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ORIGINAL SUBMISSION

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Des Moines, Iowa 50309-2058 USA
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BY:
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April 4, 2007

By Overnight Courier
Return Receipt Request

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Kemin Foods, L.C., d/b/a Kemin Health, L.C., ("Kemin"):
GRAS Notification for FloraGLO® Lutein 20% Liquid in Safflower Oil for Use in Infant Formula

Dear Sir or Madam:

In accordance with proposed 21 CFR §170.36, Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination, 62 Fed. Reg. 18938-18964, Kemin hereby submits a GRAS notification for FloraGLO® Lutein 20% Liquid in Safflower Oil for use as a food ingredient in infant formulas to provide a dietary source of lutein and zeaxanthin. Kemin's notification includes a GRAS panel report setting forth the basis for the GRAS determination, and the curricula vitae of the members of the GRAS panel for review by the Agency.

Additionally, Kemin respectfully requests that FDA expedite the review of this GRAS Notice. In the current instance, the same source of lutein, FloraGLO, was previously the subject of a GRAS notice submitted by Kemin on November 14, 2003, for use in a wide variety of foods, including infant foods, to which the Agency had no further questions. The scope of the current notice is considerably narrower, i.e. specifying the conditions of safe use of an acknowledged safe substance in one additional food—infant formula.

Although FDA does not have a regulatory requirement in the GRAS Notice process for a food to be tested clinically to demonstrate safety, experience has demonstrated that FDA expects a growth study to be a part of a GRAS notice when the intended food use

includes infant formula. As the Agency is aware, FDA has proposed[1] that a growth study be conducted for the purposes of supporting a 90-day pre-market notice of intent to market a new infant formula, a position restated just last August[2], but has not finalized this rulemaking. Kemin notes that such a growth study to assure safety of FloraGLO Lutein 20% Liquid in Safflower Oil has been conducted and has been reviewed by the expert panel as set forth in the panel report. Based on the above, Kemin requests that FDA expedite its review of this GRAS notice for use of lutein infant formula.

Please feel free to contact me should you have any questions, or need any additional information regarding this notice.

Sincerely,

Debbie Trinker, Esq.
Vice President, Regulatory Affairs

Enclosures

[1] Originally proposed 61 FR 36153, July 9, 1996, reopened for comment 28 April, 2003
[2] 71 FR at 43392, 1 August, 2006

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

FloraGLO® Crystalline lutein has previously been considered Generally Recognized as Safe (GRAS) by an Expert Panel of independent scientists for use in food. Furthermore, FloraGLO Crystalline Lutein was the subject of GRAS Notice No. GRN 000140, which The United States Food and Drug Administration (FDA) has reviewed and provided no questions regarding the conclusion that FloraGLO Crystalline Lutein is GRAS under the intended conditions of use (FDA, 2004). An ingredient that is manufactured with FloraGLO Crystalline Lutein, FloraGLO Lutein 20% Liquid in Safflower Oil, has now been determined to be GRAS, consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*, for an extended use in infant formula. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in infant formula, among experts qualified by scientific training and expertise. Therefore, the use of FloraGLO® Lutein 20% Liquid in Safflower Oil in infant formula as described below is exempt from the requirement of premarket approval.

Signed,

4/4/07

NAME
Date
ADDRESS
600 East Court Ave., Suite A
Des Moines, IA 50309-2021 USA

B. Name and Address of Notifier

Debbie Trinker, Esq.
Vice President, Regulatory Affairs
Kemin Health, L.C.
600 E. Court Avenue, Suite A
Des Moines, IA
50309-2021
USA

C. Common Name of the Notified Substance

Lutein

D. Conditions of Intended Use in Food

FloraGLO Lutein 20% Liquid in Safflower Oil is intended for use as a food ingredient in infant formulas. An overage will be used to account for losses during manufacture and shelf life. Furthermore, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal, and which is approximately the level tested in the infant clinical studies. The proposed maximum total lutein content in finished infant formula product of 250 µg/L also is approximately the upper end of the range of the lutein concentrations present naturally in human breast milk as demonstrated by Canfield *et al.* (2003).

Lutein and zeaxanthin are among the most prevalent carotenoids in the North American diet (IOM, 2000), occurring in high concentrations in green leafy vegetables, such as spinach and kale (Khachik *et al.*, 1995; Omaye *et al.*, 1997), and in chicken egg yolks (Handelman *et al.*, 1999). In the U.S., the daily intake of lutein and zeaxanthin from food, across the entire population sampled (aged 2 months and over), is estimated to range from 0.58 to 5.40 mg (IOM, 2001). In addition to their natural occurrence in various foods, lutein and zeaxanthin are available as dietary supplements (IOM, 2000); however, there are no consumption data from which to reliably estimate the intake of lutein and zeaxanthin by supplement users. Market share data indicate that lutein use in dietary supplements occurs predominantly from multi-vitamin type supplements.

The U.S. national survey data from the National Health and Nutrition Examination Survey (NHANES 2001-2, released 2004) and the food composition data from USDA National Nutrient Database for Standard Reference (Release 17, 2004) provide an adequate database for estimating lutein + zeaxanthin intake in U.S. children from 2 months through 8 years of age. Kemin Health (Des Moines, Iowa) commissioned an analysis of these databases to estimate lutein + zeaxanthin dietary intakes for the U.S. population (Sun, 2005, CONFIDENTIAL). The mean and 90th percentile intakes of lutein and zeaxanthin for children from 2 through 6 months of age were 200 and 820 µg/day and were 460 and 1,100 µg/day for children from 7 through 11 months of age.

Lutein and zeaxanthin are present in human breast milk. Schweigert *et al.* (2000) extracted lipids from human milk and determined that the predominant form of lutein in human milk is free lutein. Exposure to lutein from human breast milk varies widely based on stage of lactation, geographical location, and individual diets, and has been demonstrated to range from 3 to 232 µg/L in individual mothers from around the world (Canfield *et al.*, 2003). Mean concentrations at individual sites ranged from 15 µg/L in Australia, Canada, the UK, and the US to 43 µg/L in China and Japan. The average lutein and zeaxanthin concentration across all of the sites investigated was 25 ± 19 µg/L (Canfield *et al.*, 2003). A survey of commercial infant formulas not currently fortified with lutein demonstrates the presence of low amounts of lutein in current infant formula products worldwide. Infant formula products were analyzed using a method that extracts free lutein and zeaxanthin without saponification. Using this methodology, the mean

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innate concentration of lutein in different infant formulas, representing unfortified ready to feed (RTF) formulas and powder formulas from Ireland, Singapore, and the Philippines (n=74) was 17 ± 4.6 µg/L with a range of 6.1 to 26.0 µg/L.

To provide a conservative estimate of potential lutein exposure (µg/kg/day), the 90th percentile of dietary lutein intake and the highest potential intake from the proposed products were used. For term infant formula, an estimated daily intake of 780 mL for term infants was used, per Codex and NAS estimated mean intake, and combined with the upper limit of lutein concentration (250 µg/L) to result in a daily intake of 195 µg/day. Furthermore, reference weight was based on a female child at the 10th percentile of weight-for-age at the first age increment referenced (generally one half month older than the bottom of the range) using data from the U.S. Centers for Disease Control Growth Charts.

Under the intended conditions of use of FloraGLO Lutein 20% Liquid in Safflower Oil, a low weight-for-age child (10th percentile) who is a heavy consumer (90th percentile) of lutein from other dietary sources and consumes the highest recommended intake of proposed product will take in approximately 230 µg/kg body weight/day.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, FloraGLO Lutein 20% Liquid in Safflower Oil has been determined to be GRAS for use in infant formula on the basis of scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil as a component of infant formula. The safety of FloraGLO Lutein 20% Liquid in Safflower Oil is supported by the previous GRAS determination for FloraGLO Crystalline lutein, which was the subject of GRAS Notice No. GRN 000140, which The United States Food and Drug Administration (FDA) has reviewed and provided no questions regarding the conclusion that FloraGLO Crystalline Lutein is GRAS under the intended conditions of use (FDA, 2004). FloraGLO Crystalline Lutein was previously determined to be GRAS based on its safety, which has been established in toxicological studies in rats, mutagenicity studies conducted with *Salmonella typhimurium*, and is further supported by intervention studies conducted with healthy subjects designed to measure metabolic endpoints. The safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas is further supported by a 13-week toxicity study conducted in Wistar rats at doses up to 260 mg FloraGLO Crystalline Lutein/kg body weight/day (corresponding to 210 mg lutein+zeaxanthin/kg body weight/day) and a developmental toxicity study conducted in Sprague-Dawley rats at doses up to 1,100 mg lutein/kg body weight/day. Additionally, the results of an infant growth and safety study conducted with FloraGLO Lutein 20% Liquid in Safflower Oil at a targeted concentration of 200 µg lutein/L in infant formula, and resulting in a mean intake ranging from 190 to 250 µg lutein/day, for a period of 16 weeks corroborate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas. This determination is further supported by an expert panel evaluation of the health aspects of

FloraGLO Lutein 20% Liquid in Safflower Oil. [See Attached – EXPERT PANEL OPINION REGARDING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF FloraGLO LUTEIN 20% LIQUID IN SAFFLOWER OIL FOR USE IN INFANT FORMULA].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Debbie Trinker, Esq.
Vice President, Regulatory Affairs
Kemin Health, L.C.
600 E. Court Avenue, Suite A
Des Moines, IA
50309-2021
USA

Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, Kemin Health, L.C. will supply these data and information.

II. Detailed Information About the Identity of the Substance

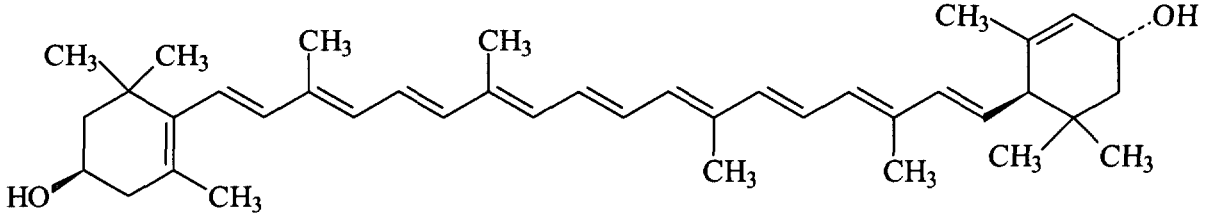
A. Identity

FloraGLO Lutein 20% Liquid in Safflower Oil is produced in accordance with current good manufacturing practice. FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured using FloraGLO Crystalline Lutein, a purified extract from the marigold (*Tagetes erecta*) flower. FloraGLO Lutein 20% Liquid in Safflower Oil contains approximately 21.8% by weight of the carotenoids lutein and zeaxanthin (20 and 1.8%, respectively).

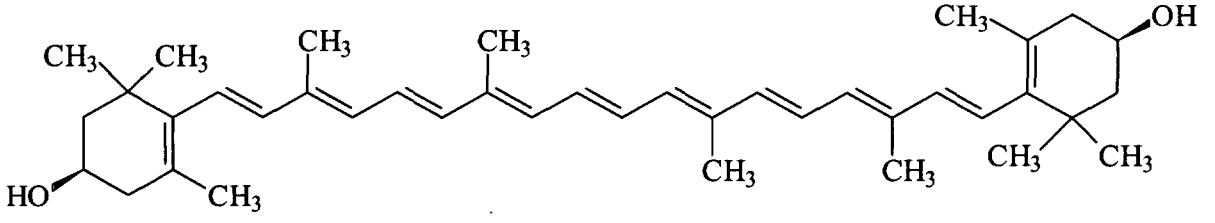
Lutein is an oxycarotenoid, or xanthophyll, containing 2 cyclic end groups (one β- and one ε-ionone ring) and the basic C_{40} isoprenoid structure common to all carotenoids (see Figure 2.4-1). Lutein occurs together with zeaxanthin, an oxycarotenoid that is isomeric with lutein, containing 2 β-ionone rings rather than one β- and one ε-ionone ring (see below). In principal, each of the polyene chain double bonds present in lutein and zeaxanthin could exist in a *cis* or *trans* conformation, giving rise to a large number of possible mono-*cis* and poly-*cis* isomers; however, in practice, the vast majority of carotenoids are in the all-*trans* configurations (Rice-Evans *et al.*, 1997; IOM, 2000), as depicted below. Small amounts of *cis* isomers of lutein and zeaxanthin, accompanied by their respective all-*trans* configurations, have been isolated and purified from extracts of marigold flowers, fresh raw kale, corn meal, spinach, and human plasma (Krinsky *et al.*, 1990; Khachik *et al.*, 1999).

The structural formula, chemical properties, and physical characteristics of lutein and zeaxanthin are presented below.

Common or Usual Name:	Lutein
Chemical Name:	xanthophyll; β,ε-carotene-3,3'-diol; vegetable lutein; vegetable luteol; Bo-Xan; all-*trans*-(+)-xanthophyll; all-trans-lutein
Chemical Abstracts Service (CAS) Number:	127-40-2
Empirical Formula and Formula Weight:	$C_{40}H_{56}O_2$
Molecular weight:	568.88
Structural Formula:	



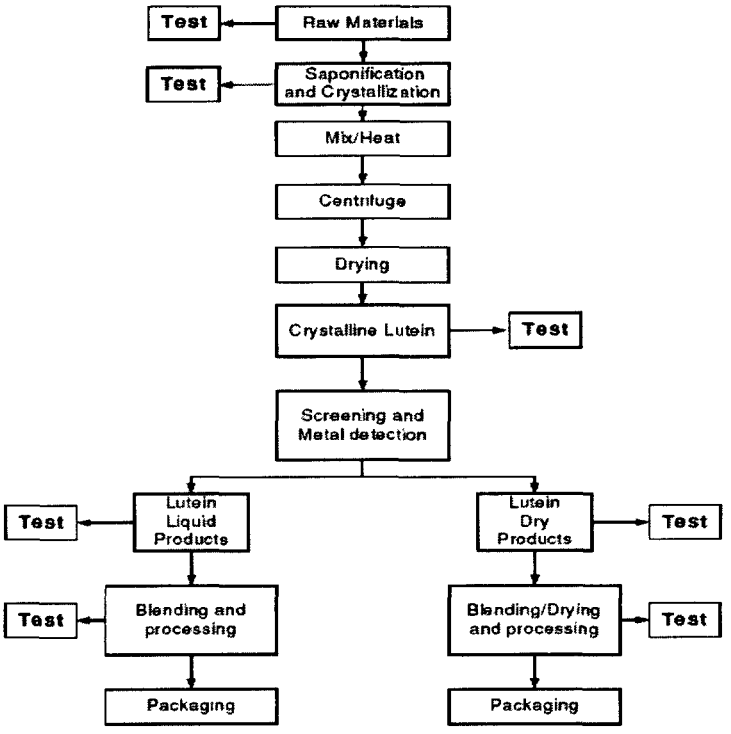
Common or Usual Name:	Zeaxanthin
Chemical Name:	β, β-carotene-3,3'-diol; all-*trans*-β-carotene-3,3'-diol; (3*R*,3'*R*)-dihydroxy-β-carotene; zeaxanthol; anchovyxanthin
Chemical Abstracts Service (CAS) Number:	144-68-3
Empirical Formula and Formula Weight:	$C_{40}H_{56}O_2$
Molecular weight:	568.88
Structural Formula:	



B. Method of Manufacture

The lutein and zeaxanthin extract is generated using a proprietary technology in a 3-step process that does not include chemical synthesis, but rather extracts the lutein from the natural source material. Marigold oleoresin (paste) is derived from the hexane extraction of dried marigold flower petals, with subsequent purification to remove the hexane residues. During the crystallization step, the marigold oleoresin is subjected to conditions to remove the fatty acids from lutein esters and zeaxanthin esters. This process employs potassium hydroxide (potash), propylene glycol, and water with mixing and heat. During this process crystals of lutein and zeaxanthin are formed. The reaction mixture from the crystallization step is diluted with water and the lutein and zeaxanthin crystals are collected by centrifugation and washed with additional water. The water used is purified by reverse osmosis. The lutein and zeaxanthin crystals are dried by the removal of the residual water, which results in dry cake base. Dry cake base is an intermediate and is additionally screened to become FloraGLO Crystalline Lutein. Dry cake base and FloraGLO Crystalline Lutein are packaged directly into drums and purged with nitrogen gas. A schematic overview of the manufacturing process of FloraGLO Crystaline Lutein is presented in Figure 1.

Figure 1. FloraGLO Crystalline Lutein Manufacturing Process



To obtain FloraGLO 20% Liquid in Safflower Oil, FloraGLO Crystalline Lutein is suspended in safflower oil. Safflower oil is typically added to infant formulas as part of the lipid component.

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C. Specifications for Food Grade Material

Specifications for FloraGLO Crystalline Lutein and FloraGLO Lutein 20% Liquid in Safflower Oil meet acceptable food grade specifications, and are presented in Tables 1 and 2, respectively. The panel reviewed the results of analysis of several non-consecutive representative lots of FloraGLO Crystalline Lutein and concluded the product complies with final product specifications.

Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein

Parameters	Specification	Method Reference
Principal Constituents		
Total Carotenoids (Pigment)	Minimum 80.0% wt	KHM-005-904
Lutein	Minimum 74.0% wt	KHM-009-904
Zeaxanthin	Minimum 4.0% wt Maximum 9.0% wt	KHM-005-904
Aggregate Constituents & Properties		
Moisture	Maximum 1.0% wt	KHM-005-913
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Protein	Maximum 100 mg/kg	KHM-005-921
Waxes	Maximum 14.0 % wt	Alturas 12/27/00
Metals		
Lead (Pb)	Maximum 0.65 ppm	AOAC993.14
Cadmium (Cd)	Maximum 1.25 ppm	AOAC 993.14
Arsenic (As)	Maximum 2.5 ppm	AOAC 993.14
Mercury (Hg)	Maximum 0.15 ppm	Analyst 86.608, Analytical Chem. 40:2085
Other Constituents		
Hexane	Maximum 50 ppm	KHM-005-023
Propylene glycol	Maximum 1,000 mg/kg	KHM-005-033
Thiophenes	Maximum 300 mg/kg	Alturas Analytics TM01-105
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 27, NF 22, 2004
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 27, NF 22, 2004
Staph enrichment	Negative/10 g	USP 27, NF 22, 2004
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.

