasonable contribution to the lutein intake of young children. Lutein-fortified FSFYC would provide an alternative dietary source of lutein for young children and have the potential to be a major ($\geq$ 5%) contributor to the lutein intake of young children who consume these products, as a supplement to a normal diet when energy and nutrient intakes may not be adequate. |
| No evidence to indicate current dietary intake of lutein by young children is inadequate? | Humans cannot synthesize lutein and therefore can only obtain lutein from dietary sources. As lutein is not covered by the *Nutrient Reference Values for Australia and New Zealand,* there is no reference value against which to compare estimated intakes of any population. Therefore it is not possible to currently make a judgement as to the adequacy or inadequacy of the estimates of current intakes of lutein by any population group, regardless of the various existing sources or potential sources of lutein in their diet. |

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

| Submitter issue | Response |
|---|---|
| *Consumption of lutein-rich foods by young children:* | Some submitters disagreed with the Applicant's contention that 'some of the richest sources of lutein are often the least preferred foods of toddlers and young children'. Submitter comments included that there is no evidence to support this claim, this should not be used as a reason to justify the proposed fortification, and various lutein-rich foods are consumed by young children even if they do not consistently eat one food.<br><br>The Applicant made this statement in their Application based on findings from studies conducted overseas among children aged 2 years and above.<br><br>This contention has not been used as rationale for the decision to permit the voluntary addition of lutein to FSFYC. |
| **Safety** | |
| *Level of evidence:*<br><br>It was suggested that there is insufficient peer reviewed or published evidence relevant to the target population to substantiate the safety of lutein from *Tagetes erecta L* when added to FSFYC. | Applications to amend the Code must be supported by the provision of an adequate and robust data package which is frequently a combination of published journal articles and unpublished studies. While there is a perception that a peer-reviewed article in a scientific journal has greater authority for a safety assessment, this must be balanced against some of the limitations due to the level of detail reported and publication bias. Efforts to minimise journal publication costs through limiting the article size, has the inevitable consequence of data being presented almost exclusively in summary or minimal form. Therefore, many of the important technical details or supporting observations are not included so that the 'pathway' to the conclusions is not always transparent. In some instances it is the paucity of important technical detail which prevents validation of the conclusions.<br><br>The peer review process which selects the articles appropriate for publication is usually based on whether the material is worthy of dissemination to other scientists to describe significant advances e.g. in the understanding of a biological process, propose, test or refute hypotheses, or describe potentially useful new test methods or materials. These articles also provide a very valuable forum for the discussion of the findings in relation to other publications. Consequently, investigations such as safety studies, which may reveal no adverse findings, are frequently not submitted for publication because they fail to meet the selection criteria for publication.<br><br>Unpublished studies submitted by applicants are frequently performed by contract laboratories and are normally performed to reporting standards determined by Good Laboratory Practice (GLP) and Quality Assurance and are complete with individual data, summaries and statistical analysis performed by experts in the fields of toxicology, histopathology and animal science. |

| Submitter issue | Response |
|---|---|
| | A major benefit of GLP is to establish minimum standards of documentation, but the extent of documentation that is specified by GLP standards is too voluminous to be included in published studies. The limitation of these unpublished studies can be that the results are usually discussed only within the context of that particular study and not refer to other companion studies. The nature of these studies also sometimes necessitates that they are evaluated as confidential commercial material but this does not devalue the quality of the data.<br><br>Therefore, in undertaking a risk assessment FSANZ evaluators consider all available data in their various forms. The strength or weighting of individual studies depends on whether the evaluator has access to all the data or only an abridged summary from which to make an independent evaluation and interpretation.<br><br>The same issues exist for the evaluation of drugs for human or veterinary use or the use of agricultural chemicals in Australia, Europe, North America and Japan.<br><br>Overall, the use of both published and unpublished studies have perceived limitations and benefits but all such studies are essential in establishing standards to protect public health. FSANZ needs to be able to consider the scientific merit of all available data in order to base its decisions on the best available evidence.<br><br>In relation to this issue, the Applicant stated that: *Wyeth Nutrition is a division of Wyeth Pharmaceutical. Consistent with Wyeth standards as global pharmaceutical company all Nutrition manufacturing and clinical studies are conducted to the same high standard and quality as applied to Wyeth drugs and vaccines. Specifically all manufacturing is conducted consistent with Good Manufacturing Practices (GMP), all clinical studies are conducted according to International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines and all analysis of clinical samples is conducted in validated assay according to Good Laboratory Guidelines (GLP).* |
| *Long term effects of lutein intake:*<br><br>It was suggested that not enough is known about the long-term effects of high intake of supplemental lutein on growth and development or its accumulation in the ovaries, testes, liver, fat and skin. | The Acceptable Daily Intake (ADI) is an estimate of the amount of a substance in food, expressed on a body weight basis (usually mg/kg body weight per day), which can be ingested daily over a lifetime, from 12 weeks of age onwards, without appreciable health risk. The potential long term effects of a substance are considered in this evaluation. The ADI includes a 100-fold safety factor. |

| Submitter issue | Response |
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| | FSANZ has estimated dietary intakes of lutein by young children from both natural sources and supplemented FSFYC (at a maximum concentration of 500 µg/L) to be well below the ADI, with the highest estimated dietary lutein and zeaxanthin intake (the 95$^{th}$ percentile intake for New Zealand children aged one to three years) representing only 11% of the ADI and the mean intake just 3-4% of the ADI (see Tables 4 and 5 of Attachment 6 for more detail). Therefore, FSANZ concludes that the risks to young children from consuming FSFYC containing lutein derived from marigold flowers at a maximum concentration of 500 µg/L is very low. |
| *Lack of studies in the target population:*<br><br>It was suggested that the hazard assessment was based on animal studies or on studies in human adults rather than studies directly on the target population (human infants and young children).<br><br>There was concern that there is a lack of studies evaluating growth and development with lutein supplementation. | The scientific evidence on the safety of lutein was evaluated by the Joint FAO/WHO Expert Committee on Food Additives and Contaminants in 2004, in order to establish the ADI. In establishing an ADI, evidence from a range of different studies in different animal species was evaluated. It was considered that the available evidence was sufficient to establish an ADI. It is standard procedure to use appropriate animal studies, including studies such as developmental studies in animals, in order to establish an ADI.<br><br>The ADI includes a 100-fold safety factor, which is considered to be sufficient to take into account differences between animals and humans, and differences between average and sensitive humans. Because the ADI is expressed on a body weight basis, it can be used for young children.<br><br>Growth and development were considered in establishing the ADI for lutein: even at the highest doses tested and over the longest duration studied, no adverse effects were seen.<br><br>Further information on the studies evaluated is at Attachment 6 (Hazard Assessment). |
| *Supplemented nutrients:*<br><br>The action of supplemented nutrients cannot necessarily be predicted from dietary studies. | A submitter presented examples (e.g. beta-carotene and lung cancer) to illustrate that a nutrient administered in supplement form can increase the risk of adverse health outcomes, though the same nutrient consumed in food form may be associated with positive health benefits.<br><br>The proposed maximum level of lutein fortification in FSFYC (500 µg/L) is not high. The requested concentration of lutein in FSFYC has the potential to be a major (≥ 5%) contributor to the intake of lutein by young children who consume these foods – 15-38% of their daily lutein intake. Table 1 in the main body of the report provides comparisons of the estimated lutein intake in fortified FSFYC with estimated intake from various natural sources. |

