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Te Mana Kounga Kai – Ahitereiria me Aotearoa

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FIRST REVIEW REPORT

APPLICATION A594

ADDITION OF LUTEIN AS A NUTRITIVE SUBSTANCE TO INFANT FORMULA PRODUCTS

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

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Executive Summary

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

Decision

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

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

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

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

FSANZ has made the following amendments to the draft variations:

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

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

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

Additionally, since Final Assessment, the European Food Safety Authority[1] (EFSA) has released a scientific opinion on the suitability of lutein in infant formula and follow-on formulae which supports FSANZ's conclusion and approach at First Review.

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

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

1. Introduction

On 8 September 2008, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Application A594 – Addition of Lutein as a Nutritive Substance to Infant Formula products, which seeks to permit the voluntary addition of lutein as a nutritive substance to infant formula products[2].

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

2. Objectives of Review

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

3. Grounds for the Review requested by the Ministerial Council

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

These issues are addressed under Section 6 of this Report.

4. Background

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

Specifically, the Applicant requested permission to add lutein from marigold (*Tagetes erecta L.*) to infant formula products[3,4,5] at a maximum concentration of 250 µg/L.

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

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

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

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

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

5. FSANZ Assessment of Application A594

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

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

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

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

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

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

6. Issues addressed in the First Review

6.1 Protection of public health and safety

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

6.1.1 Insufficient evidence to demonstrate nutritional purpose

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

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

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

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

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

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

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

6.1.2 Lack of representative data for Australia and New Zealand

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

As the target group was infants aged 3 months and 9 months, National Nutrition Survey data was not available. In this case, following best practice and using internationally accepted methodology, FSANZ used theoretical diets to estimate dietary intakes[6].

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

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

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

6.1.3 Use of small studies and difficult interpretations

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Current recommendations such as those contained in the Nutrient Reference Values for Australia and New Zealand (NRVs) are predominantly based on the prevention of deficiency across a population, not on achieving optimal intakes (NHMRC and New Zealand Ministry of Health (MoH) 2006). For infants the adequate intakes (AI)[7] are used for all macro- and micronutrients.

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

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

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

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

6.1.6 Limited data on carotenoid interactions

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

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

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

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

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

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

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

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

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

6.1.7.1 Lutein concentrations in breast milk

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

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

Table 1: Mean Lutein and Zeaxanthin Concentrations in Breast Milk

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

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

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

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

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

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

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

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

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

Table 2: Serum and Plasma Lutein Concentrations in Breastfed Infants

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

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

Table 3: Mature Breast Milk Lutein Concentrations

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

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

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

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

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

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

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

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

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

6.1.7.3 Bioavailability of lutein

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

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

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

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

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

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

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

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

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

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

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

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

6.1.7.4 European Food Safety Authority scientific opinion

Since the Final Assessment of Application A594, the recent scientific opinion of the European Food Safety Authority[8] (EFSA) has been released on the suitability of lutein in infant formula products.

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

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

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

6.1.8 Level of overage

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.1.10 Lack of assessment of benefit

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

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

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

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

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

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

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

6.2 Absence of Policy Guidance

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

In March 2008, the Food Regulation Standing Committee (FRSC) established a Working Group to develop a Policy Guideline on the intent of Part 2.9 of the Code – Special Purpose Foods. A Consultation Paper[9] was released for public comment in January 2009, with submissions due in early March 2009.

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

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

6.3 Indonesian prohibition of lutein in infant formula products

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

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

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

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

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[9] 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

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

6.4 Cost burden on industry or consumers

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

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

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

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

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

6.5 Costs associated with enforcement

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

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

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

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

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

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

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

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

7. Proposed amendments to the draft variation

7.1 Lutein concentration permitted in infant formula products

7.1.1 Bioavailability

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

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

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

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

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

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

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

7.1.2 Minimum and maximum levels of lutein

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

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

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

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

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

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

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

8. Review Options

There are three options proposed for consideration under this Review:

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

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

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

9. Decision

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

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

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

Decision

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

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

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

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

FSANZ has made the following amendments to the draft variations:

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

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

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

Additionally, since Final Assessment, the European Food Safety Authority[11] (EFSA) has released a scientific opinion on the suitability of lutein in infant formula and follow-on formulae which supports FSANZ's conclusion and approach at First Review.

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

10. Implementation and review

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

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Attachments

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

Attachment 1

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

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

To commence: on gazettal

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

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

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

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

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

Attachment 2

Executive Summary and Statement of Reasons from the Final Assessment Report

Food Standards Australia New Zealand (FSANZ) received an Application from Wyeth Australia Pty Ltd (the Applicant) on 13 November 2006 seeking to amend the *Australia New Zealand Food Standards Code* (the Code), to permit the voluntary addition of lutein as a nutritive substance to infant formula products[12].

Specifically, the Applicant has requested permission to add lutein from marigold (*Tagetes erecta L.*) to infant formula[13,14] at a maximum concentration of 250 µg/L. The Applicant requests permission to add lutein to infant formula in amounts that would provide 'comparable levels' to breastfed infants.

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

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

Regulatory Approach

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

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

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

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

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

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

- the safety of lutein.

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

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

Risk Assessment

At Final Assessment, the key risk assessment findings include:

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

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

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

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

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

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

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

Risk Management

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

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

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

Decision

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

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

Reasons for Decision

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

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

Consultation

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

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

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

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

Implementation and Review

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

Attachment 3

Statistical calculations explaining the overage required

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

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

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

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

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

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