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Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein		
Parameters	**Specification**	**Method Reference**
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

Alturas = Alturas Analytics Inc. Method; AOAC = Association of Official Analytical Chemists; BAM-FDA = Bacteriological Analytical Manual – Food and Drug Administration; CMMEF = Compendium of Methods for the Microbiological Examination of Foods; KHM = Kemin Health Method; NF = National Formulary; USP = U.S. Pharmocopeia

Table 2 Specifications for Food-Grade FloraGLO Lutein 20% Liquid in Safflower Oil		
Parameters	**Specification**	**Method Reference**
Principal Constituents		
Lutein	Minimum 21.0% wt	KHM-005-905
Zeaxanthin	Minimum 0.8% wt	KHM-005-905
Aggregate Constituents & Properties		
Moisture	Maximum 1% wt	KHM-005-035
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 29, NF 24, 2006
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 29, NF 24, 2006
Staph enrichment	Negative/10 g	USP 29, NF 24, 2006
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

AOAC = Association of Official Analytical Chemists; BAM-FDA = Bacteriological Analytical Manual – Food and Drug Administration; CMMEF = Compendium of Methods for the Microbiological Examination of Foods; KHM = Kemin Health Method; NF = National Formulary; USP = U.S. Pharmocopeia

III. Self-Limiting Levels of Use

There are no physical or chemical characteristics that will limit the levels of use; however, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal.

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IV. Basis for GRAS Determination

The determination that FloraGLO Lutein 20% Liquid in Safflower Oil is GRAS is on the basis of scientific procedures. (See Attached – EXPERT PANEL OPINION REGARDING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF FloraGLO LUTEIN 20% LIQUID IN SAFFLOWER OIL FOR USE IN INFANT FORMULA).

EXPERT PANEL OPINION REGARDING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF FloraGLO® LUTEIN 20% LIQUID IN SAFFLOWER OIL FOR USE IN INFANT FORMULA

INTRODUCTION

FloraGLO Crystalline lutein has previously been considered Generally Recognized as Safe (GRAS) by an Expert Panel of independent scientists for use in food. The Expert Panel, which included Dr. Robert Russell (Tufts University), Professor Ron Walker (University of Surrey), and Dr. Ian Munro (Cantox Health Sciences International), evaluated the composition and manufacture of FloraGLO Crystalline Lutein, the intended uses and potential exposure under the defined intended conditions of use, and data regarding the safety of FloraGLO Crystalline Lutein. Based on this review, the Expert Panel concluded that FloraGLO Crystalline Lutein is GRAS for use as a food ingredient in baked goods and baking mixes, beverages and beverage bases, breakfast cereals, chewing gum, dairy product analogs, egg products, fats and oils, frozen dairy desserts and mixes, gravies and sauces, hard candy, infant and toddler foods (not including infant formula), milk products, processed fruits and fruit juices, soft candy, and in soups and soup mixes at levels ranging from 0.3 to 3.0 mg/serving. They also concluded that FloraGLO Crystalline Lutein is GRAS for use in medical foods intended as the sole item of the diet at intakes less than or equal to 20 mg/day. Furthermore, FloraGLO Crystalline Lutein was the subject of GRAS Notice No. GRN 000140, which The United States Food and Drug Administration (FDA) has reviewed and provided no questions regarding the conclusion that FloraGLO Crystalline Lutein is GRAS under the intended conditions of use (FDA, 2004).

At the request of Kemin Health, L.C., (Kemin), the manufacturer of FloraGLO Lutein, the Expert Panel, with the addition of Dr. Susan Baker (Women and Children's Hospital of Buffalo) (hereinafter referred to as the Panel), was reconvened to evaluate the safety of and to determine the Generally Recognized as Safe (GRAS) status of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas for infants from birth to 12 months. FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured using FloraGLO Crystalline Lutein which is a purified extract from the marigold (*Tagetes erecta*) flower that contains approximately 21.8% by weight of the carotenoids lutein and zeaxanthin (20 and 1.8%, respectively). *Curricula vitae* evidencing the qualifications of the Panel for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel was requested to evaluate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil from *T. erecta* for use as a food ingredient in infant formulas in the United States (U.S.) so that the total lutein content in finished infant formula product would not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal[1]. The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled from the literature and other published sources. The data evaluated by the Panel comprises information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in infant formula, consumption estimates for the intended use, bioavailability studies in animals and infants, safety studies conducted with FloraGLO Crystalline Lutein, growth and safety studies conducted with FloraGLO Lutein 20% Liquid in Safflower Oil in infants, and other relevant data on the safety of lutein and zeaxanthin obtained from the literature.

Following independent critical evaluation of the data and information, the Panel participated in two conference calls on February 23 and March 2, 2007. During the conference call on March 2, 2007, the Panel concluded that FloraGLO Lutein 20% Liquid in Safflower Oil meets appropriate food grade specifications, is manufactured in compliance with current Good Manufacturing Practices (cGMP), and is GRAS based on scientific procedures under the conditions of use. A summary of the basis for our conclusion is set forth below.

MANUFACTURING AND SPECIFICATIONS

FloraGLO Lutein 20% Liquid in Safflower Oil is produced in accordance with current good manufacturing practice. FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured using FloraGLO Crystalline Lutein, which is considered to be GRAS. Specifications for FloraGLO Crystalline Lutein and FloraGLO Lutein 20% Liquid in Safflower Oil meet acceptable food grade specifications, and are presented in Tables 1 and 2, respectively. The panel reviewed the results of analysis of several non-consecutive representative lots of FloraGLO Crystalline Lutein and concluded the product complies with final product specifications.

Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein

Parameters	Specification	Method Reference
Principal Constituents		
Total Carotenoids (Pigment)	Minimum 80.0% wt	KHM-005-904
Lutein	Minimum 74.0% wt	KHM-009-904
Zeaxanthin	Minimum 4.0% wt Maximum 9.0% wt	KHM-005-904
Aggregate Constituents & Properties		

[1] Conversion factor of 6.72 Kcal/100mL

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Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein		
Parameters	**Specification**	**Method Reference**
Moisture	Maximum 1.0% wt	KHM-005-913
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Protein	Maximum 100 mg/kg	KHM-005-921
Waxes	Maximum 14.0 % wt	Alturas 12/27/00
Metals		
Lead (Pb)	Maximum 0.65 ppm	AOAC993.14
Cadmium (Cd)	Maximum 1.25 ppm	AOAC 993.14
Arsenic (As)	Maximum 2.5 ppm	AOAC 993.14
Mercury (Hg)	Maximum 0.15 ppm	Analyst 86.608, Analytical Chem. 40:2085
Other Constituents		
Hexane	Maximum 50 ppm	KHM-005-023
Propylene glycol	Maximum 1,000 mg/kg	KHM-005-033
Thiophenes	Maximum 300 mg/kg	Alturas Analytics TM01-105
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 27, NF 22, 2004
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 27, NF 22, 2004
Staph enrichment	Negative/10 g	USP 27, NF 22, 2004
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

Table 2 Specifications for Food-Grade FloraGLO Lutein 20% Liquid in Safflower Oil		
Parameters	**Specification**	**Method Reference**
Principal Constituents		
Lutein	Minimum 21.0% wt	KHM-005-905
Zeaxanthin	Minimum 0.8% wt	KHM-005-905
Aggregate Constituents & Properties		
Moisture	Maximum 1% wt	KHM-005-035
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 29, NF 24, 2006

Table 2 Specifications for Food-Grade FloraGLO Lutein 20% Liquid in Safflower Oil		
Parameters	**Specification**	**Method Reference**
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 29, NF 24, 2006
Staph enrichment	Negative/10 g	USP 29, NF 24, 2006
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

INTENDED USE AND ESTIMATED INTAKE

Lutein and zeaxanthin are among the most prevalent carotenoids in the North American diet (IOM, 2000), occurring in high concentrations in green leafy vegetables, such as spinach and kale (Khachik *et al.*, 1995; Omaye *et al.*, 1997), and in chicken egg yolks (Handelman *et al.*, 1999). In the U.S., the daily intake of lutein and zeaxanthin from food, across the entire population sampled (aged 2 months and over), is estimated to range from 0.58 to 5.40 mg (IOM, 2001). In addition to their natural occurrence in various foods, lutein and zeaxanthin are available as dietary supplements (IOM, 2000); however, there are no consumption data from which to reliably estimate the intake of lutein and zeaxanthin by supplement users. Market share data indicate that lutein use in dietary supplements occurs predominantly from multi-vitamin type supplements.

The U.S. national survey data from the National Health and Nutrition Examination Survey (NHANES 2001-2, released 2004) and the food composition data from USDA National Nutrient Database for Standard Reference (Release 17, 2004) provide an adequate database for estimating lutein + zeaxanthin intake in U.S. children from 2 months through 8 years of age. Kemin Health (Des Moines, Iowa) commissioned an analysis of these databases to estimate lutein + zeaxanthin dietary intakes for the U.S. population (Sun, 2005, CONFIDENTIAL). The mean and 90th percentile intakes of lutein and zeaxanthin for children from 2 through 6 months of age were 200 and 820 µg/day and were 460 and 1,100 µg/day for children from 7 through 11 months of age.

Lutein and zeaxanthin are present in human breast milk. Schweigert *et al.* (2000) extracted lipids from human milk and determined that the predominant form of lutein in human milk is free lutein. Exposure to lutein from human breast milk varies widely based on stage of lactation, geographical location, and individual diets, and has been demonstrated to range from 3 to 232 µg/L in individual mothers from around the world (Canfield *et al.*, 2003). Mean concentrations at individual sites ranged from 15 µg/L in Australia, Canada, the UK, and the US to 43 µg/L in China and Japan. The average lutein and zeaxanthin concentration across all of the sites

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investigated was 25 ± 19 µg/L (Canfield *et al.*, 2003). A survey of commercial infant formulas not currently fortified with lutein demonstrates the presence of low amounts of lutein in current infant formula products worldwide. Infant formula products were analyzed using a method that extracts free lutein and zeaxanthin without saponification. Using this methodology, the mean innate concentration of lutein in different infant formulas, representing unfortified ready to feed (RTF) formulas and powder formulas from Ireland, Singapore, and the Philippines (n=74) was 17 ± 4.6 µg/L with a range of 6.1 to 26.0 µg/L.

FloraGLO Lutein 20% Liquid in Safflower Oil is intended for use as a food ingredient in infant formulas. An overage will be used to account for losses during manufacture and shelf life. Furthermore, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal, and which is approximately the level tested in the infant clinical studies. The proposed maximum total lutein content in finished infant formula product of 250 µg/L is approximately the upper end of the range of the lutein concentrations present naturally in human breast milk as demonstrated by Canfield *et al.* (2003). FloraGLO Lutein 20% Liquid in Safflower Oil provides the optimal source for use in infant formulas, as the chemical form of lutein is the same as in human milk.

To provide a conservative estimate of potential lutein exposure (µg/kg/day), the 90th percentile of dietary lutein intake and the highest potential intake from the proposed products were used. For term infant formula, an estimated daily intake of 780 mL for term infants was used, per Codex and NAS estimated mean intake, and combined with the upper limit of lutein concentration (250 µg/L) to result in a daily intake of 195 µg/day. In contrast, reference weight was based on a female child at the 10th percentile of weight-for-age at the first age increment referenced (generally one half month older than the bottom of the range) using data from the U.S. Centers for Disease Control Growth Charts.

Under the intended conditions of use of FloraGLO Lutein 20% Liquid in Safflower Oil, a low weight-for-age child (10th percentile) who is a heavy consumer (90th percentile) of lutein from other dietary sources and consumes the highest recommended intake of proposed product will take in approximately 230 µg/kg body weight/day. This is equivalent to approximately 10 % of the Joint FAO/WHO Expert Committee on Food Additives' (JECFA) acceptable daily intake (ADI) for lutein, which is set at 2,000 µg/kg/day (JECFA, 2006) and provides approximately a 1,000-fold safety factor compared to the NOAEL of 200 mg/kg body weight/day from the rat study used to establish the JECFA ADI (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002). Whereas lutein exposure attributable solely from the proposed fortification of infant formula is equal to 44 µg/kg body weight/day, or approximately 2.2% of the JECFA ADI for lutein (providing an approximately 5,000-fold safety factor in comparison to the same NOAEL).

DATA PERTAINING TO SAFETY

FloraGLO Crystalline Lutein was previously determined to be GRAS based on its safety, which has been established in toxicological studies in rats, mutagenicity studies conducted with *Salmonella typhimurium*, and is further supported by intervention studies conducted with healthy subjects designed to measure metabolic endpoints. The safety of FloraGLO Crystalline Lutein is also corroborated by additional animal and human studies conducted with other sources of lutein, lutein-rich foods, and lutein supplements. In addition, the safety of lutein and zeaxanthin is well established in the literature based on the historical consumption of eggs and fruits and vegetables where these carotenoids predominate (*e.g.*, green leafy vegetables, such as spinach and kale). Additional studies published subsequent to the determination of the GRAS status of FloraGLO Crystalline Lutein continue to support its safety as a food ingredient.

The safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas has been further demonstrated in two clinical studies conducted in healthy term infants, corroborating the safety of lutein for infant formula use.

Lutein is the major xanthophyll found in human serum, with smaller amounts of zeaxanthin and cryptoxanthin also present (Williams *et al.*, 1998; Boileau *et al.*, 1999). Lutein is also present in breast milk (Gossage *et al.*, 2002), and, together with zeaxanthin, are the only carotenoids found in the macular region of the human retina (Bone *et al.*, 1985, 1988, 1993; Omaye *et al.*, 1997). In general, carotenoids in foods are not known to be toxic, even when ingested in large amounts (*e.g.*, >30 mg carotenoid) (Olson, 1996; Omaye *et al.*, 1997). The safety of lutein and zeaxanthin was addressed by the Institute of Medicine (IOM, 2000) following a review of the available data regarding β-carotene and other carotenoids. The IOM concluded that no adverse effects, other than carotenodermia, have been reported from the consumption of carotenoids, including lutein and zeaxanthin, in foods. Carotenodermia, characterized by a yellowish discoloration of the skin, is a harmless and reversible biological effect of high carotenoid intake (IOM, 2000). No tolerable upper intake levels were established for lutein or zeaxanthin, or for any other carotenoid (β-carotene, α-carotene, lycopene, and β-cryptoxanthin) considered by the IOM (2000).

JECFA completed a safety evaluation of lutein from *Tagetes erecta* L. and assigned a group ADI of 0 to 2 mg lutein and zeaxanthin/kg body weight (JECFA, 2006). The ADI was established based on a no observed adverse effect level (NOAEL) of 200 mg lutein/kg body weight/day (the highest dose tested) reported in a 90-day rat study (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002), to which a safety factor of 100 was applied. This safety factor was considered appropriate given the lack of adverse effects reported at much higher doses than 200 mg/kg body weight/day [up to 1,000 mg/kg body weight/day in a study of developmental toxicity (Edwards *et al.*, 2002)]. The committee noted that there were no adverse effects

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documented in any of the studies of toxicity in animals, including mice, rats, and monkeys, or in humans.

Studies of Absorption and Bioavailability

The absorption and bioavailability of lutein and zeaxanthin was previously reviewed while determining the GRAS status of FloraGLO Crystalline Lutein. The bioavailability of FloraGLO Lutein 20% Liquid in Safflower Oil from a commercial infant formula matrix has likewise been demonstrated in neonatal pigs and infant rhesus monkeys (Kullen, 2006; Kullen and Ramanujam, 2006). Data from both studies indicate a dose-dependent response in the maximal plasma lutein concentration and the lutein area under the curve. The time course of absorption appears to be rapid and is similar to that of other carotenoids (Schweigert *et al.*, 1995). Lower doses may reach peak serum concentrations more rapidly than higher doses and less complete absorption may occur with higher doses. Additionally, there were no significant differences in the serum parameters of the other carotenoids, including β-carotene, when assessed in neonatal pigs.

Data from a prospective, randomized, double-blinded clinical trial conducted in accordance with GCP/ICH guidelines and all applicable regulations indicate that lutein provided from FloraGLO Lutein 20% Liquid in Safflower Oil is also bioavailable in healthy term infants, as was demonstrated by a linear relationship between the log plasma concentration and the log dose of lutein delivered (Wyeth Nutrition, 2006a). A total of 63 infants were randomized to receive the control infant formula (S-26 Gold), S-26 Gold plus 25 µg lutein/L or S-26 Gold plus 200 µg lutein/L *ad libitum* for a period of 5 weeks. In the manufacturing of the formula, an innate amount of lutein, 20 µg/L, was present. To accommodate for manufacturing and shelf life loss, lutein was fortified at 150% of the test label claim, *i.e.* S-26 Gold plus 25 µg lutein/L was fortified with 38 µg lutein/L and S-26 Gold plus 200 µg lutein/L was fortified with 300 µg lutein/L. The final lutein content of each test formula by analysis was 20, 47, and 289 µg lutein/L for S-26 Gold, S-26 Gold plus 25 µg lutein/L, and S-26 Gold plus 200 µg lutein/L, respectively. Statistically significant increases in plasma zeaxanthin, cis-lutein/zeaxanthin, and cis-beta-carotene were observed in the Gold plus 200 µg lutein/L treatment-group when compared to the control group. Treatment with Gold plus 25 µg lutein/L did not result in significant increases in any of the plasma carotenoids when compared to the control.

These data demonstrate that lutein from FloraGLO Lutein 20% Liquid in Safflower Oil is available from the commercial infant formula matrix, and at a fortification level of 200 µg lutein/L, lutein was absorbed into the plasma of healthy term infants.