| Submitter issue | Response |
|---|---|
| | It is the dose of the nutrient consumed (estimated intake) rather than the form in which the nutrient is consumed that is considered relevant to this assessment. |
| **Labelling and claims** | |
| *Nutrition and health claims:* | Some submitters considered that all foods regulated by Standard 2.9.3 should be ineligible to carry nutrition and health related claims. Others considered claims for lutein on FSFYC should not be permitted as there is insufficient evidence to establish a minimum effective level and to support a benefit. If permitted, any claims should be scientifically substantiated.<br><br>These issues are addressed in Section 11.3.3 of the Report. |
| *Minimum claimable amount:* | Submitters generally supported prescribing a minimum claimable amount for lutein. However, some submitters considered the minimum level should reflect the purpose (e.g. 10% of the level required to reasonably achieve the nutritional purpose or the minimum effective level). Some submitters were unclear whether a minimum level of 30 µg/serve is meaningful, in the absence of a reference value for lutein.<br><br>These issues are addressed in Section 11.3.2 of the Report. |
| **Food technology** | |
| *Form of lutein:* | The proposed permission should be extended to include lutein esters, rather than free lutein alone.<br><br>The Applicant, has confirmed that their request relates to free lutein only, not lutein esters. Hence the scope of this Application, and any subsequent permission, relates to free lutein.<br><br>In addition, the current specification for lutein which the Code references (JECFA), referred to as the Compendium of Food Additive Specifications in clause 2 of Standard 1.3.4 – Identity and Purity) refers to free lutein and not lutein esters.<br>The Applicant's lutein complies with this primary reference for specifications so no new specification is required to be written. |
| *Stability of lutein:* | It was submitted that there is insufficient evidence on lutein losses during processing and over the shelf-life of the product. The Applicant noted that the fortification level of lutein in commercially produced formula includes an overage of 80%, to offset stability losses.<br><br>The Applicant has provided a number of stability trials related to elucidating the stability of lutein in FSFYC.<br><br>The summary and conclusions of these trials are provided in the Food Technology Report at Attachment 7 as well as in the summary provided in Section 10 of the Report. |

| Submitter issue | Response |
|---|---|
| **Regulatory approach** | |
| *Assessment of benefit:* | Some submitters considered that from a public health perspective, both benefit and safety should be demonstrated for vulnerable populations such as young children.<br><br>• As discussed in Section 6 of the Report, in the absence of Ministerial policy guidance, the approach to the assessment of this Application has primarily focussed on the safety of lutein. Whether lutein-fortified FSFYC would provide an alternative source of lutein and could make a reasonable contribution to the lutein intakes of young children, compared to foods that naturally contain lutein has also been assessed.<br><br>In addition, the potential for there to be a health benefit for young children who consume FSFYC with added lutein has also been examined. See Section 8.1.5 of the Report. |
| *Intent of FSFYC:* | Some submitters contended that if a substance is added for a nutritional purpose, noting the definitions of 'nutritive substance' and 'formulated supplementary food', then the nutritional benefit of that substance should be demonstrated.<br><br>As acknowledged in Section 1.4 of the main report, lutein is considered a nutritive substance in part because of its specific antioxidant properties and its proposed function in the eye as an antioxidant and blue light filter. Section 8.1.4 outlines the functions of lutein noting that at this stage, although there is established biological plausibility for lutein to provide a benefit to long-term eye health, there is insufficient evidence to make such a conclusion with any certainty.<br><br>However, consistent with the intent of FSFYC, the assessment has shown that lutein-fortified FSFYC (at the requested concentration of 500 µg/L) could potentially be a major (≥ 5%) contributor to lutein intakes of young children who consume these products as a supplement to their normal diet when energy and nutrient intakes may not be adequate. |
| **International regulations** | |
| *Consistency with international regulations:* | Some submitters considered that a permission to add lutein to FSFYC is inconsistent with international regulations, particularly Codex and the European Union regulations. However, the Applicant considered that if not approved, it would potentially create a barrier to trade as this approach would be inconsistent with some international standards.<br><br>International regulations relating to the addition of lutein to foods for young children are outlined in Section 3.2 of the Report. Codex guidelines neither expressly permit or prohibit the addition of lutein to these foods. |

| Submitter issue | Response |
|---|---|
| | Also, the proposed maximum concentration of 500 µg/L is one tenth of the level granted GRAS status by the US FDA (1 mg per serve) and is similar to the level permitted in products sold in China. |

## References:


Food Standards Australia New Zealand (2002) *The 20th Australian Total Diet Survey*.

Hulshof, P.J.M., van Roekel-Jansen, T., van de Bovenkamp, P. and West, C. (2006) Variation in retinol and carotenoid content of milk and milk products in The Netherlands. *Journal of Food Composition and Analysis* 19(1):67-75.

Ollilainen, V., Heinonen, M., Linkola, E., Varo, P. and Koivistoinen, P. (1989) Carotenoids and retinoids in Finnish foods: dairy products and eggs. *J Dairy Sci* 72(9):2257-2265.

Tan, J.S., Wang, J.J., Flood, V., Rochtchina, E., Smith, W. and Mitchell, P. (2008a) Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology* 115(2):334-341.

Tan, J.S., Wang, J.J., Flood, V., Rochtchina, E., Smith, W. and Mitchell, P. (2008b) Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology* 115(2):334-341.

United States Department of Agriculture - Agricultural Research Service (2008) *USDA National Nutrient Database for Standard Reference SR20*.

Vannoort, R.W. and Thomson, B.M. (2005) *2003/04 New Zealand Total Diet Survey*. New Zealand Food Safety Authority, Wellington. www.nzfsa.govt.nz.

**Attachment 4**

# Nutrition Assessment

## Summary

The Applicant has requested the addition of lutein to formulated supplementary foods for young children (FSFYC) to a maximum natural plus added lutein concentration of 500 µg/L. At this level of addition, FSFYC would provide no more than 100 µg of lutein (110 µg of lutein and zeaxanthin combined) in a recommended serving of 200 mL. The addition would place these formulated foods 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, the amount of lutein and zeaxanthin obtained from that serve of FSFYC would be comparable to eating ¼ teaspoon of spinach or three green peas or two teaspoons of corn. It would also compare to eating ½ of one large egg or drinking 1/3 of a cup of orange juice.

Lutein and its isomer zeaxanthin are referred to as xanthophyll carotenoids[18]. They can only be obtained from dietary sources and the body does not convert them to vitamin A. Lutein is not covered by the *Nutrient Reference Values for Australia and New Zealand*[19] or other dietary recommendations.

Dietary lutein and zeaxanthin are absorbed and subsequently accumulate in the retina at the back of the eyeball, concentrated particularly in the macula lutea or 'yellow spot'; where the evidence indicates they protect against oxidative damage to the eye. Other functions of lutein in the eye are suggested by published observations, but are less conclusive. Lutein also acts as a general non-eye specific antioxidant.

Although there is established biological plausibility for lutein to promote eye health, there is insufficient evidence to make firm conclusions in relation to any additional long-term benefit to eye health for infants from consuming lutein, including FSFYC containing added lutein.

Lutein derived from marigold (*Tagetes erecta*) in infant formula or a supplement is bioavailable. Lutein from supplements appears more bioavailable than that in yellow carrots, similarly bioavailable to that in spinach, and less bioavailable than that from eggs.

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 gut seems likely to have an effect on the bioavailability of lutein.

There are variable results from investigations of potential interactions between lutein and other carotenoids in the gut. 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 infant formula.

[18] In this report, for brevity lutein is often mentioned alone. It should be understood that lutein and zeaxanthin occur together in nature and in the form that is proposed to be added to FSFYC.
[19] This document is available online at http://www.nhmrc.gov.au/publications/synopses/n35syn.htm.

The available evidence indicates that the addition of lutein to FSFYC will provide a bioavailable source of lutein. The proposed concentration of lutein per serving of FSFYC approximates the level of lutein available from natural food sources with a moderate lutein content. It is considered that for children aged 1-3 years who consume these formulated foods, FSFYC would be able to act as a reasonable contributor to their lutein intake.

# 1. Introduction

Published material relating to the nutritional characteristics of lutein is predominantly based on consideration of adult populations. Data on adults or older children have been considered in this assessment, as these age groups consume a varied diet similar to children aged 1-3 years. Data on infants have 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 general foods and in FSFYC
- the function of lutein in the body
- the bioavailability of natural, supplemental and added forms of lutein.