Toxicological Studies

The Panel reviewed toxicological studies conducted with FloraGLO Crystalline Lutein, as well as safety studies of lutein and zeaxanthin, in general, from other sources (*e.g.*, other marigold

extracts) that were utilized in the previous determination of the GRAS status of FloraGLO Crystalline Lutein. An additional developmental/reproductive toxicity study of lutein from marigold extract conducted to GLP standards in Sprague-Dawley rats was also reviewed.

In 4-week and 13-week toxicological studies conducted with FloraGLO Crystalline Lutein, no adverse effects were reported in terms of body weight gain, organ weights, feed intake, clinical chemistry, or histopathology in Wistar rats (Kruger *et al.*, 2002). Animals were exposed to FloraGLO® Crystalline Lutein in the diet at levels up to 770 mg/kg body weight/day (delivering 640 mg lutein plus zeaxanthin/kg body weight/day) for 4 weeks, or up to 260 mg/kg body weight/day (delivering 210 mg lutein plus zeaxanthin/kg body weight/day) for 13 weeks. The no-adverse-effect levels (NOAELs) for FloraGLO Crystalline Lutein in Wistar rats corresponded to the highest doses tested in each toxicology study; 770 mg/kg body weight/day following 4 weeks of exposure, and 260 mg/kg body weight/day following 13 weeks of exposure.

Additional supportive toxicological studies conducted with rodents have investigated the effects of dietary exposure to lutein and zeaxanthin, from other sources (*e.g.*, marigold extract), for 2 to 8 weeks on body weight, feed intake, and organ weights. No changes in body weight gain, feed intake, liver weight, or spleen weight, and no external signs of toxicity were reported in BALB/c mice following 2 to 4 weeks of dietary exposure to up to 800 mg lutein/kg body weight/day and 11 mg zeaxanthin/kg body weight/day (Chew *et al.*, 1996; Park *et al.*, 1998, 1999). Similarly, no changes in body weights, feed intake, or organ weights were reported in Wistar rats following 16 days of dietary exposure to up to 45 mg lutein/kg body weight/day (Gradelet *et al.*, 1996; Jewell and O'Brien, 1999), and 8 weeks of dietary exposure to 500 mg lutein/kg body weight/day was well tolerated in experimental mice models of atherosclerosis (Dwyer *et al.*, 2001).

Female Sprague-Dawley rats mated between the ages of 10 to 13 weeks were given lutein supplements from Day 6 to 20 of gestation (Edwards *et al.*, 2002; JECFA, 2006). Beadlets containing 10% lutein (from marigold extract, 79% lutein, 5% zeaxanthin) were mixed into the rats' diets to result in doses of 250, 530, and 1,100 mg lutein/kg body weight/day. No effects on pre- or postimplantation, embryo-fetal survival, or sex ratios were reported. In the offspring, there were no adverse effects on the incidence of external or skeletal abnormalities due to treatment with lutein in any of the dose-groups. A few minor visceral abnormalities in each treatment group were reported, but these were not considered to be treatment-related as their incidence was similar to that for historical controls. A slight dose-related increase in the incidence of rudimentary extra lumbar ribs was reported in the intermediate- and high-dose groups; however, this was not considered to be of toxicological significance due to the reversibility of this minor skeletal finding. Based on the above results, it was determined that the NOAEL for embryotoxicity/teratogenicity in Sprague-Dawley rats was 1,000 mg/kg body weight/day, the highest dose tested.

Human Safety Data

The Panel reviewed the clinical data from safety/tolerance studies that were used to determine the GRAS status of FloraGLO Crystalline Lutein. To confirm the safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas, the Panel reviewed two additional studies conducted in healthy term infants. The Panel also reviewed several studies conducted with FloraGLO Crystalline Lutein or lutein from other dietary sources published since the determination of the GRAS status of FloraGLO Crystalline Lutein to corroborate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil.

Wyeth Nutrition (2006b) conducted a prospective, randomized, controlled, double-blind clinical trial with parallel groups of healthy term infants to compare infant growth and the incidence of adverse events, blood chemistry, and eye health in relation to the consumption of control formula *vs.* formula fortified with lutein (Capeding *et al.*, 2006; Wyeth Nutrition, 2006b). Infants (230) aged 0 to 14 days were randomized to receive S-26 Gold or S-26 Gold with 200 µg lutein/L for a period of 16 weeks. Ten infants were withdrawn from the study, 3 by the request of a parent/guardian, and 7 due to adverse events (4 in the S-26 Gold treatment group and 3 in the S-26 Gold with lutein treatment group), leaving 220 infants to complete the study. Lutein intake from the S-26 Gold with lutein formula ranged from a mean intake of 190 µg/day in week 4 to a mean intake of 250 µg/day in Week 12. There were no differences in average daily weight gain, mean rate of change in length, or mean rate of increase in head circumference between the treatment groups at any measurement point. A total of 103 adverse events occurred throughout the course of the study [54 in the S-26 Gold treatment group (52.4%) and 49 in the S-26 Gold with lutein treatment group (47.6%)]. Of these, 10 in the S-26 Gold and 8 in the S-26 Gold with lutein treatment groups were reported to be possibly due to the study formula. Of the 10 possibly treatment-related adverse events in the S-26 Gold group, 4 were rashes, 1 was an incident of irritability, 1 was a food intolerance, and 4 were GI disorders (1 occurrence of abdominal pain, 2 occurrences of loose stools, and 1 occurrence of vomiting). Similarly, of the 8 possibly treatment-related adverse events in the S-26 Gold with lutein group, 3 were rashes, 1 was an incident of irritability, 1 was a food intolerance, and 3 were GI disorders (1 occurrence of abdominal pain, 2 occurrences of vomiting). All adverse events but 2 were considered mild to moderate. Two serious adverse events were reported in the S-26 Gold with lutein treatment group (acute gastroenteritis and bronchopneumonia); however, both were considered unrelated to formula administration and were resolved after infant hospitalization. There were no clinically relevant differences in the mean values between the treatment groups for measures of albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, glucose, phosphorus, or total protein. All mean values fell within the range of laboratory values from Soldin *et al.* (1999), a range that was considered representative of an infant population. The Panel concluded that the infant growth and safety study corroborated the safety of FloraGLO Lutein 20% Liquid in Safflower Oil that was established through the preclinical toxicity studies.

Wyeth conducted a second prospective, randomized, double-blind clinical trial with parallel groups of healthy term infants to compare the effect of feeding S-26 Gold with or without added lutein on infant plasma lutein concentrations (Wyeth Nutrition, 2006a). The study was conducted in accordance with GCP/ICH guidelines and all applicable regulations and also included information regarding the growth and safety of the infants. A total of 63 infants were randomized to receive the control formula (S-26 Gold), S-26 Gold plus 25 µg lutein/L or S-26 Gold plus 200 µg lutein/L *ad libitum* for a period of 5 weeks. In the manufacturing of the formula, an innate amount of lutein, 20 µg/L, was present. To accommodate for manufacturing and shelf life loss, lutein was fortified at 150% of the test label claim, *i.e.* S-26 Gold plus 25 µg lutein/L was fortified with 38 µg lutein/L and S-26 Gold plus 200 µg lutein/L was fortified with 300 µg lutein/L. The final lutein content of each test formula by analysis was 20, 47, and 289 µg lutein/L for S-26 Gold, S-26 Gold plus 25 µg lutein/L, and S-26 Gold plus 200 µg lutein/L, respectively. Infant body weight and weight gain, length and length increase, and head circumference and head circumference increase were not statistically different between the treatment groups after 5 weeks of treatment. When compared to the U.S. Centers for Disease Control (CDC) reference population, values for weight-for-age, weight-for-length, and head circumference-for-age indicated that the infants in the study population had appropriate growth. Nineteen adverse events occurred in 15 infants: 10 in the control group, 6 in the Gold plus 25 treatment group, and 3 in the Gold plus 200 treatment group. None of the adverse events was considered to be serious, all resolved during the study, and none was the cause of discontinuation of formula consumption or removal of the infant from the study. While some of the infants withdrew from the study, this was not considered to be associated with the consumption of the study formula containing lutein.

Human safety data published since the GRAS determination of FloraGLO Crystalline Lutein also continues to support its safety at higher levels than is the subject of this notification. A dietary intervention study conducted in patients with age-related macular degeneration using FloraGLO capsules supports the safety of 10 mg lutein/day for a period of 12 months (Richer *et al.*, 2004). Recently published intervention studies conducted with healthy subjects also support the safety of lutein supplementation at levels up to 6 mg lutein/day for periods of up to 60 days (Kiokias and Gordon, 2003; Morganti *et al.*, 2004; Zhao *et al.*, 2006). There were no adverse effects due to lutein supplementation reported in any of the studies. In addition, Shao and Hathcock (2006) conducted a risk assessment for orally administered lutein and concluded that 20 mg *all-trans* lutein/day should be designated as the observed safe level (OSL). Shao and Hathcock (2006) utilized the methodology from the Council for Responsible Nutrition (CRN) Vitamin and Mineral Safety (Hathcock, 2004) and human clinical trial data to determine the OSL for lutein. Of note in their evaluation of the data was the complete absence of any reports of adverse effects, at any of the doses investigated (which ranged to up to 40 mg/day) in all of the published human clinical trials that were evaluated. The authors also noted that in the U.S., the average background consumption of lutein from food sources is low, and therefore, the OSL need not be corrected for background exposure to lutein from the diet.

In addition, studies investigating the relationship of lutein and zeaxanthin to chronic disease published since the GRAS determination for FloraGLO Crystalline Lutein have reported no adverse relationships between increased serum levels of lutein and zeaxanthin, or dietary intake of lutein and zeaxanthin, and eye health (*i.e.*, risk of AMD, risk of cataracts) (Gale *et al.*, 2003; Kang *et al.*, 2003; Cardinault *et al.*, 2005; Delcourt *et al.*, 2006; Vu *et al.*, 2006), and no adverse relationships were reported between increased serum or plasma levels of lutein and zeaxanthin and the risk for subsequent myocardial infarction (Hak *et al.*, 2003), progression of intima-media thickness of the common carotid arteries (Dwyer *et al.*, 2004), or generalized cardiovascular disease (Sesso *et al.*, 2005), while an inverse relationship was reported between dietary intake of lutein and zeaxanthin and risk for coronary heart disease mortality (Connor *et al.*, 2004) and coronary artery disease (Osganian *et al.*, 2003). Only 1 epidemiological study reported a positive relationship between dietary intake of lutein and zeaxanthin and the risk for myocardial infarction (Kabagambe *et al.*, 2005). This study also reported an increased risk for myocardial infarction with increased levels of lutein and zeaxanthin in adipose tissue; however, the increased risk was only significant in the 5th quintile for both measures of lutein and zeaxanthin (dietary intake and levels in adipose tissue).

Since the GRAS determination for FloraGLO Crystalline Lutein, lutein and zeaxanthin have also been investigated in several other epidemiological studies examining their relationship to such health concerns as Alzheimer's disease, preeclampsia, respiratory infections, osteoporosis, prelabor rupture of the membranes preterm (PPROM), and inflammatory poly arthritis (Rinaldi *et al.*, 2003; Semba *et al.*, 2003; Williams *et al.*, 2003; van der Horst-Graat *et al.*, 2004; van Herpen-Broekmans *et al.*, 2004; Mathews and Neil, 2005; Pattison *et al.*, 2005; Maggio *et al.*, 2006). There were no adverse relationships between plasma levels, serum levels, or dietary intake of lutein and zeaxanthin and risk for adverse health effects except for risk for PPROM. A positive relationship was reported between serum levels of lutein and risk for PPROM (Mathews and Neil, 2005); however, epidemiological studies provide only correlational data and no other reports of an association between increased serum lutein and increased risk for PPROM were identified in the literature. Thus, the Panel considers this correlation to be of little toxicological significance.

SUMMARY

FloraGLO Crystalline lutein has previously been considered GRAS by an Expert Panel of independent scientists for use in food and has been the subject of a successful GRAS notification, GRAS Notice No. GRN 000140. Subsequent to the GRAS notification, JECFA has completed a safety evaluation of lutein from *Tagetes erecta* L. and assigned an ADI of 0 to 2 mg lutein and zeaxanthin/kg body weight (JECFA, 2006). FloraGLO Lutein 20% Liquid in Safflower Oil is currently intended for use as a food ingredient in infant formulas in the U.S. Furthermore, if lutein is added to infant formulas from this source, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37.2 µg/ 100 kcal.

Under the intended conditions use of FloraGLO Lutein 20% Liquid in Safflower Oil, a low weight-for-age child (10th percentile) who is a heavy consumer (90th percentile) of lutein from other dietary sources and consumes the highest recommended intake of proposed product will take in approximately 230 µg/kg body weight/day. This is approximately 10% of the JECFA ADI for lutein (JECFA, 2006) and provides approximately a 1,000-fold safety factor compared to the NOAEL of 200 mg/kg body weight/day from the rat study used to establish the JECFA ADI (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002). Whereas lutein exposure attributable solely from the proposed fortification of infant formula is equal to 44 µg/kg body weight/day, or approximately 2.2% of the JECFA ADI for lutein (providing an approximately 5,000-fold safety factor in comparison to the same NOAEL).

Lutein and zeaxanthin are present in human breast milk. In the largest survey to date of breast milk carotenoids, exposure to lutein from human breast milk was demonstrated to range from 3 to 232 µg/L in individual mothers from around the world (Canfield *et al.*, 2003). The proposed maximum total lutein content in finished infant formula product, 250 µg/L, is approximately the upper end of this range and allows for endogenous lutein and overages to compensate for losses during manufacture and shelf life. . FloraGLO Lutein 20% Liquid in Safflower Oil provides the optimal source for use in infant formulas, as the chemical form of lutein is the same as in human milk.

The Panel reviewed preclinical data and concluded that the 13-week toxicity conducted in Wistar rats at doses up to 260 mg FloraGLO Crystalline Lutein/kg body weight/day (corresponding to 210 mg lutein+zeaxanthin/kg body weight/day) (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002) and the developmental toxicity study conducted in Sprague-Dawley rats at doses up to 1,100 mg lutein/kg body weight/day (Edwards *et al.*, 2002; JECFA, 2006) were central to the GRAS determination of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formula. The Panel also acknowledged that the safety of FloraGLO Lutein 20% Liquid in Safflower Oil was supported by studies conducted using FloraGLO Crystalline Lutein in Fischer 344 rats, tabby cats, and beagle dogs at doses up to 120 mg lutein/kg body weight/day for periods ranging from 8 to 12 weeks (Jenkins *et al.*, 2000; Kim *et al.*, 2000a,b). Additional studies conducted with other sources of lutein and zeaxanthin in mice, rats, and Cynomolgus monkeys at doses ranging from 20 to 800 mg/kg body weight/day for periods of 2 to 52 weeks further support the safety of FloraGLO Lutein 20% Liquid in Safflower Oil (Chew *et al.*, 1996; Gradelet *et al.*, 1996; Park *et al.*, 1998, 1999; Jewell and O'Brien, 1999; Dwyer *et al.*, 2001; Schierle *et al.*, 2002).

Intervention studies conducted in healthy adults indicate no adverse effects at doses of up to 20 mg FloraGLO Crystalline Lutein/day for 42 days (Schalch *et al.*, 2001). Additionally, no adverse effects were reported in patients with retinal degenerative diseases at doses of 10 to 30 mg lutein/day from unspecified sources for periods of 6 to 12 months (Aleman *et al.*, 2001; Duncan *et al.*, 2002; Richer *et al.*, 2004; Bahrami *et al.*, 2006). The absorption and bioavailability of

lutein, provided as FloraGLO Lutein 20% Liquid in Safflower Oil from a RTF commercial infant formula, was confirmed in neonatal pigs, rhesus monkeys, and healthy term infants (Kullen, 2006; Kullen and Ramanujam, 2006; Wyeth Nutrition, 2006a). Data from an intervention study demonstrated that oral exposure to FloraGLO Lutein 20% Liquid in Safflower Oil at a targeted concentration of 200 µg lutein/L in infant formula, resulting in a mean intake ranging from 190 to 250 µg lutein/day, for a period of 16 weeks did not result in any adverse health effects in healthy term infants (Capeding *et al.*, 2006; Wyeth Nutrition, 2006b). The Panel considered the results of the infant study to corroborate the safety of FloraGLO Lutein 20% Liquid in Safflower for use in infant formula.

FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured to food grade specifications from the marigold plant, using the same manufacturing process as that for FloraGLO Crystalline Lutein, and there are no indications that the source of material or method of manufacture contribute to any adverse health effects under the intended conditions of use.

Overall, when viewed in its entirety, the scientific evidence presented herein provides no indication that FloraGLO Lutein 20% Liquid in Safflower Oil will produce adverse effects on human health when consumed under the intended conditions of use in infant formulas.

CONCLUSION

We, the Expert Panel, have independently and collectively critically evaluated the available pertinent scientific evidence, and conclude that FloraGLO Lutein 20% Liquid in Safflower Oil, meeting appropriate food grade specifications and manufactured in accordance with current Good Manufacturing Practice, is Generally Recognized as Safe (GRAS), based on scientific procedures, under the intended conditions of use in infant formulas, as specified herein.

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CONCLUSION

We, the Expert Panel, have independently and collectively critically evaluated the available pertinent scientific evidence, and conclude that FloraGLO Lutein 20% Liquid in Safflower Oil, meeting appropriate food grade specifications and manufactured in accordance with current Good Manufacturing Practice, is Generally Recognized as Safe (GRAS), based on scientific procedures, under the intended conditions of use in infant formulas, as specified herein.