# 2. Concentration of lutein and zeaxanthin in general foods and in FSFYC

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*., 2004b). 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, 2008) 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 (foods likely to be eaten by one to three year old children) are presented in Table 1, with a description of the form of food chosen. The USDA data set contains compositional data for food items in various forms (e.g. raw, cooked by different methods, frozen, canned etc). The lutein and zeaxanthin content of food varies between different forms of the same food. The data shows that vegetables, especially green leafy vegetables, have the greatest lutein and zeaxanthin contents.

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 | 18,246 |
| **Spinach,** cooked, boiled, drained, without salt | 11,308 |
| **Peas,** green, frozen, cooked, boiled, drained, without salt | 2,400 |
| **Lettuce, cos or romaine,** raw | 2,313 |
| **Broccoli,** raw | 1,403 |
| **Brussels Sprouts,** cooked, boiled, drained, without salt | 1,290 |
| **Breakfast Cereal,** (average of several) | 977 |
| **Corn,** sweet, yellow, canned, cream style, no salt added | 949 |
| **Carrots,** cooked, boiled, drained, without salt | 687 |
| **Beans,** green, frozen, cooked, boiled, drained, without salt | 564 |
| **Egg,** whole, cooked, hard boiled | 354 |
| **Egg,** whole, raw, fresh | 331 |
| **Celery,** raw | 283 |
| **Wheat flour,** wholegrain | 220 |
| **Nectarines,** raw | 130 |
| **Oranges,** raw | 129 |
| **Tomatoes,** red, ripe, raw | 123 |
| **Orange juice** | 115 |
| **Peaches,** raw | 91 |
| **Bread,** wheat | 48 |
| **Pears,** canned in juice | 34 |
| **Cucumber**, with peel | 23 |

Source: (United States Department of Agriculture 2008)

The variable concentration of lutein in foods is also illustrated in Table 2. Table 2 allows comparisons of the lutein content of foods presented in household serve sizes with the proposed lutein content of FSFYC. These estimates of household measures are approximate, as solid food in chopped, diced shredded or other forms does not neatly fill a level household measure. The serve sizes expressed in grams in the third column of Table 2 are more accurate estimates of the foods' lutein and zeaxanthin content.

Brightly coloured plant foods tend to be the highest natural sources of lutein. For example, 1 tablespoon of shredded green cos lettuce provides roughly the same amount of lutein as 6 tablespoons of the less brightly coloured lettuce variety known as iceberg or crisp head lettuce.

The Applicant has stated that FSFYC will contain a maximum of 500 µg/L of added and natural lutein, which would provide no more than 100 µg of lutein (110 µg of lutein and zeaxanthin combined) in a recommended serving of 200 mL. The following table compares the serve sizes of various foods that would provide the same amount of lutein and zeaxanthin as one 200 mL serve of FSFYC with added lutein and zeaxanthin. For example, the same amount of lutein and zeaxanthin that is proposed to be contained in one serve of FSFYC could be obtained from eating ¼ teaspoon of spinach or one teaspoon of green peas, or from drinking 1/3 cup of orange juice (refer column 4 of Table 2).

**Table 2: Comparison of the lutein and zeaxanthin concentrations in selected foods with the maximum concentration of lutein and zeaxanthin in FSFYC as proposed by the Applicant**

| Food item | Lutein[1] (µg/100g) | Serve size (grams) which provides equivalent amount of lutein & zeaxanthin to 1 serve of FSFYC | Approximate estimate of household measure which provides equivalent amount of lutein & zeaxanthin to 1 serve of FSFYC [3] |
|---|---|---|---|
| **FSFYC** [2] | NA | 200 mL | 4/5 cup |
| **Kale** | 18,246 | 0.5 | 1/6 teaspoon |
| **Spinach** | 11,308 | 0.9 | ¼ teaspoon |
| **Green Peas** | 2,400 | 4 | 1 teaspoon or 3 peas |
| **Lettuce, cos or romaine** | 2,313 | 4 | ½ of one inner leaf or 1 tablespoon shredded |
| **Broccoli** | 1,403 | 7 | 1 tablespoon |
| **Brussels Sprouts** | 1,290 | 8 | 1/3 of one sprout |
| **Breakfast cereal** | 977 | 10 | 1/3 cup |
| **Corn** | 949 | 11 | 2 teaspoons |
| **Carrots** | 687 | 14 | 1 tablespoon of slices |
| **Beans** | 564 | 18 | 1 ½ tablespoons |
| **Egg, cooked** | 354 | 28 | ½ large egg or 1/5 cup chopped egg |
| **Celery** | 283 | 35 | 2 small stalks or 1/3 cup chopped celery |
| **Lettuce, iceberg** | 277 | 36 | 2 and ½ large leaves or 6 tablespoons shredded |
| **Nectarines** | 130 | 77 | ½ medium nectarine or ½ cup slices |
| **Oranges** | 129 | 78 | ¾ of one small orange or 2/5 cup of orange sections |
| **Tomatoes** | 123 | 81 | 3 thick slices or ½ cup of cherry tomatoes |
| **Orange juice** | 115 | 87 | 1/3 cup |
| **Peaches** | 91 | 110 | ¾ cup slices |
| **Bread** | 48 | 208 | 6-7 slices (25-30g per slice) |
| **Pears** | 34 | 294 | 1 and 1/5 cup of pear halves |
| **Cucumber** | 23 | 435 | 4 and 1/5 cup of slices |

Source: (United States Department of Agriculture 2008)

[1] These data are for total xanthophyll carotenoids i.e. lutein plus zeaxanthin combined. Food composition tables usually do not provide separate values for lutein and its isomer zeaxanthin. The column heading is chosen to simplify the presentation of data only.

[2] With added lutein from *T. erecta L,* to provide a maximum concentration of 500 µg/L when reconstituted as directed.

[3] One level metric cup = 250 mL. One level metric tablespoon = 20 mL. One level metric teaspoon = 5 mL.

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 a FSFYC, which is equal to 4-6 μg per serving of FSFYC. As this value is small, the innate source and proposed added source of lutein in FSFYC are not considered separately in this assessment.

# 3. Function of lutein in the body

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

## 3.1 Non vitamin A carotenoids

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.

Lutein and zeaxanthin contain oxygen and are referred to as xanthophyll carotenoids. 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*[20] or other dietary recommendations.

## 3.2 Physiological functions of lutein

The presence of lutein and zeaxanthin has been detected in many tissues, but they are particularly prevalent in the eye where their respective concentrations can exceed those in serum by up to several thousand-fold (Handelman *et al.*, 1988; Schmitz *et al*., 1993). They are the only carotenoids present in the lens (Yeum *et al.*, 1995), where they, along with *meso*-zeaxanthin, a non-dietary carotenoid thought to derive from lutein, comprise the 'macular pigment' (Beatty *et al.*, 1999; Bone *et al.*, 1997; Landrum and Bone 2001). Their presence in the lens gives it its characteristic yellow color (Bernstein *et al*., 2001; Bone *et al*., 1988; Rapp *et al*., 2000).

Other carotenoids have not been found to be concentrated in tissue this way, suggesting that lutein and zeaxanthin are unique in this respect (Alves-Rodrigues and Shao, 2004). Further, lutein and zeaxanthin levels in the eye are preferentially preserved over serum concentration following a decreased intake (Johnson *et al*., 2000; Zeimer *et al.*, 2009). It is therefore clear that there is a strong biological drive to ensure the presence of lutein and zeaxanthin in the eye.

The possible roles of lutein and zeaxanthin in the eye include: protection of eye tissue from oxidation; a direct optical role such acting as a blue light filter; and a role in influencing the development of the eye early in life (Hammond 2008).

The human eye is naturally exposed to considerable oxidative stress through light, with particular sensitivity to blue light (Snodderly, 1995).

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

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.

Lutein has been shown to act as a filter of blue light in the eye (Junghans *et al*., 2001). Lutein and zeaxanthin have also been shown to act as antioxidants in the eye (Kim *et al*., 2006), and, much like other carotenoids, more generally in the body (Lim *et* al., 1992; Tomey *et al.*, 2007; Trevithick-Sutton *et al*., 2006, Zhang *et al*., 1991).

Further, rhesus monkeys, a broadly accepted animal model of primate eye physiology, fed lutein free diets had no detectable macular pigment (Neuringer *et al*., 2004), and a dip in the density profile of retinal pigment epithelium cell density at the foveal centre where there would normally be a peak (Leung *et al*., 2004). This indicates an integral role of lutein and zeaxanthin in the structural development of the eye. However, a diet devoid of lutein and zeaxanthin is highly unlikely in young children, and this research does not indicate at what intake these structural changes would be prevented.

The published data clearly show that lutein and zeaxanthin are functional components of the eye; no other carotenoid has been shown to be able to take their place. Further, increased intakes of lutein, either from food or supplement use, have been shown to increase the density of the macular pigment in some but not all individuals (Aleman *et al.*, 2007, Berenschot *et al.*, 2000; Bone *et al.*, 2007; Hammond *et al.*, 1997; Nolan *et al.*, 2007, Zeimer *et al.*, 2009).

### 3.3 Long-term health benefit of lutein consumption in young children

The ability of increased lutein intake to increase macular pigment density; observations that higher intakes of lutein are sometimes associated with lower risk of age-related macular degeneration; and the ability of lutein to reduce oxidative stress in the eye have led to speculation that increasing lutein intakes may reduce the risk of conditions such as age-related macular degeneration (Alves-Rodrigues and Shao, 2004; Beatty *et al.*, 1999; Snodderly, 1995).

As age-related macular degeneration is generally experienced late in life, corroborating a preventative role of dietary lutein in early childhood with any certainty would require a large group to be followed up for many decades. Even then it would not be possible to differentiate the benefit of intakes early in life with those from intakes in subsequent life stages.

In the absence of longitudinal data with follow-up starting in early childhood, results from studies in adults constitute the best available evidence. A recent systematic review and meta-analysis examining the role of lutein, among other antioxidants, in the primary prevention of age-related macular degeneration reported that *high antioxidant levels in the healthy retina did little to prevent the development of early AMD* [age-related macular degeneration] (Chong *et al.*, 2007). As none of the studies included young children, they could not investigate the question of possible benefit from lutein consumption early in life. Therefore, the negative finding in adults does not rule out the possibility of benefit over a longer period.

Studies of secondary prevention are not relevant to this assessment, as young children do not suffer from age-related macular degeneration.

At this stage, although there is established biological plausibility for lutein to provide a benefit to long-term eye health, there is insufficient evidence to make such a conclusion with any certainty.

# 4. Relative bioavailability of added forms of lutein

## 4.1 Assessment of available studies

The bioavailability of lutein has been assessed by measuring changes in concentration of lutein in blood. Three unpublished studies provided by Wyeth comparing the bioavailability of lutein in breast milk with that in infant formula clearly demonstrate lutein from the proposed source, *T. erecta*, added to infant formula increase blood lutein concentrations in infants (Wyeth, 2006a; Wyeth, 2006b; Wyeth, 2007). The studies did not compare the bioavailability of lutein in formula with that of foods such as young children are likely to be consuming. Further, in response to the first review request for Application A594 – Addition of Lutein as Nutritive Substance Infant Formula Products, FSANZ requested additional information from Wyeth about these studies including further information on sample handling and preparation, and analysis. Several aspects of the Wyeth studies indicated their results were not likely to be accurate enough to establish the quantitative bioavailability of lutein in breast milk relative to lutein in infant formula with confidence. Despite some deficiencies, the studies do confirm that lutein from *T. erecta* is qualitatively bioavailable in an infant formula like matrix. The comparison of quantitative bioavailability between breast milk and infant formula is not a pivotal issue in this assessment as FSFYC is not intended as a substitute for breast milk.

Using a randomised crossover design, nine healthy young adults received 1.7 mg lutein/day from eating foods made with yellow carrots or from a lutein supplement[21] (Molldrem *et al*., 2004). Over a 14-day period, participants consumed their allocated treatment disguised in dyed muffins, smoothies and soup for seven days followed by seven 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 yellow carrots | 1.36 (0.53) | P < 0.004 |
| | | 1.7 mg in oil (supplied by Kemin) added to foods made using cooked white carrots | 2.09 (0.58) | |

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

[21] The supplement was obtained from Kemin Industries, who derive lutein from the marigold *Tagetes erecta*. The supplement was therefore from the same source of lutein as is being considered for addition to FSFYC.

In a crossover study, 10 healthy men received for nine days a lutein supplement[24], lutein-enriched eggs, or spinach, each providing 6 mg lutein; blood samples were taken intermittently over the treatment periods (Chung *et al.*, 2004). 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 derived from marigold (*T. erecta*) in infant formula or a supplement is bioavailable. Lutein from supplements appears more bioavailable than that in yellow carrots, similarly bioavailable to that in spinach, and less bioavailable than that from eggs.

## 4.2 Interaction of lutein and zeaxanthin with other carotenoids

There are variable results from investigations of potential interactions between lutein and other carotenoids during digestion and absorption. There are some studies in which significant interactions were observed (Micozzi *et al*., 1992; Kostic *et al*., 1995; Van den Berg and Van Vliet, 1998). There is also a study which showed that serum lutein levels were not significantly different ($p<0.05$) after consuming spinach (lutein source) compared with spinach and tomato (concurrent intake of lutein and lycopene) (Riso *et al*., 2004). These studies are summarised briefly below.

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).

Kostic *et al.* (1995) investigated the effects on serum lutein following single oral doses of lutein and/or β-carotene in eight adults. 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 concluded that 'carotenoids clearly interact with each other during intestinal absorption, metabolism and serum clearance, although individual responses can differ markedly'. It should be noted that supraphysiological amounts of lutein and β-carotene were used in this study. The dose used was 0.5 μmol/kg body weight; equivalent to a range of lutein supplementation of 15,000 to 26,000 μg/day dependent upon the participant's body weight.

Van den Berg and Van Vliet (1998) measured lutein and zeaxanthin interfering with the absorption of β-carotene because of decreases in both the AUCs of β-carotene and retinyl palmitate in their study.

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 nine 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 infant formula.

The Applicant has also conducted a supplementation trial in which 63 infants were randomised to receive infant formula containing lutein and zeaxanthin at concentrations of 20, 47, and 289 μg/L for five weeks (Wyeth, 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.

### 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 gut seems likely to have an effect on the bioavailability of lutein.

The effect of fat intakes on lutein bioavailability 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 ester 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 88% and 207% for the low and high fat intakes respectively ($p<0.001$). In contrast, the bioavailability of vitamin E, α- and β-carotene was similar when these compounds were consumed with either a low fat or a high fat spread. The small amount of fat in the low fat spread was sufficient to optimise the uptake of vitamin E and also α- and β-carotene in these adult subjects. However, the larger amount of fat was needed to optimise the uptake of lutein ester.

While this study by Roodenburg et al (2000) is methodologically sound, the study design does not enable FSANZ to make an estimation of the minimum amount of fat that would be required to be consumed by young children to ensure uptake of lutein from their diet. This study measured the effect on serum lutein of 15 healthy adults consuming an 8 mg dose of lutein ester in supplemental form under strict test conditions. The adult test diets studied were unlike a real-life diet of children aged one to three years. The test lutein was in ester form, not free form. And the 8 mg dose in this study is much higher than the mean estimated dietary intakes of lutein and zeaxanthin for Australian and New Zealand children.