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REFERENCES

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Place of Birth:

Education:

1963	B.A. Harvard University, cum laude, Government
1967	M.D. Columbia University, College of Physicians and Surgeons

Postdoctoral Training
Internship and Residency:

1967-1968	Internship - Medicine, University of Chicago
1968-1969	Junior Assistant Resident - Medicine, University of Chicago
1971-1972	Senior Assistant Resident - Medicine, University of Chicago

Fellowship:

1972-1974	NIH Fellow in Gastroenterology, University of Chicago
1979	Summer Program - "International Food and Nutrition Policies" Massachusetts Institute of Technology

Military Service:

1969-1971	Preventive Medicine Orientation, Brooke Army Medical Center, San Antonio, Texas. Global Medicine, Walter Reed Army Institute of Research, Washington, DC. Epidemiologist, 20th Preventive Medicine Unit, Long Binh, Vietnam, Rank of Major.

Licensure:

1968-1990	
1975-1991	
1981-	
1968	Diplomate National Board of Medical Examiners
1973	Diplomate American Board of Internal Medicine
1977	Diplomate American Board of Gastroenterology
2001	Massachusettts Board of Nutritionists #595

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Academic Appointments:

1974-1975	Visiting Assistant Professor of Medicine, Shiraz University, Shiraz, Iran.
1975-1977	Assistant Professor of Medicine, University of Maryland School of Medicine.
1977-1981	Associate Professor of Medicine, University of Maryland School of Medicine.
1981-1988	Associate Professor of Medicine, Tufts University School of Medicine.
1982-1988	Adjunct Associate Professor of Nutrition,Tufts University School of Nutrition.
1988-	Professor of Medicine and Professor of Nutrition, Tufts University.

Hospital and Research Appointments:

1975-1981	Staff Physician, Department of Medicine, Section of Gastroenterology, University of Maryland Hospital, and Veterans Administration Hospital, Baltimore, MD.
1981-	Director of Human Studies, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA.
1981	Staff Physician Department of Medicine, Sections of Gastroenterology and Clinical Nutrition, New England Medical Center, Boston, MA
1983-	Associate Director, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA (Acting Director 12/83-3/84) (1/85-10/86).
1987-	Senior Scientist, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA.
1988-	Staff Physician, Nutrition Support Service, New England Medical Center, Boston, MA.
1997-	Clinical Laboratory Director, Jean Mayer USDA Human Nutrition Research.Center on Aging at Tufts University, Boston, MA
2001-	Director, USDA Human Nutrition Research Center on Aging, Tufts University

Awards and Honors:

1971	Association of United States Army Award, Global Medicine.
1974	Chicago Society of Gastroenterology, Research Award.
1979-1981	Clinical Investigatorship, Veterans Administration Career Development Program.
1991-1992	United States Department of Agriculture-Agriculture Research Service Outstanding paper of the year.
1994	American College of Nutrition, Grace A. Goldsmith Award
1995	Ethyl Austin Martin Distinguished Lecturer in Human Nutrition
1997	George Randolph and Patricia Scott Award, Mayo Clinic.
1997	Willard Visek Award, University of Illinois

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1999	Robert H. Herman Award, American Society of Clinical Nutrition
1999	Distinguished Lecturer - American College of Physicians, "Nutrition Update."
1999	Charles Brown Award in Geriatrics, Temple University.
1999	Oliver Smith Award, New England Medical Center

Major Committee Assignments - National and International:

1974-1979	Consultant, Food and Drug Administration, Panel on Review of Vitamin, Mineral and Hematinic Drug Products.
1978	Consultant, National Iranian Cancer Foundation, Tehran, Iran.
1980-1984	Member, Committee on Nutrition Research, American Society for Clinical Nutrition.
1980-1984	Chairman, Council on Nutrition and Gastroenterology, American College of Nutrition
1981-1989	Secretary-Treasurer, American College of Nutrition.
1981-1995	Board of Directors, American College of Nutrition
1982	Ad hoc Member, National Digestive Diseases Advisory Board.
1983-1988	Member, Council on Aging, American Gastroenterological Association.
1984	Member, U.S./Japan Malnutrition Panel, ad hoc Advisory Committee.
1984-1985	Chairman, Program Committee, American Society of Clinical Nutrition.
1984-1985	Chairman, Council of Gerontology, American College of Nutrition.
1985	Ad hoc Member, Federation of American Societies for Experimental Biology Expert Panel on Vitamin A Nutriture.
1985	Member, Advisory Panel on Nutrition and Electrolytes, United States Pharmacopeia Convention, Inc.
1985-1994	Member, International Advisory/Technical Board, Center for Studies of Sensory Impairment, Aging, and Metabolism, Guatemala City, Guatemala
1986-1989	Governing Board, GI Gerontology Research Group, American Gastroenterology Association (Chairman 1989)
1987-1991	National Dairy Council Scientific Advisory Board (Chairman 1990).
1987	Ad hoc Member, Committee on Parenteral and Enteral Nutrition Standards for Long Term Nutrition Care. American Society of Parenteral and Enteral Nutrition.
1987	Member, American Institute of Nutrition Nominating Committee
1988-1994	Chairman, Agriculture Research Service, US Department of Agriculture, Human Subjects Research Committee
1989	Member, NIH Consensus Development Panel on Therapeutic Endoscopy and Bleeding Ulcers
1989	Advisory Board, Post Center for Nutrition and Health Education
1989-1992	Member, Graduate Nutrition Education Committee, American Institute of Nutrition (AIN).
1989-1999	Speakers Bureau, National Dairy Council Visiting Professorship Program in Nutrition.

1990	Nominating Committee, American Gastroenterology Association-Growth, Development and Nutrition Section.
1990-1992	Pretest Committee, American Board of Internal Medicine.
1991	UNICEF Consulting Team-Southern Iraq.
1992-1994	The American Society for Clinical Nutrition, Council Liaison to the Publications Management Committee.
1992-1995	Councilor to the American Society for Clinical Nutrition.
1994	Consultant, Biosphere 2.
1995	Program-Chair, American Society for Clinical Nutrition Annual Meeting.
1995-2000	Member, Steering Committee and Meeting Chairman (1997), Carotene Research Interaction Group (CARIG).
1995-1998	Councilor to the American College of Nutrition.
1996	Consultant on Nutrition Fraud - Federal Trade Commission.
1996	Committee on Dietary Guidelines, American Cancer Society.
1996-1998	American Dietetic Association - Older Americans Campaign Expert Advisory Committee.
1996-2001	Board Member, External Advisory Committee, University of Illinois at Urbana-Champaign, University of Nutritional Sciences.
1996-1997	FANSA Ad Hoc Working Group on Dietary Supplements. American Institute of Nutrition.
1996-1998	Panel Member on Folate and other B Vitamins, Food and Nutrition Board - Institute of Medicine, National Academy of Sciences.
1996-1999	United States Department of Agriculture Scientific Review Board for the Lower Mississippi Delta Nutrition Intervention Research Initiative (Delta NIRI).
1997-1999	International Scientific Committee (ISC) - Auvergne Human Nutrition Research Center. Clermont-Ferrand, France.
1997-1999	Advisory Board - Genetic Studies on Vitamin A: Metabolism and Function, Columbia University College of Physicians & Surgeons.
1998	Member, Joint WHO/Tufts University Consultation on Nutrition Guidelines for the Elderly.
1998-	Member, Awards Committee, American College of Nutrition
1998-2000	Chairman, Steering Committee, Carotene Interaction Group (CARIG)
1998-2000	Chairman of Panel on Micronutrients, Food and Nutrition Board, Institute of Medicine, National Academy of Science.
1998	Consultant National Technology Transfer Committee, Boston, 1998
1999	Member, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Co-Vice Chair (2000).
1999	Member, U. S. Administration on Aging, Nutrition 2030 Expert Advisory Council
1999-	Member, AGA Task Force on Geriatrics
1999-	Member, Food and Drug Administration's Food Advisory Committee
2000-	Board of Directors, Life Sciences Research Office. Inc.

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2000-	Chairman, Expert Committee on Nutrition and Electrolytes, U.S. Pharmacopeia and Member, Nutrition and Electrolytes Advisory
2001-	Golden Rice Humanitarian Advisory Board
2001-2002	Vice-President, American Society of Clinical Nutrition
2002-	President, American Society of Clinical Nutrition
2002-2005	American Gastroenterology Asssociation Committee on Public Affairs and Advocacy
2002-2005	International Carotenoid Society
2002-	Member, DRI Standing Committee, IOM, NAS
2002	NIH (NIDDK) Boundary Team member
2002-	Sight and Life Research Institute, Johns Hopkins School of Medicine Board

Regional and Local:

1972-1974	Hyde Park Kenwood Community Conference, Chicago, IL.
1976-1980	Member, Committee on Human Nutrition Education, University of Maryland School of Medicine, Baltimore, MD (Chairman, 1980-1981).
1976-1981	Member, Nutrition Care Committees,VA Medical Center and University of Maryland Hospital, Baltimore, MD.
1980-1981	Course Director, Basic Human Nutrition,University of Maryland School of Medicine, Baltimore, MD.
1981-1988	Member, Committee on Human Nutrition Education, Tufts University School of Medicine, Boston, MA.
1981-1988	Member, Tufts New England Medical Center Clinical Study Unit Advisory Committee, Boston, MA
1983-1988	Member, Board of Advisors, Georgia Institute of Human Nutrition
1983	Co-Director, Clinical Nutrition Course, Tufts University School of Medicine, Boston, MA, and School of Nutrition Science and Policy, Medford, MA.
1985-1988	Member, Famine Policy Center Committee, Tufts University School of Nutrition Science and Policy.
1985-1988	Member, Health Sciences Campus Planning Committee, Tufts University School of Nutrition Science and Policy.
1985-1987	Board of Directors, Frances Stern Nutrition Center, Tufts New England Medical Center Hospitals, Boston, MA.
1985-	Chairman, Human Studies Committee, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA.
1991	Chairman, Task Force on Nutrition Organization at Tufts University School of Nutrition Science and Policy, Medford, MA.
1993	Chairman, Scientific Appointments and Promotions Committee, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA and Tufts University School of Nutrition Science and Policy Medford, MA.

1994-	Member, Finance and Fund Raising Committee, Tufts University School of Nutrition Science and Policy, Medford, MA. Chairman, 2000
1994-1999	Chairman, Committee on Committees, Tufts University School of Nutrition Science and Policy, Medford, MA., Member, 2000
1999	Chairman, University-Wide Aging Initiative, Tufts University
2000	Faculty Representative,Tufts University Trustees' Development Committee

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Editorial Boards:

1976-	Contributing Editor - Nutrition Reviews (Associate Editor since 1985)
1982-1989	Editorial Board - Journal of the American College of Nutrition
1983-1986	Editorial Board - Tufts University Health Science News
1983-	Editorial Board - Tufts Health and Nutrition News Letter
1986-1991	Advisory Board Member - Contemporary Issues in Clinical Nutrition
1989-1993	Editorial Board - Rx Nutrition (Physician Continuing Education Program)
	1989-Editorial Board - Age and Nutrition
1997-	Editor-in-Chief - Nutrition and Clinical Care
1997-	Editorial Board - Nutrition Today
1998-	Editorial Board - American Journal of Clinical Nutrition
1998-	Editorial Board - Cyberrounds Nutrition Website
1998-	Editorial Board - Nutrition Commentator Website
1998-	Editorial Board - European Journal of Nutrition
1998-	Associate Editor – Digestive Health and Nutrition
1999-	Co-Editor - Present Knowledge of Nutrition, 8th Edition
2001-	Associate Editor, American Journal of Clinical Nutrition
2002-	Editor-in-Chief – Nutrition Reviews

Memberships:

1978-	American College of Nutrition (Fellow)
	American Society of Clinical Nutrition
1979-1983	International Association for the Study of the Liver
1979-	American Society for Nutrition Sciences
1981-	American Gastroenterological Association
1982-1986	Massachusetts Medical Society
1982-	American College of Physicians (Fellow)
1990-	Society for International Nutrition Research
1999-	American Aging Association
2002-	Association for Patient-Oriented Research

Thesis Advisor:

1979-1981	Michelle Garrett-Laster, MS in Nutrition, University of Maryland, College Park, MD. "The role of vitamin A deficiency in causing impaired taste and olfaction among patients with chronic liver disease".
1981-1986	Daniel Bankson, Ph.D. in Nutritional Biochemistry and Metabolism, Massachusetts Institute of Technology, Boston, MA "The effect of protein malnutrition and aging on visual function".
1983-1987	Stephen Krasinski, Ph.D. in Nutritional Science, Tufts University, Medford, MA. "Vitamin A absorption and hepatic clearance as a function of aging."
1987-1992	William Boisvert, Ph.D. in Nutritional Science, Tufts University, Medford, MA. "Riboflavin requirements of elderly humans".

1988-1992	Xiang-Dong Wang, Ph.D. in Nutritional Science, Tufts University, Medford, MA. "Intestinal carotene metabolism in the ferret".
1990-1995	Jing Yu, PhD in Nutritional Science, Tufts University, Medford, MA. "Beta carotene chemoprevention in ferret - cancer model".
1991-1995	Nadine Sahyoun, Ph.D in Nutritional Science, Tufts University, Medford, MA."Nutritional predictors of mortality".
1992-1998	Ming-Fen Lee, Ph.D. in Nutritional Science, Tufts University, Medford, MA."Regulation of the human lactase gene".
1994-1999	Elmi Tibaduiza, Ph.D. in Nutritional Science, Tufts University, Medford, MA. "Beta apo carotenoids and gene expression".
1996-	Nalinee Chongviriyaphan, "Retinoids and Signal Transduction."
2001-	Ali Kashani-Farid, "Genetic determinants of low HDL levels in the Iranian population and their correlations with oxidizability of both aqueous and lipid compartments of the plasma.

PUBLICATIONS - ORIGINAL JOURNAL ARTICLES

1. Sowell JM, Russell RM, Ionata VJ. Tuberculin tine test conversion among United States Army enlisted personnel in Vietnam. Military Medicine 1973;138(2):96-98.

2. Russell RM, Multack R, Smith V, Krill A, Rosenberg IH. The use of dark adaptation as a reversible indicator of subclinical vitamin A deficiency in patients with chronic small intestinal disease. Lancet 1973;2:1161-1164.

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Ribaya-Mercado JD, Solomons NW, Medrano Y, Bulux J, Dolnikowski G, Russell RM, Wallace CB. Sequential Application of Two Forms of Deuterium-Labeled Retinyl Ester Whole-Body-Dilution Tracers to Monitor the Impact of One-Year of Sugar Fortification with Vitamin A on Vitamin Status of Nicaraguan Schoolchildren (XXI International Vitamin A Consultative Group (IVACG) 2003 to be presented).

Liu C, Lian F, Russell RM and Wang X-D. Effects of Lycopene Supplementation on Plasma Levels of Insulin-Like Growth factor-Binding Protein 3 and Lung Suqamous Metaplasia in Smoke-Exposed Ferrets. AACR Annual International Conference "Frontiers in Cancer Prevention Research", October 14-18, 2002, Boston, MA (to be presented).

Hu KQ, Liu C, Russell RM and Wang X-D. Cigarette Smoke Exposure Up-Regulate Carotene Excentric Cleaving Enzyme, Carotene-9′,10′-Monooxygenase, in Lungs of Ferrets with or without Lycopene Supplemenation. AACR Annual International Conference "Frontiers in Cancer Prevention Research", October 14-18, 2002, Boston, MA (to be presented).

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EDUCATION

1970 Ph.D., Toxicology and Pharmacology, Queen's University, Kingston, Ontario, Canada
1967 M.Sc., Nutrition, McGill University, Montreal, Canada
1962 B.Sc., McGill University, Montreal, Canada

ACCREDITATION

1999 Fellow of The Academy of Toxicological Sciences
1988 Fellow of Royal College of Pathologists, London, England

EMPLOYMENT HISTORY

2006-Present **CANTOX Health Sciences International,** Mississauga, Ontario. Executive Vice President and Senior Scientific Consultant

1999-Present **University of Toronto,** Professor, Department of Nutritional Sciences, Faculty of Medicine and Associate Director, Program in Food Safety, Nutrition and Regulatory Affairs.

1999-2006 **CANTOX Health Sciences International,** Mississauga, Ontario. President.

1985-1999 **CanTox Inc.,** Consultants in Health and Environmental Sciences, Mississauga, Ontario. Consultant Toxicologist & Principal.

1983-1992 **Canadian Centre for Toxicology,** Guelph, Ontario, Canada. Director

1981-1983 **Health and Welfare, Canada,** Food Directorate, Health Protection Branch. Ottawa, Canada. Director General.

1976-1981 **Health and Welfare, Canada,** Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Ottawa, Canada. Director.

1975-1976 **Health and Welfare, Canada,** Bureau of Chemical Safety, Health Protection Branch, Ottawa, Canada. Chief, The Division of Toxicology.

1974-1976 **Health and Welfare, Canada,** Bureau of Chemical Safety, Health Protection Branch. Ottawa, Canada. Section Head, The Division of Toxicology.

1963-1974 **Health and Welfare, Canada,** Health Protection Branch, Ottawa, Canada. Research Scientist.

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COMMITTEE MEMBERSHIPS

2006-Present	Chair, Faculty of Agriculture and Environmental Sciences Advisory Board, McGill University
2005-Present	Member at Large, Executive Committee, Toxicology and Safety Evaluation Division, Institute of Food Technologists
2004	Chairman, Panel Member, The Tooth Whitening Products Task Force of COLIPA, The European Cosmetics Industry Association
2002-2006	Technical Advisory Committee, World Food Program (WFP), The Food Aid Organization of the United Nations
2001	Chairman, Safety Assessment of Foods Derived from Genetically Modified Microorganisms. World Health Organization, Headquarters, Geneva, Switzerland – September 2001
2000-Present	Member, Georgetown Dialogue Science Council, Georgetown University Center for Food and Nutrition Policy (CFNP)
2000-Present	Consultant, FEMA Expert Panel
1999	Center for Food Safety and Applied Nutrition (CFSAN) Research Program Committee, Food and Drug Administration
1998-2001	Member, Minister's Advisory Board, Canadian Food Inspection Agency
1996-2002	Chairman, Institute of Medicine, Subcommittee on Upper Safe Reference Levels of Nutrients
1996	Member, Ad Hoc Expert Panel, Life Sciences Research Office, Federation of American Societies for Experimental Biology (FASEB)
1993-Present	Member FAO/WHO Expert Committee on Food Additives
1989	Chairman, Expert Group to Develop a Threshold of Regulation for Indirect Food Additives
1989-1991	Member, Scientific Committee, International Food Biotechnology Council
1985-2000	Member, FEMA Expert Panel
1985	Member ILSI-NF, Nutrition and Safety Committee (FNSC)
1985	Member, NAS, Committee on Carcinogenicity of Cyclamates.
1984	Member, Committee on Food Chemicals Codex.
1983-1984	Member, Panel of Chemical Carcinogenesis Testing and Evaluation (National Toxicology Program)
1983	Member, The Nutrition Foundation Project on the Use of Mouse Hepatoma Data.
1981-1983	Expert Committee on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, The Nutrition Foundation, Inc.
1981-1982	Expert Advisory Committee to The Nutrition Foundation, Inc., on the Assessment of the Safety of Lead and Lead Salts in Foods.
1981	Chairman, International Committee on Hazards Associated with Dioxin in the Great Lakes.
1981	Chairman, WHO Ad Hoc Meeting on the Future of Joint Expert Committees in the Context of the International Program on Chemical Safety, Geneva.
1980-1983	Chairman, Health Protection Branch/Food Industry Liaison Committee.
1980-1983	Chairman, Interdepartmental Committee on Canning Regulations.
1980	Member, Federal Interdepartmental Salmonella Committee.
1980	Member, Senior Level Committee (U.S., U.K., Canada).
1980	Member, International Life Sciences Institute Experts in Pathology and Toxicology.
1980	Member, Technical Committee: WHO International Program on Chemical Safety.
1978-1980	Expert Committee on Food Safety - Agriculture Canada
1978-1980	Food Safety Council, Social and Economic Committee.
1978-1979	U.S. National Academy of Sciences, Subcommittee on Risk Assessment - Safe Drinking Water Committee.
1978	Chairman, Tripartite Toxicology Committee (U.S., U.K., Canada).
1977-1981	International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC), subcommittee 3.
1977-1979	U.S. National Cancer Institute, Cause and Prevention Scientific Review Committee.
1976-1984	WHO/FAO Joint Expert Committee on Food Additives.
1976-1980	Food Safety Council, Toxicology Committee.

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1976-1979	Canadian Council on Animal Care.
1976-1979	Interdepartmental Committee on Toxicology Needs in Canada.
1976-1978	National Research Council Task Force on Mercury and Captan.
1975-1976	U.S. National Academy of Sciences Committee on Toxicology
1975-1976	WHO/FAO Committee on Criterion Documents on the Toxicology of Environmental Chemicals.

EDITORIAL RESPONSIBILITIES

1982-1996	Editorial Board	Journal of the American College of Toxicology
1979-1991	Advisory Board	Neurotoxicology
1978-1989	Editorial Board	Journal of Environmental Pathology and Toxicology

PROFESSIONAL AFFILIATIONS

Professional Society Memberships:

Member, Society of Toxicology
Member, Toxicology Forum
Member, Society of Toxicology of Canada
Member, American College of Toxicology
Member, Institute for Risk Research
Member, International Society of Regulatory Toxicology and Pharmacology
Member, Institute of Food Technologists

Contributions to Professional Societies:

2004-Present	The Academy of Toxicological Sciences, Board or Directors
1981	Professional Standards Evaluation Board in General Toxicology, Academy of Toxicological Sciences
1978-1979	Society of Toxicology, Nominating Committee
1978-1979	Society of Toxicology, Finance Committee
1976-2006	Toxicology Forum, Inc., Board of Directors

AWARDS

2006	Joint FAO/ WHO Committee on Food Additives (JECFA) – on the 50th Anniversary of the Committee for his long service as an Expert Advisor to the Secretariat.
2005	Institute of Food Technologists "Bernard L. Oser Food Ingredient Safety Award" for his contributions to the scientific knowledge of food ingredient safety or leadership in establishing principles for food ingredient safety evaluation or regulation.
1998	International Society of Regulatory Toxicology and Pharmacology's International Achievement Award for his guiding role as Chairman of the Expert Panel of Members – An Interpretive Review of the Effects of Chlorinated Organic Chemicals.
1975	Society of Toxicology "Achievement Award" for outstanding contributions to the science of toxicology by an individual 35 years of age or younger.

SCIENTIFIC PUBLICATIONS AND MONOGRAPHS

Munro, I.C., Taylor, S.L., Veldkamp, P., and van Dissel, J.T. 2007. The Safety of Whey Protein Concentrate Derived from the Milk of Cows Immunized Against *Clostridium difficile*. Accepted for publication in Reg Toxicol Pharmacol.

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PRESENTATIONS

Munro, I.C. and Roberts, A.S. 2006. How to Market Your Functional Foods and Nutraceuticals in the US, Canada, Europe and Japan. CANTOX Seminar co-sponsored by the Canadian Embassy, November 29, held at the Canadian Embassy in Tokyo, Japan.

Munro, I.C. 2006. Historical Perspective of Post-Market Monitoring. Presented at ILSI Europe – Workshop on The Application of Post-Market Monitoring to Novel Foods, Barcelona, Spain, November 15-17.

Munro, I.C. 2006. Talk 1: Regulation of Food Ingredients in Canada; Talk 2: The Approval Process of the Joint FAO/WHO Expert Committee on Food Additives (JECFA); Talk 3: Regulatory Challenges for Food Ingredients in Asia; Talk 4: Key Elements In Developing a Global Regulatory Strategy. Presented in Cooperation with the Institute of Food Technologists (IFT) Continuing Education Program, Fall 2006 Short Courses, Scottsdale, Arizona, October 5-6.

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Munro, I.C. 2006. The Maximized Survey-Derived Daily Intake (MSDI) as a Practical and Conservative Method to Estimate Intake of Flavouring Substances. Presented at the FEMA Expert Panel Meeting, Sorrento, Italy, September 16-18.

Munro, I.C. 2006. Thresholds for Food Flavorings Used by JECFA. Presented at FDA Grand Rounds on Thresholds: Crossing the Thresholds of Tomorrow, College Park, Maryland, June 8.

Munro, I.C. 2006. New Developments in Flavor Science. Flavor and Extract Manufacturers Association, 97th Annual Convention, Sunny Isles Beach, Florida, May 9.

Munro, I.C. 2006. The Canadian Food Regulatory System – It's Strengths and Limitations. Presented at Smarter Regulations of Foods in Canada Conference, Ottawa, Ontario, March 21-22.

Munro, I.C. 2006. Talk 1 - Can the Concept of Thresholds Help? Promises and Problems. Talk 2 - Regulatory Differences in Risk Assessment Requirements For Food Products From Biotech And Conventionally Bred Crops. The ILSI/ILSI North America Annual Meeting, San Juan, Puerto Rico, January 16-18.

Munro, I.C. 2005. Assessing the Safety of Biotechnology-Derived Foods. Korean Food and Drug Administration, Seoul, Korea, December 2.

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Munro, I.C. 2005. Talk 1 - Thresholds of Toxicological Concern and Safety Evaluation of Food Ingredients. Talk 2 - The Threshold of Toxicological Concern Concept. ECB Workshop on Chemical Similarity and TTC Approaches, Ispra, November 7-8.

Munro, I.C. 2005. Safety Evaluation of Ferric Sodium Ethylenediaminetetraacetate (NaFeEDTA) For Use as a Source of Iron in Foods. Symposium on the Role of NaFeEDTA in Iron Deficiency Control, Beijing, China, November 3.

Munro, I.C. 2005. Talk 1 - Nutritional Assessment of GM Foods. Talk 2: Assessing the Safety of Nutritionally Enhanced GM Foods. Presented at Foods Derived from GM Crops: Issues for Consumers, Regulators and Scientists, New Delhi, India, September 26-27.

Munro, I.C. 2005. The Feasibility of Postmarket Monitoring of Foods Derived Through Biotechnology to Identify Effects on Human Health. Presented at EUROTOX 2005, Cracow, Poland, September 12-13.

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Munro, I.C. 2003. 1. The JECFA Procedure for the Safety Evaluation of Flavoring Substances. 2. The FEMA GRAS Program for Flavors. Presented at the Safety Assessment of Flavors – Indonesia Roundtable, Jakarta, Indonesia, December 9.

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Munro, I.C. 2003. Managing and Interpreting Vitamin and Mineral Science. Presented at the EANS one-day workshop on "Risk Assessment and Beyond: Vitamins and Minerals", April 30, Brussels, Belgium.

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Munro, I.C. 2003. Current Dietary Supplement Safety Issues. Presented at the Food and Drug Law Institute's Conference: Dietary Supplements...At a Crossroads, January 16-17, Washington, D.C.

Munro, I.C., Hlywka, J., and Reid, J. 2003. Determining Unintended Health Effects of Biotechnology Derived Foods. Presented at the Workshop of the Committee on Identifying and Assessing the Unintended Effects of Genetically Engineered Foods on Human Health, The National Academies, January 7, Wash., D.C.

Munro, I.C. and Roberts, A.S. 2002. Functional Foods and Nutraceuticals - How to Launch Nutraceuticals on the U.S. Market. A workshop conducted by Dr. Ian Munro and Dr. Ashley Roberts in association with Archimex, November 26, Paris, France.

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Munro, I.C. 2002. The Precautionary Principle and the Scientific Risk Assessment Process. Presented at the International Society of Regulatory Toxicology and Pharmacology Meeting, June 21-22, Arlington, VA.

Munro, I.C. 2002. OECD/FAO Substantial Equivalence Framework for Whole Food Safety Assessment. Presented at the 41st Annual Meeting & ToxExpo, March 17-21, Nashville, TN.

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Munro, I.C. 2000. Safety Evaluation of Foods Derived from Genetically Modified Crops. Presented at the Brazilian Association of Food Industries' "Safety Assessment of Biotechnology Derived Foods" seminar, December 5, 6 & 7, São Paulo, Brazil.

Munro, I.C. 2000. Risk Assessment of Packaging Materials. Presented at the 2nd International Symposium on Food Packaging. Ensuring Safety and Quality of Foods, November 8-10, Vienna, Austria.

Munro, I.C. 2000. EUROTOX/SOT Debate. An evaluation demonstrating that foods derived from GM crops are as safe as their traditional counterparts is an appropriate paradigm for assessing the safety of genetically modified foods. For the motion: Ian C. Munro (SOT). EUROTOX 2000, XXXVIII European Congress of Toxicology, September 17-20, London, England.

Munro, I.C. 2000. Safety of Foods Produced by rDNA Technology. Presented at the Institute of Medicine/Food and Nutrition Board Meeting, July 20, Woods Hole, MA.

Munro, I.C. 2000. Society of Toxicology/EUROTOX Debate Presentation. 2000 Society of Toxicology Annual Meeting, March 21, Philadelphia, PA.

Munro, I.C. 2000. Developing Integrated Scientific & Regulatory Strategies, Resolving Complex Scientific Issues, and Facilitating Timely Regulatory Approvals. TNO Nutrition and Food Research Institute, February 29, Zeist, The Netherlands.

Munro, I.C. 2000. Applying a Threshold of Regulation Concept to the Safety Evaluation of Packaging Materials. Nutripack Food & Beverage Packaging Congress, January 26-27, Paris, France.

Munro, I.C. 1999. Key Safety Issues in Bringing a Functional Food or Nutraceutical to Market. Nutraceutical Opportunities Summit, December 8-9, Toronto, Ontario.

Munro, I.C. 1999. The Concept of Thresholds in Safety Assessment. ILSI Europe Workshop on Threshold of Toxicological Concern for Chemical Substances Present in the Diet, October 5-6, Paris France.

Munro, I.C., Bechtel, D., Schinkel, H., and McColl, D. 1999. Functional Foods: International Comparisons of the Scientific and Regulatory Attributes Affecting Product Development and Market Access.

Munro, I.C., McColl, D., Bailey, R., Coutrelis, N., and Schinkel, H. 1999. Special Forum: International Regulatory Issues in Marketing Functional Foods: Barriers and Opportunities. Institute of Food Technologist's Annual Meeting, July 24-28, Chicago, IL.

Munro, I.C. 1999. 1) Safety Assessment of Process Flavors. 2) Perspective of the Food and Nutrition Board's Subcommittee on Upper Reference Levels of Nutrients. 1999 Annual Summer Meeting of The Toxicology Forum, July 12 - 16, Aspen, Colorado.

Munro, I.C. 1999. The Crucial Role of Safety and Efficacy Principles for Nutraceuticals, Functional and Medical Foods - Nutraceutical, Functional & Medical Foods Conference, May 6-7, Toronto, Ontario.

Munro, I.C. 1999. Assessing the Safety of Flavoring Substances. Flavor and Extract Manufacturers' Association of the United States - 90th Annual Convention, May 2-5, Palm Beach, Florida.

Munro, I.C. 1999. Concepts in Safety Evaluation of HPV Food Substances. Vision 20/20 Workshop: TestSmart - A Humane and Efficient Approach to SIDS Data, April 26-27, Fairfax, Virginia.

Munro, I.C. 1999. Effect of Intake Level on the Safety Evaluation of Flavoring Substances. Scientific Committee on Food - DGIII - DGXXIV Joint Workshop on Chemically Defined Flavouring Substances, March 25, Brussels, Belgium.

Munro, I.C., Berndt, W., Borzelleca, J., Flamm, G., Lynch, B., Kennepohl, E., Bär, A., and Modderman, J. 1999. Erythritol: An Interpretive Summary of the Biochemical, Metabolic, Toxicological and Clinical Data. Poster presentation at the Society of Toxicology Annual Meeting, March 14-18, New Orleans, Louisiana.

Munro, I.C. 1998. FNB Model for Development of Tolerable Upper Intake Levels. Presented at the European Toxicology Forum Meeting, May 13, Brussels, Belgium.

Munro, I.C. 1998. International Perspectives for Ensuring Safe Food. Presented at the Institute of Medicine, April 29, Washington, D.C.

Munro, I.C. 1997. The Development of Tolerable Upper Intake Levels for Nutrients. Presented at the Insight Information Inc. Conference - New Nutrition Recommendations - Capitalizing on New Opportunities, December 11, Toronto, Ontario.

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Munro, I.C. 1997. A Model for the Development of Upper Levels. Presented at the Dietary Reference Intakes Conference - New Vision, New Challenges, Ontario Institute for Studies in Education, November 24, Toronto, Ontario.

Munro, I.C. 1997. A Model for the Development of Tolerable Upper Intake Levels for Nutrients. Presented at the Calcium Workshop, Program in Food Safety, University of Toronto, October 30, Toronto, Ontario.

Munro, I.C. 1997. A Model for the Development of Tolerable Upper Intake Levels for Nutrients. Presented at Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride Workshop, Institute of Medicine, September 23, Washington, D.C.

Munro, I.C., Daniels, J.M., and Lynch, B.S. 1997. A Review of the Safety of Vitamin B6 (Pyridoxine): Implications for Determining the Safe Upper Intake from Dietary Supplements. Presented at Vitamin B6: New Data, New Perspectives, Council for Responsible Nutrition, September 8, London, England.

Munro, I.C., and Kroes, R. 1997. Application of a Threshold of Regulation Concept in the Safety Evaluation of Certain Flavoring Substances. Presented at the Forty-ninth Meeting of the Joint FAO\WHO Expert Committee on Food Additives, June 17-26, Rome, Italy.

Bechtel, D., Locke, L., and Munro, I.C. 1997. Need for Scientific Substantiation for Functionality of Food Components for Health Promotion. Presented at the ILSI N.A. Workshop - The Future of Functional Foods for Health Promotion: A Public Health Opportunity, June 4-5, Washington, D.C.

Munro, I.C. 1997. Need for Scientific Substantiation for Functionality of Food Components for Health Promotion. Presented at the ILSI N.A. Workshop - The Future of Functional Foods for Health Promotion: A Public Health Opportunity, June 4-5, Washington, D.C.

Munro, I.C. 1997. 2,4-D - Safety and Exposure. Presented to Poisons Centre staff, academic pharmacology staff and postgraduate students at the University of Dunedin, March 13, Dunedin, New Zealand.

Munro, I.C. 1997. 2,4-D - Safety and Exposure. Presented to toxicologists and occupational health specialists from the New Zealand Ministry of Agriculture and Ministry of Environment, March 12, Wellington, New Zealand.

Munro, I.C. 1997. Development of a Procedure for the Safety Evaluation of Flavouring Substances. Presented at the International Symposium on Flavours and Sensory related Aspects, March 6-7, Cernobbio (Como), Italy.

Munro, I.C. 1996. 1) Current Issues in the Evaluation of the Safety of Food and Food Ingredients. 2) Issues in the Safety Assessment of Carbohydrate/Fat Substitutes. Presented at the ASCEPT Toxicology Workshop, June 17-18, Canberra, Australia.

Munro, I.C. 1995. Interpretive Review of the Potential Adverse Effects of Chlorinated Organic Chemicals on Human Health and the Environment. Report of an Expert Panel. Presented at Dioxin 95, 15th International Symposium on Chlorinated Dioxins and Related Compounds, August 21-25, Edmonton, AB.

Munro, I.C. 1995. The Safety Evaluation of Flavoring Substances: The GRAS Process. Presented at the Second Workshop - Harmonization and Food Safety, April 20-21, Hong Kong.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1994. Macronutrient Substitutes: Safety Factor Alternatives and Human Mimetic Models. Thirty-third Annual Meeting of Society of Toxicology, Dallas, TX.

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Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1994. Macronutrient Substitutes: Alternatives to Traditional Safety Testing. Annual Meeting of Institute of Food Technologists, Atlanta, Georgia.

Munro, I.C. 1993. Harmonization of Conventional Toxicology Studies - A Commentary. Presented at ILSI Conference on RedBook II, December 16, Washington, DC.

Munro, I.C. 1993. The Exposure and Toxicity of 2,4-D. Presented at The Toxicology Forum, Aspen, CO. (July).