Eight milligrams per day is more than 20 times, almost 12 times and almost 11 times the estimated mean daily intakes of lutein and zeaxanthin of Australian children aged 1 year, New Zealand children aged 1-3 years and Australian children aged 2-3 years, respectively (refer Tables 2 and 3 of Attachment 6).

## 5. Conclusion

Dietary lutein and zeaxanthin are absorbed and subsequently accumulate in the retina at the back of the eyeball, concentrated particularly in the macula lutea or 'yellow spot'; where the evidence indicates they protect against oxidative damage to the eye. Other functions of lutein in the eye are suggested by published observations, but are less conclusive. Lutein also acts as a general non-eye specific antioxidant.

Although there is established biological plausibility for lutein to promote eye health, there is insufficient evidence to make firm conclusions with respect to the benefits to young children of consuming lutein containing FSFYC.

Lutein derived from marigold (*T. erecta*) in infant formula or a supplement is bioavailable. Lutein from supplements appears more bioavailable than that in yellow carrots, similarly bioavailable to that in spinach, and less bioavailable than that from eggs. The bioavailability of lutein is likely to be enhanced by concurrent intake of fat.

It is therefore considered that for children aged 1-3 years who consume FSFYC with added lutein, such formulated foods would act as a reasonable contributor to their lutein intake.

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**Attachment 5**

# Dietary Intake Assessment

## Summary

Dietary intakes of lutein and zeaxanthin were calculated using constructed theoretical diets, the 1995 Australian National Nutrition Survey (NNS) data and the FSANZ dietary modelling computer program DIAMOND. 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.

A number of scenarios were examined in order to estimate current intakes of lutein and zeaxanthin and the intakes following fortification of Formulated Supplementary Foods for Young Children (FSFYC) at a minimum concentration of 150 µg/L and a maximum concentration of 500 µg/L (equivalent to 165-550 µg/L of lutein and zeaxanthin):

1. *Baseline* – estimated lutein and zeaxanthin intakes assessed in the current regulatory environment (i.e. before permission to add lutein and zeaxanthin to FSFYC is in effect in Australia and New Zealand).

2. *Minimum Scenario* – estimated lutein and zeaxanthin intakes after permission to add lutein and zeaxanthin to FSFYC at a minimum concentration of 165 µg/L is in effect in Australia and New Zealand.

3. *Maximum Scenario* – estimated lutein and zeaxanthin intakes after permission to add lutein and zeaxanthin to FSFYC at a maximum concentration of 550 µg/L is in effect in Australia and New Zealand.

The increases in mean dietary intakes of lutein and zeaxanthin between *Baseline* and the two fortification scenarios (*Minimum Scenario* and *Maximum Scenario*) were 18-61% for Australian children aged 1 year, 6-23% for New Zealand children aged 1-3 years, and 8-28% for Australian children aged 2-3 years respectively.

Estimated mean and high percentile dietary lutein and zeaxanthin intakes were well below the ADI for Australian and New Zealand children aged 1-3 years, which is for added sources only. The highest estimated dietary lutein and zeaxanthin intake, as a proportion of the reference health standard (9% ADI) was the 90$^{th}$ percentile intake for New Zealand children aged 1-3 years following the lutein and zeaxanthin fortification of FSFYC at 550 µg/L – *Maximum Scenario*. However, FSANZ 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 children aged 1-3 years were vegetables, fruits (including juices) and grain/cereal based foods. Green peas, carrots, leafy vegetables, and oranges were particularly important contributors.

Following the fortification of FSFYC with lutein and zeaxanthin, FSFYC are predicted to be major contributors to the lutein and zeaxanthin intakes for 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 (*T. erecta* L.), as a nutritive substance, to 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) (US 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 1). 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.

**Table 1: Estimated mean and 90th percentile dietary intakes 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 and 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 2,000 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.

FSANZ considered that a dietary intake assessment was necessary in order to estimate the current and potential dietary intakes of lutein and zeaxanthin and the impact of allowing the addition of the lutein and zeaxanthin to 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 combined intakes.

# 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 intake of 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 intake 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 intake 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 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 for the dietary intake assessment was identified as children aged 1-3 years since 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 National Nutrition Survey (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. The Australian NNS data were used in the assessment of lutein and zeaxanthin intakes for Australian children aged 2-3 years.

The target group was identified as children aged 1-3 years, however 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 used to estimate dietary lutein and zeaxanthin intakes for these population groups (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 = food chemical 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 US Department of Agriculture (USDA) nutrient database (US 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 concentrations for FSFYC that were used in the dietary intake assessments were 165 µg/L and 550 µg/L.

## 3.6 Scenarios for dietary intake assessments

A number of scenarios were examined in order to estimate current intakes of lutein and zeaxanthin and the intakes following fortification of FSFYC with lutein at a minimum concentration of 150 µg/L and a maximum concentration of 500 µg/L (equivalent to 165-550 µg/L of lutein and zeaxanthin).

All scenarios took into account naturally occurring lutein and zeaxanthin in foods 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. Lutein is also a food colouring agent (INS 161b) that is permitted to be added to a variety of foods under Schedule 1 of Standard 1.3.1. FSANZ examined its food additive database to determine the types of products that contain the additive 161b. While this database is not necessarily representative of the Australian and New Zealand food supplies, it is often used for indicative purposes. Very few products were found to have lutein listed in the ingredient listing: one sweet biscuit, one dry sauce mix, one mayonnaise, and one carbohydrate modified confectionery. Consequently, it was considered that lutein added as a food colouring agent was unlikely to contribute greatly to the lutein and zeaxanthin intakes of children aged 1-3 years.

### *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).

### *3.6.2 Minimum Scenario model*

This model represents estimated lutein and zeaxanthin intakes for each population group after permission to add lutein and zeaxanthin to FSFYC at a minimum concentration of 165 µg/L, assuming a minimum claimable amount of 30 µg lutein/serve (200 mL), is in effect in Australia and New Zealand.

### *3.6.3 Maximum Scenario model*

This model represents estimated lutein and zeaxanthin intakes for each population group after permission to add lutein and zeaxanthin to FSFYC at a concentration of up to 550 µg/L is in effect in Australia and New Zealand, assuming the maximum permitted concentration of lutein is used.

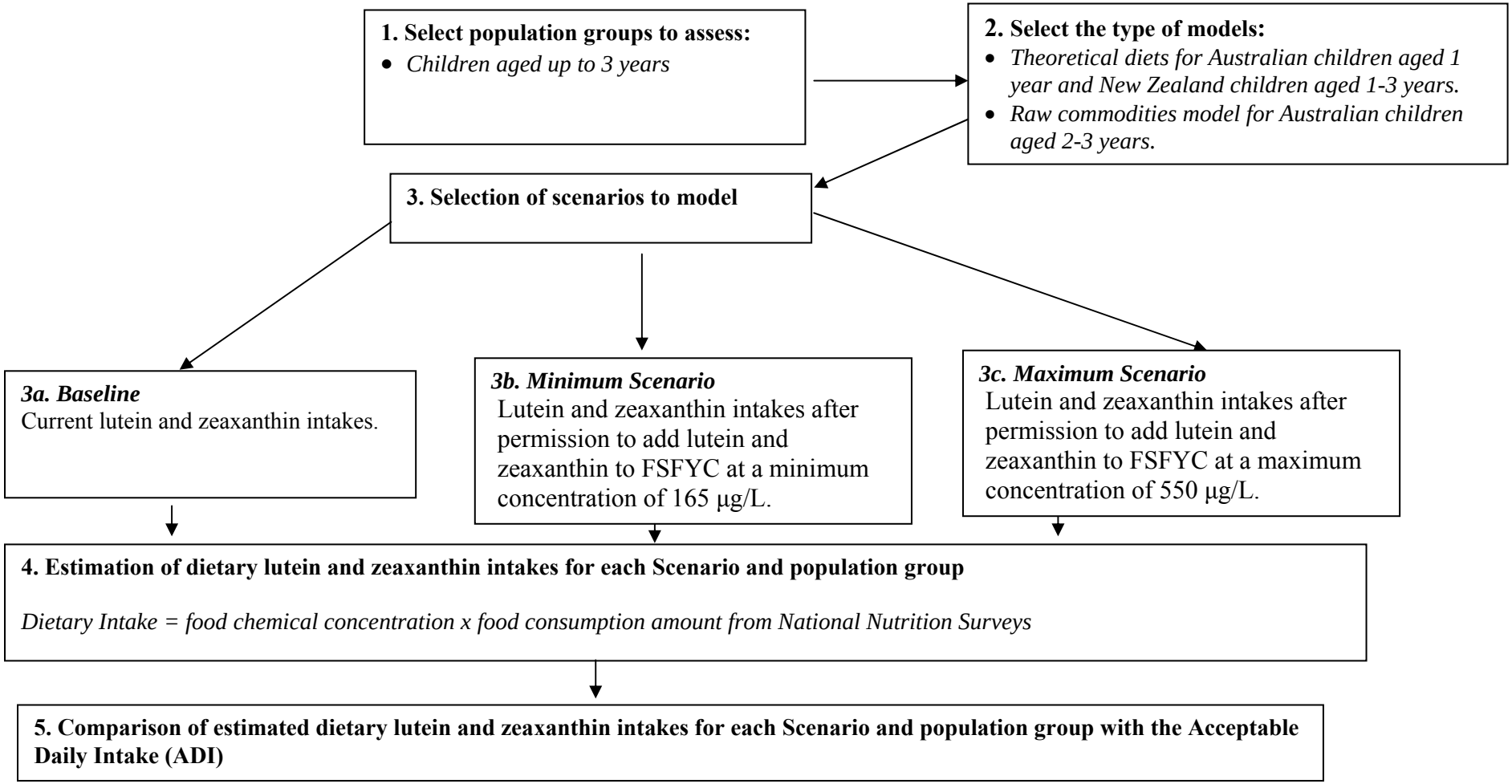


*Figure 1: Dietary modelling approach used for assessing lutein and zeaxanthin intakes for New Zealand and Australia*

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

Dietary intake assessments were conducted to estimate potential dietary lutein and zeaxanthin intakes for each population group if permission to add lutein and zeaxanthin to FSFYC is granted. The method used is summarised in Figure 1.

### *3.7.1 Theoretical diets constructed for Australian children aged 1 year and New Zealand children aged 1-3 years*

New Zealand research shows that, among children aged 1-3 years who drink at least one glass (200 mL) of FSFYC each day, average consumption of FSFYC is 460 mL per day. Eighteen per cent of all 1-3 year old children in this study consumed FSFYC, with 85% of these consuming more than one glass per day (New Zealand Food Safety Authority, 2006).

The theoretical diet for Australian children aged one 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 (as made up). In the theoretical diets used in this assessment, it was assumed that there was complete replacement of milk (full fat, reduced fat and low fat), infant formula and follow-on formula with FSFYC (423 g/day Australia, 281 g/day New Zealand). In the assessments conducted using the 1995 NNS for 2-3 year old Australian children, it was assumed that FSFYC replaced all full fat and unspecified fat content fluid milk. The data for FSFYC consumption from the 2006 New Zealand study were therefore similar to those used in the theoretical diet for Australian children aged 1 year but were higher than used for the theoretical diet for New Zealand children aged 1-3 years.

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. High percentile ($90^{th}$ percentile) dietary lutein and zeaxanthin intakes were estimated and then compared to the ADI, using the equation:

$$90^{th} \text{ percentile intake} = \text{mean intake} \times 2$$

(Ratio derived from Office of Premarket Approval, C.F.S.A.N., U.S. FDA, 1995)

#### 3.7.1.1 Australian children aged one 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 $50^{th}$ 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 $50^{th}$ percentile one year old boy was 9.6 kg.

It was assumed that 35% of energy intake was derived from milk and 65% 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 intakes 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). 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 1.

### *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. Ninety-three per cent 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 for the New Zealand Food Safety Authority (NZFSA 2006) reported that, for New Zealand 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 Australian NNS, the average consumption of full fat and unspecified fat content fluid cow's milks (and therefore of FSFYC in this assessment) was 403 g/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 NNS 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 90$^{th}$ 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.

## 4.2 Concentration Data

- It was assumed that USA data (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) or through the use of lutein as a food colouring.

### 4.3 General

- Naturally-occurring sources of lutein and zeaxanthin have been included in the dietary intake assessment; and
- 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 NNS food consumption data provides the best estimate of actual consumption of a food and the resulting estimated dietary intake of a food chemical 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 (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 NNS, there have been significant changes to the 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 (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.

A limitation of estimating dietary intake over a period of 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 Australian children aged 1 year and New Zealand children aged 1-3 years 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 NNS 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 to 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 | | | 90th percentile | | |
| | | *Baseline* | *Minimum Scenario* | *Maximum Scenario* | *Baseline* | *Minimum Scenario* | *Maximum Scenario* |
| Australia | 1 | 385 | 455 | 620 | 770 | 910 | 1,240 |
| New Zealand | 1-3 | 680 | 720 | 835 | 1,360 | 1,440 | 1,670 |

**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 intakes of lutein and zeaxanthin (µg/day) | | | | | |
|---|---|---|---|---|---|---|
| | Mean | | | 90th percentile | | |
| | *Baseline* | *Minimum Scenario* | *Maximum Scenario* | *Baseline* | *Minimum Scenario* | *Maximum Scenario* |
| 2-3 | 740 | 800 | 945 | 1,550 | 1,590 | 1,740 |

The increases in mean dietary intakes of lutein and zeaxanthin between *Baseline* and the two fortification scenarios (*Minimum Scenario* and *Maximum Scenario*) were 18-61% for Australian children aged 1 year, 6-23% for New Zealand children aged 1-3 years, and 8-28% for Australian children aged 2-3 years. These increases in mean lutein and zeaxanthin intakes were equivalent to the amount of lutein and zeaxanthin from approximately 3-17 g of broccoli or 30-180 g of oranges.

The estimated mean *Baseline* dietary intake predicted by FSANZ for Australian children 1 year was 385 µg/day and was 740 µg/day for 2-3 years. The Applicant predicted mean *Baseline* intakes for Australian children 1-3 years to be 344 µg/day. The results from the Applicant and the FSANZ assessment are not directly comparable since the two assessments examined different age groups and used different methodologies.

The Applicant estimated that FSFYC (600 ml) would be expected to contribute an additional 300 µg lutein per day. This would result in total mean intakes of around 940 µg/day for American children aged 1-3 years. However, the FSANZ assessment estimated that the mean consumption of FSFYC would be 423 mL/day for Australian children aged 1 year, 281 mL per day for New Zealand children aged 1-3 years and 403 mL per day for Australian children aged 2-3 years. The estimated mean lutein and zeaxanthin intakes were up to 620 µg/day for 1 year old Australian children (*Maximum Scenario*), 835 µg/day for New Zealand children aged 1-3 years, and 945 µg/day for Australian children aged 2-3 years, following the fortification of FSFYC 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%), fruits (10%), grain/cereal based foods (8%), green peas (8%), carrots (7%), leafy vegetables (7%), onions (7%), sweet corn (6%), broccoli/cauliflower (5%), and all other vegetables (14%).

For the *Minimum Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were fruit and vegetables juices (17%), FSFYC (15%), fruits (8%), grain/cereal based foods (7%), green peas (6%), carrots (6%), leafy vegetables (6%), onions (6%), sweet corn (5%) and all other vegetables (16%).

For the *Maximum Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were FSFYC (38%), vegetables (34%), fruit and vegetables juices (13%), and fruits (6%).

### *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%), fruits including juices (12%), grain/cereal foods (11%), green peas (10%), pumpkin (9%), carrots (8%), and all other vegetables (15%).