Munro, I.C. 1992. Novel Foods, Workshop on Novel Foods and Novel Food Processes. Presented at the Program in Food Safety, Nutrition and Regulatory Affairs, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto. Toronto, ON. (November).

Munro, I.C. 1992. Toxicology and Drug Development: Managing the Issues. Presented to Ciba-Geigy Canada Ltd., Mississauga, ON. (October).

Munro, I.C. 1992. Adverse Effects and Indoor Air Pollution. Presented at the Thirteenth Annual Meeting of the American College of Toxicology, San Francisco, CA. (October).

Munro, I.C. 1992. Toxicology of Benzoyl Peroxide. Presented at The Toxicology Forum, Aspen, CO. (July).

Munro, I.C., Borzelleca, J.F., and Squire, R.A. 1991. The Safety of Xylitol for Use in Food. Report of an Expert Panel.

Munro, I.C. 1991. Food Safety. Presented at a Food Safety Seminar Embassy of the United States, Ottawa, Ontario, Canada.

Munro, I.C., and Orr, J. 1991. Dioxins in Paper Products. Canadian Paediatric Society Workshop on Infant Diapers.

Munro, I.C., and Orr, J. 1991. The Saccharin Lesson. Presented at the Symposium on Chemical Carcinogenesis: The Relevance of Mechanistic Understanding in Toxicological Evaluation. Berlin, Germany.

Munro, I.C. 1991. Impact of Agricultural Activities on Health Risks From Drinking Water. Presented at the Interdisciplinary Symposium on Agriculture and Water Quality Centre for Soil and Water Conservation. University of Guelph, ON.

Munro, I.C. 1990. Scientific Aspects of the IFBC Report. Presented to the Toxicology Forum. Washington, DC.

Munro, I.C., and Hall, R.L. 1990. Food Safety and Quality - Impact of Biotechnology. Presented at the Agricultural Biotechnology, Food, Safety and Nutritional Quality for the Consumer Second Annual Meeting. Ithaca, NY.

Munro, I.C. 1990. Food Safety and Environmental Issues in the year 2010. Presented to the Western Canadian Wheat Growers' Association, Regina, Saskatchewan, Canada.

Munro, I.C. 1990 & 1989. Issues in Food Safety, "Later in Life Learning Series", Toronto Ontario and The Environmental Forum, Belleville, Ontario.

A MORE DETAILED LIST OF PUBLICATIONS AND PRESENTATIONS IS AVAILABLE UPON REQUEST

Apr-07

Curriculum Vitae

Professor Ronald WALKER PhD, FRSC, CChem, FIFST
Emeritus Professor of Food Science,
Food Safety Group,
School of Biomedical & Life Sciences,
University of Surrey,
GUILDFORD GU2 5XH.
United Kingdom

Professor Walker is a Food Toxicologist with research interests in mechanisms of toxicity of food additives and contaminants (including mycotoxins and intrinsic natural toxicants). He has more than 150 research publications.

Membership of Scientific Societies:

Fellow of the Institute of Food Science and Technology
Fellow of the Royal Society of Chemistry
Member of: Biochemical Society
British Toxicology Society

For 20 years has been involved in regulatory committees dealing with safety evaluation and risk assessment of food additives and contaminants and novel foods, both at national and international levels, viz:

1. **INTERNATIONAL COMMITTEES:**

Joint WHO/FAO Expert Committee on Food Additives (JECFA):

served as WHO Temporary Adviser from 1981 to 1992.
Member and Chairman, 1993, 1996, 1998, 2000, 2001; Vice-Chairman 1995, 1997, 1999, 2001.

International Programme on Chemical Safety (WHO, International Labour Organisation and U.N. Environmental Programme):

Member and rapporteur of an *ad hoc* Working Group on Updating Methodology for Testing and Assessing Chemicals in Food, 1983 to 1987.
Member of *ad hoc* Working Group drafting Environmental Health Criteria Monograph on General Principles and Methods for Chemical Safety (Human Health Protection), 1993 - 1996.

Joint WHO/FAO Meeting on Chemicals in Food, Food Standards and Food Trade 1991: Temporary Adviser to WHO Secretariat

European Commission; Scientific Committee for Food (SCF):

Member of *ad hoc* Working Group on Nitrates, Nitrites and *N*-nitrosamines, 1988-90.
Member of Contaminants Working Group for Nitrates, Nitrites and *N*-nitroso compounds, 1993-1995
Appointed member of the Plenary Committee, 1999; Member of Working Groups on Food Additives, Food Contaminants, Food Flavours and Upper Safe Levels of Nutrients. Member of Ad hoc working groups on Dioxins and Polycyclic aromatic hydrocarbons

2. **NATIONAL COMMITTEES:**

U.K. Ministry of Agriculture, Fisheries and Food:

MAFF Advisory Committee on Food Safety Research, Member 1984-1985.

U.K Ministry of Agriculture, Fisheries & Food and AFRC:

Food Safety and Applied Nutrition Research Consultative Committee, Chairman, 1988-1989.

U.K. Department of Health/MAFF:

Advisory Committee on Novel Foods and Processes. Member, 1988 - 2000.
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). Member, 1989 - 1997.
Novel Foods Panel, Committee on Medical Aspects of Food Policy (COMA) Member, 1995 - 1999

U.K. House of Commons:

Expert Scientific Adviser to the **House of Commons Select Committee on Agriculture Inquiry into Food Safety** November 1997-March 1998

3. **Other**

International Life Sciences Institute (Europe) Chairman, Scientific Committee on Toxicology/Food Safety: 1992 - 1999

Editor of the Journal "Food Additives and Contaminants" 1983-2000

Curriculum Vitae

Susan Sestini Baker

Current Academic Title Professor of Pediatrics with Tenure

Education

PhD: Massachusetts Institute of Technology, 1982, Human Nutrition
MD: Temple University School of Medicine, 1972, Medicine
BA: University of Pittsburgh, 1968, Biology

Boards
1978 Pediatrics
1990 Pediatric Gastroenterology/Nutrition
1997 Pediatric Gastroenterology/Nutrition (recertification)
2002 Pediatric Gastroenterology/Nutrition (recertification)

Professional Appointments

SUNY Professor of Pediatrics, 2000-present
Children's Hospital of Buffalo, Co-Director, Digestive Diseases Nutrition Center, 2000 present
Children's Hospital of Buffalo, Medical Director, Gastroenterology Laboratory, 2000-present
Medical University of South Carolina, Professor of Pediatrics, 1996-2000
Medical University of South Carolina, Co-Director, Pediatric Gastroenterology and Nutrition, 1993-2000
Medical University of South Carolina, Associate Professor of Pediatrics, 1993-1996
University of Massachusetts Medical Center, Co-Director, Pediatric Gastroenterology and Nutrition, 1986-1993
University of Massachusetts Medical Center, Associate Professor of Pediatrics, 1991-1993
University of Massachusetts Medical Center, Assistant Professor of Pediatrics, 1986-1991
Harvard Medical School, Director, Nutrition Support, 1982-1986
Harvard Medical School, Assistant Professor of Pediatrics, 1985-1986

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Harvard Medical School, Instructor of Pediatrics, 1982-1985
Harvard medical School, Fellow in Gastroenterology, 1981-1984
Harvard Medical School, Clinical Fellow in Nutrition, 1978-1982
Harvard Medical School, Research Fellow in Nutrition, 1978-1982
Bamalete Lutheran Hospital, Ramotswa Village, Botswana, Medical Officer, 1977-1978
Charles Johnson Memorial Hospital, Nqutu, KwaZulu, RSA, 1975-1977
Children's Hospital of Buffalo, Resident in Pediatrics, 1973-1975
Children's Hospital of Buffalo, Intern in Pediatrics, 1972-1973

Awards and Honors

1995	Moderator Nutrition Program American Gastroenterology Association San Diego, CA
1996-Pres	Listed as one of The Best Doctors in America by American Health Magazine
2004	Moderator Obesity Program American Gastroenterology Association
2000	Honored American Board of Pediatrics
2001	American Academy of Pediatrics award for service
2005	FDA Advisory Service Award

Actual Publications

Refereed Journals

1. Baker RD, Baker SS. Underweight – a nutritional risk. S Afr Med J 1977;51(10):295.

2. Larsen JV, Baker SS, Baker RD. The midwifery nursing association: an experiment in a rural obstetric unit. SA Nurs J 19766;43:7-8.

3. Baker RD, Baker SS. Incontinentia pigmenti in a black baby: a case report. S Afr Med J. 1978;53:29-31.

4. Baker RD, Baker SS, Marge G, Reuter H. The successful use of soya-maize mixture in the treatment of kwashiorkor. S Afr Med J 1978;53:674-677.

5. Johnson RA, Baker SS, Fallon, et al. An occidental case of cardiomyopathy and selenium deficiency. N Eng J Med 1981;304:1210-1212.

6. King WW, Michel L, Wood WC, Malt RA, Baker SS, Cohen HJ. Reversal of selenium deficiency with oral selenium. N Eng J Med 1981;304:1305.

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7. Baker SS, Cohen HJ. Altered oxidative metabolism in selenium deficient rat granulocytes. J Immunology 1983;130:2856-2860.

8. Baker SS, Walter WK, King MD, Michel L, Wood WC, Malt RA, Cohen HJ. Reversal of biochemical and functional abnormalities in erythrocytes secondary to selenium supplementation. JPEN 1983;7:293-296

9. Baker SS, Lerman RH, Krey SH, Crocker KS, Hirsh EF, Cohen HJ. Selenium with TPN: Reversal of biochemical and functional abnormalities by selenium supplementation. Am J Clin Nutr 1983;38:769-774.

10. Baker SS, Cohen HJ. Increased sensitivity to H_2O_2 in glutathione peroxidase deficient granulocytes. J Nutrition 1984;14:2003-2009.

11. Cohen HJ, Chovaniec ME, Mistretta D, Baker SS. Selenium repletion and glutathione peroxidase-differential effects on plasma and red blood cell enzyme activity. Am J Clin Nutr 1985;41:735-747.

12. Baker SS, Queen P, Dwyer E. Metabolic derangements in children requiring parenteral nutrition. JPEN 1986;10:279-281.

13. Speir C, Baker SS, Newberger PE. Relationship between in vitro selenium supply, glutathione peroxidase activity and phagocytic function of the HL-60 myeloid cell line. J Biol Chem 1985;260:8951-8955.

14. Baker SS, Suthutvorauvut U, Walker WA. Short term neonatal starvation in rabbits. I. Effect on microvillus membrane function. J Pediatr Gastroenterol Nutr 1987;6:961-967.

15. Baker SS, Baker RD. Pediatricians want to be called (lett) Am J Dis Child 1989;143:520.

16. Baker SS, Campbell C, Walker WA. Short term starvation in neonatal rabbits. Decreased microvillus membrane binding of cholera toxin. J Nutr 1989;119:280-286.

17. Baker SS, Campbell C. Short term malnutrition in neonatal rabbits. Effect on gastrointestinal epithelial proliferation. J Nutr 1989;119:785-789.

18. Baker SS, Baker RD, Campbell C, Long S. Short term malnutrition in neonatal rabbits: Effect on function and synthesis of free radical metabolizing enzymes. J Peditar Gastroenterol Nutr 1990;11:247-251.

19. Baker SS, Campbell C. Enterocyte injury by oxygen dependent processes. Gastroenterology 1991;101:716-721.

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20. Baker SS, Compton C. Hemolytic anemia and a question of chronic active hepatitis. New Eng J Med 1991;324:180-189.

21. Baker SS, Baker RD. CaCo-2 Cell development of free radical metabolizing enzymes. In Vitro Cell Dev Biol 1992;28A:643-647.

22. Baker SS, Baker RD. CaCo-2 Cell metabolism of oxygen derived free radicals. Dig Dis Sci 1993;38:2273-88.

23. Baker SS. "Dust thou are..." Pediatr Gastroenterol Nutr 1993;16:365-367.

24. Baker RD, Baker SS, LaRosa K, Whitney C, Newburger PE. Selenium regulation of glutathione peroxidase in human hepatoma cell line Hep 3B. Arch Biochem Biophys 1993;304:53-57.

25. Avissar N, Kerle A, Baker SS, Cohen HJ. Extracellular glutathione peroxidase mRNA and protein in human cell lines. Arch Biochem Biophys 1994;309:239-246.

26. Baker RD, Baker SS, LaRose K. Polarized CaCo-2 cells: Effect of reactive oxygen metabolites on enterocyte barrier function. Dig Dis Sci 1995;09:510-518.

27. Young MH, Brennan LC, Baker SS, Baker RD. Physical and psychological response to successful treatment of encopresis and chronic constipation. J Develop and Behav Ped 1995;16(4):226-232.

28. Davis A, Baker SS, Leary RA. Advancing clinical privileges for nutrition support practitioners: the dietitian as a model. Nutr Clin Practice 1995;10:98-103.

29. Davis A, Baker SS. Nutritional supplementation. The use of modular nutrients in pediatrics JPEN 1996;20:228-236.

30. Baker SS. Corporate managed care (lett). N Eng J Med 1996;334:1062.

31. Baliga P, Reuben, Baker RD, Baker S, Cofer J, Rajagopalan P. Intestinal transplantation: An early experience. Transplan Proc 1996;28:2734-2735.

32. Rao RK, Baker RD, Baker SS, Gupta A, Holycross M. Oxidant-induced disruption of the intestinal epithelial barrier function: role of protein tyrosine phosphorylation. Am J Physiol 1997;273:G812-G823.

33. Kulling D, Green J, Pai GS, Baron PL, Baker SS, Swein D, Hoffman BJ. Familial adenomatous polyposis registry in South Carolina. J South Carolina Med Assoc 1997;93:405-409.

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34. Baker SS, Davis A. Hypocaloric oral therapy during an episode of diarrhea can lead to severe malnutrition. J Pediatr Gastro Nutr 1998;27:1-5.

35. Rao RK, Baker RD, Baker SS. Bovine milk inhibits proteolytic degradation of epidermal growth factor in human gastric and duodenal lumen. Peptides 1998;19:495-504.

36. Baker RD, Baker SS, Rao R. Selenium deficiency in tissue culture: implications for oxidative metabolism. J Pediatr Gastroenterol Nutr 1998;27:387-39.

37. Marchand V, Uflaker R, Baker SS, Baker RD. Congenital hepatic arterioportal fistula in a three year old child. J Pediatr Gastroenterol Nutr 1998;28:435-441.

38. Rao RK, Baker RD, Baker SS. Epidermal growth factor delays oxidant-induced disruption of the intestinal epithelial barrier function. Biochem Pharmacol 1999;57:685-697.

39. Baker SS. Cochran WJ. Flores CA. Georgieff MK. Jacobson MS. Jaksic T. Krebs NF. American Academy of Pediatrics. Committee on Nutrition. Calcium requirements of infants, children, and adolescents. Pediatrics. 104:1152-7, 1999.

40. Baker SS, Liptak GS, Colletti RB, Croffie JM, DiLorenzo C, Ector W, Nurko S. Constipation in infants and children: evaluation and treatment. J Pediatr Gastroenterol and Nutr 1999;29:612-626.

41. Hobbie C, Baker SS, Bayerl C. Parental understanding of basic infant nutrition: misinformed feeding choices. J Pediatr Health Care 2000;14:26-31.

42. Rao RK, Li L, Baker RD, Baker SS, Gupta A. Glutathione oxidation and PTPase inhibition by hydrogen peroxide in Caco-2 cell monolayers. Am J Physiol Gastrointest Liver Physiol 2000;279(2):G332-40.

43. Boujaoude L, Baker S, Baker RD. Iron and hepatitis C. J Pediatr Gastroenterol Nutrition 2000;31:91-92.

44. Marchand V, Baker SS, Stark TJ, Baker RD. Randomized, double-blind placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2000;31:264-269.

45. Baker SS. Maintenance of certification in the USA: a program for assessment of continuing competence. J Pediatr Gastroenterol Nutr 2001;32:117-8.

46. Baker SS. Unregulated dietary supplements: bitter medicine for children. J Pediatr Gastroenterol Nutr 2001;33:439-41.

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47. Baker SS. Motil KJ. Heyman MB. Research agenda for pediatric gastroenterology, hepatology and nutrition: nutrition and obesity. Report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition for the Children's Digestive Health and Nutrition Foundation. Journal of Pediatric Gastroenterology & Nutrition. 35 Suppl 3:S281-5, 2002.

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49. Neto UF, Baker S, Nelson EAS, Shulman R. The political environment: effects on growth and development – working group report of the first world congress of pediatric gastroenterology, hepatology and nutrition. J Pediatric Gastroenterol Nutr 2002;35:S22-233.

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53. Baker SS, Barlow S, Cochran W, Fuchs G, Klish W, Krebs N, Strauss R, Tershakovec A, Udall J. Overweight children and adolescents: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutrition 2005;40:533-543.

54. Borowitz D, Durie PR, Clarek LL, Werlin SL, Taylor CJ, Semler J, DeLisle RC, Lewindon P, Lichtman SM, Sinaasappel M, Baker RD, Baker SS, Verkade HJ, Lowe ME, Stallings VA, Janghorbani M, Butler R, Heubi J. Gastrointestinal outcomes and confounders in cystic fibrosis. J Pediatr Gastroenterol Nutrition. 2005;41:273-285.

55. Koletzko B, Baker S, Cleghorn G, Neto UF, Gropalan S, Hernell O, Hock QS, Jirapinyo P, Lonnerdal B, Pencharz P, Pqyrembel H, Ramirez-Mayans J, Shamir R, Turck D, Yamashiro Y, Zong-Yi D. Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. J Pediatr Gastroenterol Nutr 2005;41:584-599.

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56. Baker SS, Liptak GS, Colletti RB, Croffie JM, DiLorenzo C, Ector W, Nurko S. Guideline for the Diagnosis and Treatment of Constipation in Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr, 43:e1-e13, 2006.