For the *Minimum Scenario*, the major contributors to lutein and zeaxanthin intakes were silverbeet (22%), fruits including juices (12%), grain/cereal foods (10%), peas (10%), pumpkin (8%), carrot (8%), FSFYC (5%), and all other vegetables (14%).

For the *Maximum Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were silverbeet (19%), FSFYC (15%), fruits including juices (10%), grain/cereal foods (9%), green peas (9%), pumpkin (7%), carrots (7%), and all other vegetables (13%).

### *6.2.3 Australian children aged 2-3 years*

The major contributors from food (≥ 5%) to lutein and zeaxanthin intakes at *Baseline* for Australian children aged 1 year were oranges (19%), green peas (14%), fruits except oranges (12%), grains (9%), pumpkin (9%), leafy vegetables (8%), sweet corn (6%), broccoli (5%) and all other vegetables (13%).

For the fortification *Minimum Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were oranges (18%), green peas (13%), fruits except oranges (11%), grains (9%), pumpkin (8%), FSFYC (8%), leafy vegetables (7%) sweet corn (5%), and all other vegetables (17%).

For the fortification *Maximum Scenario*, the major contributors (≥ 5%) to lutein and zeaxanthin intakes were FSFYC (22%), oranges (15%), green peas (11%), fruits except oranges (9%), grains (7%), pumpkin (7%), leafy vegetables (6%) and all other vegetables (19%).

## 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 2,000 μg/kg bw/day, which is for added sources only (see Attachment 5 for details). However, 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 90$^{th}$ percentile intakes of lutein and zeaxanthin were all well below the ADI (see Tables 4 and 5). FSANZ estimated mean lutein and zeaxanthin intakes were <5% ADI for both the *Minimum Scenario* and *Maximum Scenario*. Ninetieth percentile intakes were estimated at <10% ADI for both the *Minimum Scenario* and *Maximum Scenario*.

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, 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 up to 6% of the ADI. If intakes of naturally occurring lutein and zeaxanthin are not considered, intakes of added lutein and zeaxanthin would represent a much lower proportion of the ADI.

The Applicant estimated lutein intake 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.

**Table 4: Estimated mean and 90th percentile intakes of lutein and zeaxanthin for Australian children aged one year and New Zealand children aged 1-3 years, as a percentage of the ADI**

| Country | Age (years) | Estimated dietary intakes of lutein and zeaxanthin^ (%ADI*) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Mean | | | 90th percentile | | |
| | | *Baseline* | *Minimum Scenario* | *Maximum Scenario* | *Baseline* | *Minimum Scenario* | *Maximum Scenario* |
| Australia | 1 | 2 | 2 | 3 | 4 | 5 | 6 |
| New Zealand | 1-3 | 4 | 4 | 4 | 7 | 8 | 9 |

^ Estimated using theoretical diets

* ADI for lutein and zeaxanthin = 2,000 µg/kg bw/day

**Table 5: Estimated mean and 90th percentile intakes of lutein and zeaxanthin for Australian children aged 2-3 years, as a percentage of the ADI**

| Age (years) | Estimated dietary intakes of lutein and zeaxanthin# (%ADI*) | | | | | |
|---|---|---|---|---|---|---|
| | Mean | | | 90th percentile | | |
| | *Baseline* | *Minimum Scenario* | *Maximum Scenario* | *Baseline* | *Minimum Scenario* | *Maximum Scenario* |
| 2-3 | 2 | 3 | 3 | 5 | 5 | 6 |

# Estimated using 1995 NNS. * ADI for added lutein and zeaxanthin = 2,000 µg/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 |

# Appendix 2

**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 |

| Food | Food Consumption Amount (grams per 14 days) | Food Consumption Amount (grams per day) |
|---|---|---|
| Chocolate, plain milk | 20 | 1.4 |
| Coffee beans, ground | 0 | 0 |
| 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 |

| Food | Food Consumption Amount (grams per 14 days) | Food Consumption Amount (grams per day) |
|---|---|---|
| Melon | 30 | 2.1 |
| Milk, flavoured | 0 | 0 |
| 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 |

| Food | Food Consumption Amount (grams per 14 days) | Food Consumption Amount (grams per day) |
|---|---|---|
| Snack bars | 30 | 2.1 |
| Soup | 50 | 3.6 |
| 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 |
| Weet-bix | 210 | 15 |
| Wine, still red | 0 | 0 |
| Wine, still white | 0 | 0 |
| Yeast extract | 25 | 1.8 |
| Yoghurt | 870 | 62 |

**Attachment 6**

# Hazard Assessment

## Summary

This Application seeks permission for lutein and zeaxanthin to be added to 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 L*) 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 90-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) has been observed, but the dose at which it has been observed varies between individuals and between ethnicities. Carotenodermia 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 intake, 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 *T. 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 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 *T. 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 Formula. The Final Assessment Report for Application A594 is available on the FSANZ website at http://www.foodstandards.gov.au/standardsdevelopment/applications/applicationa594lutei3490.cfm.

Therefore, the aims of the current assessment were to:

- review the assessment conducted as part of Application A594; and
- determine the safety of lutein and zeaxanthin added to FSFYC.

## 2. Summary of studies considered for Application A594

### 2.1 Animal studies

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

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

For lutein, the mean $C_{max}$, mean $T_{max}$, and mean area under the curve (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.

This study was conducted according to Good Laboratory Practice.

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

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

| Parameter | 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 two-fold increase in AUC observed between the two groups, however, the high background lutein levels and the difference between low and high dose background levels make this study difficult to interpret.

This study was conducted according to Good Laboratory Practice.

## 2.2 Human studies

*2.2.1 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.

This study was conducted according to Good Clinical Practice.

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

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

One hundred and ten 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 both groups were below the mean values for the US reference data. The infants in the study demonstrated growth over the study that was comparable to the mean US values for three of the four measurements. For head-circumference-for-age, the Philippine infants in neither group demonstrated the same rate of increase as observed in the US population. However, when compared to data from a Philippine reference population of almost 27,000 children, the data of the study population followed the growth curve established from the Philippine data.

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

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

This study was conducted according to Good Clinical Practice.

## 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 issues were considered 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 intake of lutein would have been greater than 15 mg/day if dietary intakes had also been included.

- The anticipated mean intake 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 intake 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 a very low 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 occurrences 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 7

# 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 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. This JECFA specification is for the free lutein, not the lutein ester (refer to Attachment 3 for response to a submitter's comment). The preparation is from a natural extract, not a synthetically synthesised chemical. 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 carried in vegetable oil with approved food additives being antioxidants and emulsifiers. These food additives would not be expected to have any technological additive function in the final formulated supplementary foods for young children. Stability results for powdered products, as in the most common FSFYC, indicated some losses of lutein occurred during storage. 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 (commonly referred to an overage). The Applicant has requested a maximum level of 500 µg/L to ensure they always achieve a level of 200 µg/L when the solution is made up.

For their commercial operations, the Applicant aims for an overage of 180% to account for losses during storage and distribution to ensure the product meets their label concentration up till the end of the product's shelf life. The extra allowance is to ensure their product will always meet the requirements of the Code. Manufacturers of FSFYC are required to produce product to ensure that lutein concentrations in commercial product are always between the regulatory ranges of minimum and maximum limits. The request is comparable to that commonly used for dosing sensitive vitamins to food.

Lutein is not being considered for an extension of use as a food additive, where it can act as a permitted colour in FSFYC, since its proposed use is not for this purpose. The addition of lutein as a nutritive substance up to a level of 500 µg/L will not impact on other ingredients in the formulated supplementary foods for young children.

## Introduction

FSANZ 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 matrix, being 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.

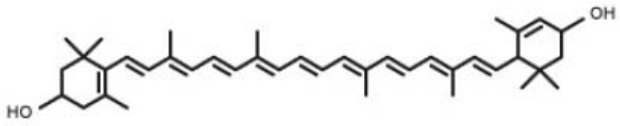
## Background

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.