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58. Borowitz D, Lin R, Baker SS. Comparison of Monoclonal and Polyclonal ELISAs for Fecal Elastase in Patients With Cystic Fibrosis and Pancreatic Insufficiency. J Pediatr Gastroenterol Nutr, 44:219-223, 2007.

59. Baker RD. Dee D. Baker SS. Response to pegylated interferon alpha-2b and ribavirin in children with chronic hepatitis C. Journal of Clinical Gastroenterology 41:111-114, 2007.

Books

1. Baker S, Henry RR. Parents Guide to Nutrition. Addison-Wesley, 1986.

2. Baker SS, Baker RD, Davis A. Pediatric Enteral Nutrition. Chapman and Hall Publishers, 1994.

3. Baker RD, Baker SS, Davis A. Pediatric Parenteral Nutrition. Chapman and Hall Publishers, 1997.

4. Baker SS, Baker RD, Davis AM. Pediatric Nutrition Support. Jones and Bartlett, Jones and Bartlett Publishers, 2006

Non-refereed journals for a professional audience

1. Baker RD, Baker SS. Prevention of cardiovascular heart disease through dietary intervention. Nutrition News in Pediatrics Wyeth, 1989

2. Baker RD, Baker SS. Dietary fiber for children. Nutrition News in Pediatrics Wyeth, 1989.

3. Baker RD, Baker SS. Food faddism. Nutrition News in Pediatrics Wyeth, 1989.

4. Baker RD, Baker SS. Acquired immune deficiency syndrome (AIDS) in children: nutritional support. Nutrition News in Pediatrics Wyeth, 1989.

5. Baker RD, Baker SS. Nutritional needs of handicapped children. Nutrition News in Pediatrics Wyeth, 1989.

6. Baker RD, Baker SS. Adolescence: A time of nutritional transition – feeding the teenage athlete. Nutrition News in Pediatrics Wyeth, 1989

7. Baker SS. Nutrition in children. Current Opinions in Gastro 1992;8:302-307.

8. Baker SS, Boullard-Blackunas K, Davis A. Common oral motor and gastrointestinal/nutritional problems in children referred to early intervention programs. Seminars in Pediatr Gastroenterol and Nutr 1993;4:3-8.

9. Baker SS. AAP, ADA evaluate fluoride supplementation schedule. AAP News 1994;10:24.

10. Baker SS. Feeding the sick child. Pediatric Basics 1994;68:12-16.

11. Baker SS. Introduce fruits, vegetables and grains. Pediatric Basics 1994;69:16-18.

12. Baker SS. Resurgence of rickets prompts new advice on vitamin D. AAP News 2000;17:92.

13. Nurko S, Baker SS, Coletti RB, et al. Managing Constipation: Evidence put to practice 2002;18:56-65

14. Kessler DB, Baker SS, Silverman LA. Growth assessment and growth failure. Consensus in Pediatrics 2004;1(no. 5):1-32.

15. Baker SS, Borowitz D, Baker RD. Pancreatic Exocrine Function in Patients with Cystic Fibrosis. Current Gastroenterology Reports 2005;7:227-233.

16. Baker SS. Counseling parents on feeding their children. Current Opinion in Clinical Nutrition and Metabolic Care 2007;

Contributions to and/or in books

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1. Baker SS. Protein calorie malnutrition in the hospitalized pediatric patient. In: Nutrition in Pediatrics – Basic Science and Clinical Aspects. Walker WA, Watkins J, eds. Little Brown and Company, 1984.

2. Baker SS. Nutritional biochemistry of micronutrient minerals. In: The Theory and Practice of Nutriton in Pediatrics. Grand JF, Sutphen JL, eds. Butterworth Company, 1986

3. Baker SS. Home total parenteral nutrition. In: The Theory and Practice of Nutrition in Pediatrics. Grand RJ, Sutphen JL, eds. Butterworth Company, 1986.

4. Baker SS. Magnesium depletion in short small bowel. In: Clinical Nutrition: A Case Management Approach. Blackburn GL, Bill SJ, Mullen J, eds. W. B. Saunders Company, 1989.

5. Baker SS. Contribution to Nutrition Section. Pediatric Medicine. Avery ME and First LR, eds. Williams and Wilkins, Baltimore, 1988.

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Publications or media presentations offering professional expertise, e.g. radio shows for a non-professional audience

More than 200 interviews including 4 national media tours (15-20 TV interviews and 10-15 radio interviews/media tour), Good Morning America, Larry King Live, three segments for the Discovery Channel. As spokesperson for the American Academy of Pediatrics interviewed and quoted by many of the major newspapers and news magazines including the Chicago Tribune, Washington Post, New York Times, Wall Street Journal, LA Times, USA Today, Time Magazine, News Week, US News and World Report, etc.

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Invited Presentations, Courses Taught, Educational Activities (highly selected, 1997-present only)

1997

1. Medical University of South Carolina, Charleston, SC, Gastrointestinal Development, Development of the Gastrointestinal Tract, CME for Neonatology
2. North American Society for Gastroenterology and Nutrition 4th Annual Postgraduate Course, Toronto, Canada, Nutrient Additives for Infant Formulas, CME for Pediatric Gastroenterologists.
3. Crohns and Colitis Foundation of America Symposium on Inflammatory Bowel Disease in Children. Nutrition Requirements in Inflammatory Bowel Disease, Cincinnati, OH.
4. 17th Annual Ross/NASPGN Seminar of Gastroenterology and Nutrition, Are there Roles for Nutrient Additives in Infant Formula? Carefree, Arizona

1998

1. Medical University of South Carolina, Charleston, SC, Gastrointestinal Development, Development of the Gastrointestinal Tract, CME for Neonatology
2. American Academy of Pediatrics, National Meeting, Course, San Francisco, CA, Abdominal Pain.
3. American Academy of Pediatrics, National Meeting, Course, San Francisco, CA, Growth Curves.
4. American Academy of Pediatrics, National Meeting, Course, San Francisco, CA,Vegetarian Diets.
5. American Academy of Pediatrics, National Meeting, Course, San Francisco, CA, Oral Rehydration Therapy.
6. American Academy of Pediatrics, National Meeting, Course, San Francisco, CA, Enteral Feeds: Trouble Shooting.
7. North American Society for Pediatric Gastroenterology and Nutrition, Orlando, FL, Program Directors, Development of the Organization Process.
8. North American Society for Pediatric Gastroenterology and Nutrition, Orlando, FL, Activity of the American Board of Pediatrics
9. American Board of Pediatrics, Charleston, SC, State of Pediatric GI/Hepatology/Nutrition

1999

1. Medical University of South Carolina, Charleston, SC, Gastrointestinal Development, Development of the Gastrointestinal Tract, CME for Neonatology
2. American Board of Pediatrics, Banff, Canada, State of Pediatric GI/Hepatology/Nutrition
3. Frontiers in Pediatrics (CME Course sponsored by the Department of Pediatrics, MUSC), Constipation, Charleston, SC

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2000

1. Medical University of South Carolina, Charleston, SC, Gastrointestinal Development, Development of the Gastrointestinal Tract, CME for Neonatology
2. Plenary Session, AAP National meeting, Chicago, IL Nutritional Rickets in Breastfeeding Infants
3. Selected short subjects, AAP National meeting, Chicago, IL New Information on Vitamins and Minerals in Infants and Toddlers
4. Buffalo Pediatric Society, Buffalo, NY Vitamin D Nutrition in Infants and Toddler

2001

New York State Dietetics Annual meeting, Saratoga Springs, NY,
Nutrition and Rickets: A new-Old Disease

2002

1. Fat Malabsorption and Pancreatitis, First Year Medical Students, SUNY, Buffalo
2. Acute and Chronic Diarrhea, First Year Medical Students. SUNY, Buffalo

Children's Calcium and Bone Health,
Annual Meeting, American Academy of
Pediatrics, SC Chapter, Hilton Head, SC

2005

Celiac Disease, Grand Rounds, Mayo Clinic, Rochester, MN
Nutrition Support in Pediatrics, Mayo Clinic, Rochester, MN
Pancreatic Enzyme Therapy in Cystic Fibrosis, Mayo Clinic, Rochester, MN
Nutrition in Cystic Fibrosis, Veterans Hospital, Buffalo, NY
Prevention of Food Allergies: Strategies in the First Year of Life American Academy of Pediatrics National Conference, Washington, DC
Celiac Disease, Grand rounds, Sister's Hospital, Buffalo, NY

Service to the Profession

1989	American Academy of Pediatrics Sub Committee on Protein Hydrolysates
1990	Federation of American Societies for Experimental Biology Committee on Scientific Review of Enteral Foods
1991	American Academy of Pediatrics, Advisory Committee for Healthy Start
1991	Member USDA Human Nutrition Competitive Grants Study Section
1991	American Academy of Pediatrics Representative to NIDR Workshop: Changing Patterns in Systemic Fluoride Intake
1991-2001	American Academy of Pediatrics Committee on Nutrition
1994-1997	North American Society of Pediatric Gastroenterology and Nutrition

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	Patient Care Committee
1995-2005	Chairperson, Institute of Pediatric Nutrition
1994-2000	American Board of Pediatrics, Gastroenterology Subboard
1996-1999	American Gastroenterological Association, Program Evaluation Committee
1996-2000	National Chairperson, Crohns and Colitis Foundation of America Pediatric Affairs Committee
1997	American Board of Pediatrics, Credentials Committee
1998-2000	Chairperson, American Board of Pediatrics, Gastroenterology Subboard
1997-2000	NASPGN, Team Leader, Clinical Guidelines
1997-2001	Chairperson, American Academy of Pediatrics, Committee on Nutrition
1998-2000	Executive Council – North American Society for Pediatric Gastroenterology and Nutrition
2000	Program Evaluation Committee, North American Society of Pediatric Gastroenterology and Nutrition
2000-2001	Chairperson, North American Society of Pediatric Gastroenterology and Nutrition Patient Care Committee
2001-2004	Chairperson, North American Society of Pediatric Gastroenterology and Nutrition Committee on Nutrition
2002-2004	Institute of Medicine, Committee on the Evaluation of the Addition of Ingredients New to Infant Formula
2004-2005	FDA Subcommittee of the Food Advisory Committee Center for Food Safety and Applied Nutrition
2005	Delegate to Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Use (CCNFSDU)
2005	USDA: National Advisory Council on Maternal, Infant and Fetal Nutrition
2006	Abstract Review of the Pediatric Academic Societies Annual Meeting, Obesity and Metabolism (Abstract presentations San Francisco, April 29-May 2)
2006	Planning Committee for New York State Childhood Obesity Prevention Invitational Summit

Editorships

1997-2005	Journal of Parenteral and Enteral Nutrition
1999-2001	Healthy Start
1995-1998	Nutrition Research
2002-2004	American Academy of Pediatrics Birth through 5

University/Hospital Service

1989-1993	Chairman, Nutrition Advisory Committee, University of Massachusetts Medical Center
1994 – 1998	CRC Grant Review Committee, Medical University of South Carolina

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1995 - 2000	Hospital Nutrition Advisory Committee, Children's Hospital of South Carolina
1994 - 2000	Promotions/Tenure Committee, Medical University of South Carolina
1996	Committee on Conscious Sedation, Children's Hospital of SC
1997 - 2000	Committee on Computerization of Patient Data Medical University of South Carolina
1999	Specialty Laboratory Task Force, Medical University of South Carolina
2000-present	Chair for Continuing Medical Education accredation for GI and Radiology, GI and Pathology and Inflammatory Bowel Diseases courses
2001-2001	LCME Committee, SUNY at Buffalo
2001-2004	Search Committee for Division Director, Adult Gastroenterology
2001-present	Fellowship Training Program Director, Pediatric Gastroenterology and Nutrition
2003	Search Committee for Dean of the School of Public Health and Health Professions
2002-2004	Faculty Council, SUNY at Buffalo
2002-present	Chair, Continuing Medical Education Committee for Pediatric Gastroenterology
2004-2006	Admissions committee for MD/PhD program at SUNY, Buffalo
2006	Committee for Internal Graduate Medical Education Review for Pediatric Surgery Training Program
2005-2006	Chair, Search Committee for Division Chief for Emergency Medicine

Department Service

2001-pres Billing Committee, UPA

Grant Support

1988-1991 PI 50% time

1992-1994 PI 50% time

From 1994 through 2000 I devoted my efforts to obtaining funding for a junior research PhD. He was successful in obtaining two R01s. He is now an Associate Professor of Pediatrics at the University of Tennessee.

2001-2002 Co-PI 25% time Centers for Disease Control,

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Trainees

Research	Years	Current Position
NY (Clinical PhD Advisor)	1991-1993	Practitioner, Child Psychology New York,
(Clinical PhD Advisor)	1990-1992	Practitioner, Child Psychology, Stowe, MA
(Clinical PhD Advisor)	1989-1991	Child Psychology
Carolina (Student Research Avisor)	1998	Medical Student, University of North

Fellows

	1997-2000	Assistant Professor of Pediatrics, St. Justine's Hospital, Montreal, Canada
	1999-2001	Assistant Professor of Pediatrics, Ann Arbor, Michigan
	2003-2003	Resigned from fellowship
	2004-present	
	2005-Present	
	2006-Present	
	1995-2001	Associate Professor of Physiology, University of Tennessee

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SUBMISSION END

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Kemin Health, L.C.
600 E. Court Ave., Ste. A
Des Moines, Iowa 50309-2058 USA
tel: **515.248.4000** fax: 515.248.4051
www.kemin.com

May 30, 2007

Via Email
And Courier, Return Receipt Requested

Ms. Moraima Ramos-Valle
Consumer Safety Officer
Office of Food Additive Safety
Division of Biotechnology and GRAS Notice Review
5100 Paint Branch Parkway
College Park, MD 20740-3835
Attn: Mail Code HFS-255

RE: GRAS Notification Number GRN 221 Lutein in Infant Formula:
Kemin Response to Request for Clarification

Dear Ms. Ramos-Valle:

Kemin Health, L.C., ("Kemin") is pleased to respond to the May 21, 2007 request from the Food and Drug Administration ("FDA") for clarification to items in Kemin's Generally Recognized as Safe ("GRAS") Notification for FloraGLO® Lutein 20% Liquid in Safflower Oil for Use in Infant Formula ("Notification") and Expert Panel Opinion ("Expert Opinion"). We note the following in response to the FDA's inquiries:

1. **Comment:** There is a discrepancy in the percentages of lutein and zeaxanthin in GRN 221 as listed on pages 1 and 4, respectively, of the Notification and Expert Opinion regarding the percentages of lutein and zeaxanthin in GRN 221.
   Clarification: According to specifications, the percentage of lutein is 20% and zeaxanthin is 0.8%. Please see the attached revised Notification and Expert Opinion providing these corrections.

2. **Comment:** Clarify/explain the variation in the lutein-to-zeaxanthin ratios between FloraGLO Crystalline Lutein (page 7) [74%: 4%] and FloraGLO Lutein 20% Liquid in Safflower Oil (page 8) [21%:0.8%].
   Clarification: The specifications for both FloraGLO Crystalline Lutein and FloraGLO Lutein 20% Liquid in Safflower Oil are internal specifications for lutein and zeaxanthin. The zeaxanthin numbers are based on historical variation in zeaxanthin content in marigolds, as well as stability studies that indicate shelf life losses of zeaxanthin in the finished product.

3. **Comment:** Page 2 of the Notification and page 4 of the Expert Opinion identify the SUN reference as confidential.
   Clarification: These references are now characterized as [Unpublished]. Please see the attached revised Notification and Expert Opinion providing these revisions.

4. **Comment:** References missing from the reference list:
   Page 4-Rice-Evans et al., 1997
   Page 4-Krinsky et al., 1990 and Khachik et al. 1999
   Page 11 of 20- Maggio et al. 2006
   Clarification: Please see the attached revised Notification and Expert Opinion providing these references.

5. **Comment:** Lutein is intended for use in infant formula and throughout the submission only term infants are mentioned. Are you intending to use lutein just in term formula or pre-term and term formulas?
   Clarification: Kemin intends to use lutein just in term formula.

We believe the above information should be fully responsive to the FDA's inquiries, but should the Agency have any additional questions, please do not hesitate to contact us.

Sincerely,

(b)(6)

Deborah Shur Trinker, Esq.
Vice President, Regulatory Affairs

Enclosures

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

FloraGLO® Crystalline lutein has previously been considered Generally Recognized as Safe (GRAS) by an Expert Panel of independent scientists for use in food. Furthermore, FloraGLO Crystalline Lutein was the subject of GRAS Notice No. GRN 000140, which The United States Food and Drug Administration (FDA) has reviewed and provided no questions regarding the conclusion that FloraGLO Crystalline Lutein is GRAS under the intended conditions of use (FDA, 2004). An ingredient that is manufactured with FloraGLO Crystalline Lutein, FloraGLO Lutein 20% Liquid in Safflower Oil, has now been determined to be GRAS, consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*, for an extended use in infant formula. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in infant formula, among experts qualified by scientific training and expertise. Therefore, the use of FloraGLO® Lutein 20% Liquid in Safflower Oil in infant formula as described below is exempt from the requirement of premarket approval.

Signed,

NAME ADDRESS	Date

B. Name and Address of Notifier

Debbie Trinker, Esq.
Vice President, Regulatory Affairs
Kemin Health, L.C.
600 E. Court Avenue, Suite A
Des Moines, IA
50309-2021
USA

C. Common Name of the Notified Substance

Lutein

D. Conditions of Intended Use in Food

FloraGLO Lutein 20% Liquid in Safflower Oil is intended for use as a food ingredient in infant formulas. An overage will be used to account for losses during manufacture and shelf life. Furthermore, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal, and which is approximately the level tested in the infant clinical studies. The proposed maximum total lutein content in finished infant formula product of 250 µg/L also is approximately the upper end of the range of the lutein concentrations present naturally in human breast milk as demonstrated by Canfield *et al.* (2003).