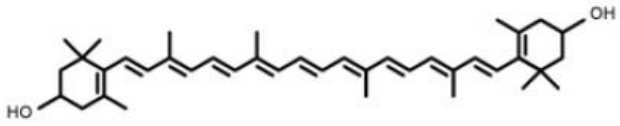
Carotenoids are synthesised by higher plants and certain fungi, algae and bacteria, but they are not synthesised by animals, including humans, though they may be biochemically modified by them. This means that humans cannot produce lutein and its presence comes from exogenous food sources. Lutein has 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.




Lutein




Zeaxanthin

*Figure 1: Chemical structures of lutein and zeaxanthin*

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

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

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

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

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

The JECFA specifications for the lutein extract of this Application requires 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 percentage of lutein and zeaxanthin as approximately 77% and 7% respectively. The other minor components include other carotenoids and waxes.

**Manufacture of lutein extract**

The lutein extract of the Application is prepared from marigold (*T. erecta* L.) flowers. A lutein oleoresin is prepared from a hexane extract of marigold flowers, which is then saponified with potassium hydroxide in either methanol or propylene glycol (also called 1,2-propanediol in the Application). The lutein extract is crystallised to partially purify it, though it contains other carotenoids (mainly zeaxanthin) and waxes. The lutein preparation is from a natural extract, not a synthetically synthesised chemical.

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

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

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

The food additives would not be expected to have any technological additive function in the final formulated supplementary foods for young children. The addition of lutein as a nutritive substance up to a level of 500 µg/L will not impact on other ingredients in the formulated supplementary foods for young children.

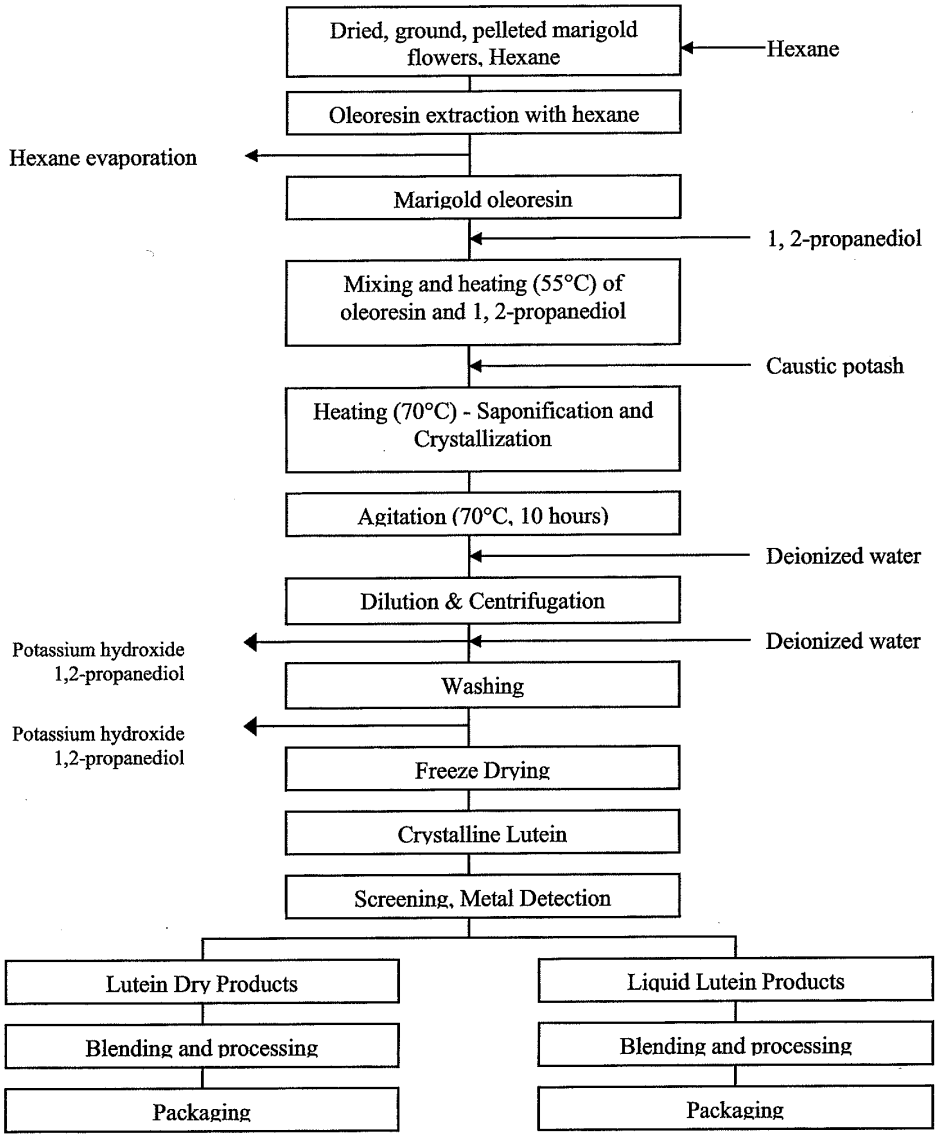



*Figure 2: Schematic of the lutein preparation manufacturing process*

**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. It is important to note that this specification is for the free lutein, not the lutein ester (this is relevant to a submitter's issue).

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

**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 and formulated supplementary foods for young children type products. Although limited liquid ready-to-feed products are commercially available, formulated supplementary foods for young children are mainly available as powders, therefore stability results have been given for powders.

The Applicant performed stability trials on lutein concentration in both pilot plant and 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 both 27°C and 70% RH (relative humidity) (ambient temperature), and 37°C and 75% RH (high temperature for accelerated storage conditions).

Analyses were performed every 3 months up to 12 months with some 18 month results for the ambient temperature trials and either 3 or 6 months for high temperature storage conditions. After 12 months at 27°C and 70% RH, the largest losses were 35%. The results also indicated that largest losses occurred early during storage and then the losses stabilised (explained by the initial availability of oxygen in the package which diminishes as it oxidises the lutein). 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.

**Overages**

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

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

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.

**Justification for Applicant's overage**

The Applicant has sought regulatory permission for the maximum level of 500 µg/L of lutein in formulated supplementary foods for young children in the Code. This is when their powdered products are made up to label suggestions to provide 200 µg/L. They have justified this figure from their stability results which they conclude they need and use an average 180% overage to account for losses of lutein with storage to the end of shelf life of the product. Over and above that, the Applicant has wanted to ensure that there is sufficient tolerance in the regulations to allow for variability of manufacture, analyses and storage conditions so they can always market their product, that is no product will have a lutein concentration outside the range permitted in the Code.

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

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

Since the Applicant can not control the conditions customers store their product, which could be more extreme during the shelf life of the product compared to the test conditions used for stability testing the Applicant will also want some allowance to ensure the product always contains the claimed amount of lutein.

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

**Conclusion**

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. The manufacture and specifications of the lutein preparation are consistent with internationally approved JECFA specifications. Stability results reported for the product over its shelf life support the Applicant's request for overdosing with lutein.

Lutein is a natural carotenoid with the commercial lutein extract prepared from marigold (*Tagetes erecta* L.) flowers, not a synthetic chemical. 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 commercial lutein preparation that is subsequently added to food is carried in vegetable oil with approved food additives being antioxidants and emulsifiers. These food additives would not be expected to have any technological additive function in the final formulated supplementary foods for young children. Stability results indicated some losses of lutein occurred during storage. 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 (commonly referred to as overages).

The Applicant has requested a maximum level of 500 µg/L**,** to ensure they always achieve a label concentration of 200 µg/L when the solution is made. The request is comparable to that commonly used for dosing sensitive vitamins to food.

Lutein is not being considered for an extension of use as a food additive, where it can act as a permitted colour, since its proposed use is not for this purpose. The addition of lutein as a nutritive substance up to a level of 500 μg/L will not impact on other ingredients in the formulated supplementary foods for young children.

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