Lutein and zeaxanthin are among the most prevalent carotenoids in the North American diet (IOM, 2000), occurring in high concentrations in green leafy vegetables, such as spinach and kale (Khachik *et al*., 1995; Omaye *et al.*, 1997), and in chicken egg yolks (Handelman *et al.*, 1999). In the U.S., the daily intake of lutein and zeaxanthin from food, across the entire population sampled (aged 2 months and over), is estimated to range from 0.58 to 5.40 mg (IOM, 2001). In addition to their natural occurrence in various foods, lutein and zeaxanthin are available as dietary supplements (IOM, 2000); however, there are no consumption data from which to reliably estimate the intake of lutein and zeaxanthin by supplement users. Market share data indicate that lutein use in dietary supplements occurs predominantly from multi-vitamin type supplements.

The U.S. national survey data from the National Health and Nutrition Examination Survey (NHANES 2001-2, released 2004) and the food composition data from USDA National Nutrient Database for Standard Reference (Release 17, 2004) provide an adequate database for estimating lutein + zeaxanthin intake in U.S. children from 2 months through 8 years of age. Kemin Health (Des Moines, Iowa) commissioned an analysis of these databases to estimate lutein + zeaxanthin dietary intakes for the U.S. population (Sun, 2005 [Unpublished]). The mean and 90th percentile intakes of lutein and zeaxanthin for children from 2 through 6 months of age were 200 and 820 µg/day and were 460 and 1,100 µg/day for children from 7 through 11 months of age.

Lutein and zeaxanthin are present in human breast milk. Schweigert *et al.* (2000) extracted lipids from human milk and determined that the predominant form of lutein in human milk is free lutein. Exposure to lutein from human breast milk varies widely based on stage of lactation, geographical location, and individual diets, and has been demonstrated to range from 3 to 232 µg/L in individual mothers from around the world (Canfield *et al.*, 2003). Mean concentrations at individual sites ranged from 15 µg/L in Australia, Canada, the UK, and the US to 43 µg/L in China and Japan. The average lutein and zeaxanthin concentration across all of the sites investigated was 25 ± 19 µg/L (Canfield *et al.*, 2003). A survey of commercial infant formulas not currently fortified with lutein demonstrates the presence of low amounts of lutein in current infant formula products worldwide. Infant formula products were analyzed using a method that

extracts free lutein and zeaxanthin without saponification. Using this methodology, the mean innate concentration of lutein in different infant formulas, representing unfortified ready to feed (RTF) formulas and powder formulas from Ireland, Singapore, and the Philippines (n=74) was 17 ± 4.6 µg/L with a range of 6.1 to 26.0 µg/L.

To provide a conservative estimate of potential lutein exposure (µg/kg/day), the 90th percentile of dietary lutein intake and the highest potential intake from the proposed products were used. For term infant formula, an estimated daily intake of 780 mL for term infants was used, per Codex and NAS estimated mean intake, and combined with the upper limit of lutein concentration (250 µg/L) to result in a daily intake of 195 µg/day. Furthermore, reference weight was based on a female child at the 10th percentile of weight-for-age at the first age increment referenced (generally one half month older than the bottom of the range) using data from the U.S. Centers for Disease Control Growth Charts.

Under the intended conditions of use of FloraGLO Lutein 20% Liquid in Safflower Oil, a low weight-for-age child (10th percentile) who is a heavy consumer (90th percentile) of lutein from other dietary sources and consumes the highest recommended intake of proposed product will take in approximately 230 µg/kg body weight/day.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, FloraGLO Lutein 20% Liquid in Safflower Oil has been determined to be GRAS for use in infant formula on the basis of scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil as a component of infant formula. The safety of FloraGLO Lutein 20% Liquid in Safflower Oil is supported by the previous GRAS determination for FloraGLO Crystalline lutein, which was the subject of GRAS Notice No. GRN 000140, which The United States Food and Drug Administration (FDA) has reviewed and provided no questions regarding the conclusion that FloraGLO Crystalline Lutein is GRAS under the intended conditions of use (FDA, 2004). FloraGLO Crystalline Lutein was previously determined to be GRAS based on its safety, which has been established in toxicological studies in rats, mutagenicity studies conducted with *Salmonella typhimurium*, and is further supported by intervention studies conducted with healthy subjects designed to measure metabolic endpoints. The safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas is further supported by a 13-week toxicity study conducted in Wistar rats at doses up to 260 mg FloraGLO Crystalline Lutein/kg body weight/day (corresponding to 210 mg lutein+zeaxanthin/kg body weight/day) and a developmental toxicity study conducted in Sprague-Dawley rats at doses up to 1,100 mg lutein/kg body weight/day. Additionally, the results of an infant growth and safety study conducted with FloraGLO Lutein 20% Liquid in Safflower Oil at a targeted concentration of 200 µg lutein/L in infant formula, and resulting in a mean intake ranging from 190 to 250 µg lutein/day, for a period of 16 weeks corroborate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas.

This determination is further supported by an expert panel evaluation of the health aspects of FloraGLO Lutein 20% Liquid in Safflower Oil. [See Attached – EXPERT PANEL OPINION REGARDING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF FloraGLO LUTEIN 20% LIQUID IN SAFFLOWER OIL FOR USE IN INFANT FORMULA].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Debbie Trinker, Esq.
Vice President, Regulatory Affairs
Kemin Health, L.C.
600 E. Court Avenue, Suite A
Des Moines, IA
50309-2021
USA

Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, Kemin Health, L.C. will supply these data and information.

II. Detailed Information About the Identity of the Substance

A. Identity

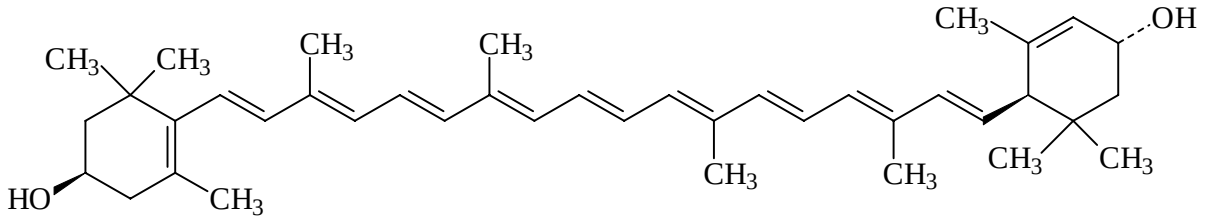
FloraGLO Lutein 20% Liquid in Safflower Oil is produced in accordance with current good manufacturing practice. FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured using FloraGLO Crystalline Lutein, a purified extract from the marigold (*Tagetes erecta*) flower. FloraGLO Lutein 20% Liquid in Safflower Oil contains approximately 20.8% by weight of the carotenoids lutein and zeaxanthin (20 and 0.8%, respectively).

Lutein is an oxycarotenoid, or xanthophyll, containing 2 cyclic end groups (one β- and one ε-ionone ring) and the basic C_{40} isoprenoid structure common to all carotenoids (see Figure 2.4-1). Lutein occurs together with zeaxanthin, an oxycarotenoid that is isomeric with lutein, containing 2 β-ionone rings rather than one β- and one ε-ionone ring (see below). In principal, each of the polyene chain double bonds present in lutein and zeaxanthin could exist in a *cis* or *trans* conformation, giving rise to a large number of possible mono-*cis* and poly-*cis* isomers; however, in practice, the vast majority of carotenoids are in the all-*trans* configurations (Rice-Evans *et al.*, 1997; IOM, 2000), as depicted below. Small amounts of *cis* isomers of lutein and zeaxanthin, accompanied by their respective all-*trans* configurations, have been isolated and

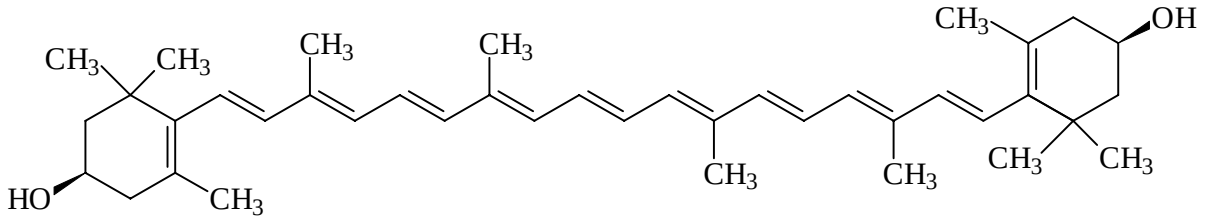
purified from extracts of marigold flowers, fresh raw kale, corn meal, spinach, and human plasma (Krinsky *et al.*, 1990; Khachik *et al.*, 1999).

The structural formula, chemical properties, and physical characteristics of lutein and zeaxanthin are presented below.

Common or Usual Name:	Lutein
Chemical Name:	xanthophyll; β,ε-carotene-3,3'-diol; vegetable lutein; vegetable luteol; Bo-Xan; all-*trans*-(+)-xanthophyll; all-trans-lutein
Chemical Abstracts Service (CAS) Number:	127-40-2
Empirical Formula and Formula Weight:	$C_{40}H_{56}O_2$
Molecular weight:	568.88
Structural Formula:	



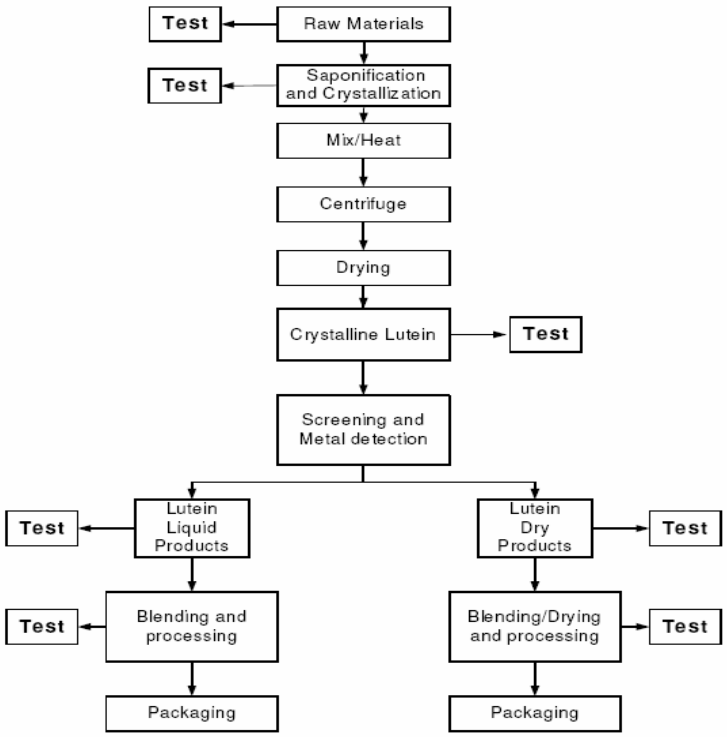
Common or Usual Name:	Zeaxanthin
Chemical Name:	β, β-carotene-3,3'-diol; all-*trans*-β-carotene-3,3'-diol; (3*R*,3'*R*)-dihydroxy-β-carotene; zeaxanthol; anchovyxanthin
Chemical Abstracts Service (CAS) Number:	144-68-3
Empirical Formula and Formula Weight:	$C_{40}H_{56}O_2$
Molecular weight:	568.88
Structural Formula:	



B. Method of Manufacture

The lutein and zeaxanthin extract is generated using a proprietary technology in a 3-step process that does not include chemical synthesis, but rather extracts the lutein from the natural source material. Marigold oleoresin (paste) is derived from the hexane extraction of dried marigold flower petals, with subsequent purification to remove the hexane residues. During the crystallization step, the marigold oleoresin is subjected to conditions to remove the fatty acids from lutein esters and zeaxanthin esters. This process employs potassium hydroxide (potash), propylene glycol, and water with mixing and heat. During this process crystals of lutein and zeaxanthin are formed. The reaction mixture from the crystallization step is diluted with water and the lutein and zeaxanthin crystals are collected by centrifugation and washed with additional water. The water used is purified by reverse osmosis. The lutein and zeaxanthin crystals are dried by the removal of the residual water, which results in dry cake base. Dry cake base is an intermediate and is additionally screened to become FloraGLO Crystalline Lutein. Dry cake base and FloraGLO Crystalline Lutein are packaged directly into drums and purged with nitrogen gas. A schematic overview of the manufacturing process of FloraGLO Crystaline Lutein is presented in Figure 1.

Figure 1. FloraGLO Crystalline Lutein Manufacturing Process



To obtain FloraGLO 20% Liquid in Safflower Oil, FloraGLO Crystalline Lutein is suspended in safflower oil. Safflower oil is typically added to infant formulas as part of the lipid component.

C. Specifications for Food Grade Material

Specifications for FloraGLO Crystalline Lutein and FloraGLO Lutein 20% Liquid in Safflower Oil meet acceptable food grade specifications, and are presented in Tables 1 and 2, respectively. The panel reviewed the results of analysis of several non-consecutive representative lots of FloraGLO Crystalline Lutein and concluded the product complies with final product specifications.

Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein

Parameters	Specification	Method Reference
Principal Constituents		
Total Carotenoids (Pigment)	Minimum 80.0% wt	KHM-005-904
Lutein	Minimum 74.0% wt	KHM-009-904
Zeaxanthin	Minimum 4.0% wt Maximum 9.0% wt	KHM-005-904
Aggregate Constituents & Properties		
Moisture	Maximum 1.0% wt	KHM-005-913
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Protein	Maximum 100 mg/kg	KHM-005-921
Waxes	Maximum 14.0 % wt	Alturas 12/27/00
Metals		
Lead (Pb)	Maximum 0.65 ppm	AOAC993.14
Cadmium (Cd)	Maximum 1.25 ppm	AOAC 993.14
Arsenic (As)	Maximum 2.5 ppm	AOAC 993.14
Mercury (Hg)	Maximum 0.15 ppm	Analyst 86.608, Analytical Chem. 40:2085
Other Constituents		
Hexane	Maximum 50 ppm	KHM-005-023
Propylene glycol	Maximum 1,000 mg/kg	KHM-005-033
Thiophenes	Maximum 300 mg/kg	Alturas Analytics TM01-105
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 27, NF 22, 2004
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 27, NF 22, 2004
Staph enrichment	Negative/10 g	USP 27, NF 22, 2004
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.

Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein		
Parameters	**Specification**	**Method Reference**
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

Alturas = Alturas Analytics Inc. Method; AOAC = Association of Official Analytical Chemists; BAM-FDA = Bacteriological Analytical Manual – Food and Drug Administration; CMMEF = Compendium of Methods for the Microbiological Examination of Foods; KHM = Kemin Health Method; NF = National Formulary; USP = U.S. Pharmocopeia

Table 2 Specifications for Food-Grade FloraGLO Lutein 20% Liquid in Safflower Oil		
Parameters	**Specification**	**Method Reference**
Principal Constituents		
Lutein	Minimum 20.0% wt	KHM-005-905
Zeaxanthin	Minimum 0.8% wt	KHM-005-905
Aggregate Constituents & Properties		
Moisture	Maximum 1% wt	KHM-005-035
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 29, NF 24, 2006
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 29, NF 24, 2006
Staph enrichment	Negative/10 g	USP 29, NF 24, 2006
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

AOAC = Association of Official Analytical Chemists; BAM-FDA = Bacteriological Analytical Manual – Food and Drug Administration; CMMEF = Compendium of Methods for the Microbiological Examination of Foods; KHM = Kemin Health Method; NF = National Formulary; USP = U.S. Pharmocopeia

III. Self-Limiting Levels of Use

There are no physical or chemical characteristics that will limit the levels of use; however, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal.

IV. Basis for GRAS Determination

The determination that FloraGLO Lutein 20% Liquid in Safflower Oil is GRAS is on the basis of scientific procedures. (See Attached – EXPERT PANEL OPINION REGARDING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF FloraGLO LUTEIN 20% LIQUID IN SAFFLOWER OIL FOR USE IN INFANT FORMULA).

V. References

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EXPERT PANEL OPINION REGARDING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF FloraGLO® LUTEIN 20% LIQUID IN SAFFLOWER OIL FOR USE IN INFANT FORMULA

INTRODUCTION

FloraGLO Crystalline lutein has previously been considered Generally Recognized as Safe (GRAS) by an Expert Panel of independent scientists for use in food. The Expert Panel, which included Dr. Robert Russell (Tufts University), Professor Ron Walker (University of Surrey), and Dr. Ian Munro (Cantox Health Sciences International), evaluated the composition and manufacture of FloraGLO Crystalline Lutein, the intended uses and potential exposure under the defined intended conditions of use, and data regarding the safety of FloraGLO Crystalline Lutein. Based on this review, the Expert Panel concluded that FloraGLO Crystalline Lutein is GRAS for use as a food ingredient in baked goods and baking mixes, beverages and beverage bases, breakfast cereals, chewing gum, dairy product analogs, egg products, fats and oils, frozen dairy desserts and mixes, gravies and sauces, hard candy, infant and toddler foods (not including infant formula), milk products, processed fruits and fruit juices, soft candy, and in soups and soup mixes at levels ranging from 0.3 to 3.0 mg/serving. They also concluded that FloraGLO Crystalline Lutein is GRAS for use in medical foods intended as the sole item of the diet at intakes less than or equal to 20 mg/day. Furthermore, FloraGLO Crystalline Lutein was the subject of GRAS Notice No. GRN 000140, which The United States Food and Drug Administration (FDA) has reviewed and provided no questions regarding the conclusion that FloraGLO Crystalline Lutein is GRAS under the intended conditions of use (FDA, 2004).

At the request of Kemin Health, L.C., (Kemin), the manufacturer of FloraGLO Lutein, the Expert Panel, with the addition of Dr. Susan Baker (Women and Children's Hospital of Buffalo) (hereinafter referred to as the Panel), was reconvened to evaluate the safety of and to determine the Generally Recognized as Safe (GRAS) status of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas for infants from birth to 12 months. FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured using FloraGLO Crystalline Lutein which is a purified extract from the marigold (*Tagetes erecta*) flower that contains approximately 20.8% by weight of the carotenoids lutein and zeaxanthin (20 and 0.8%, respectively). *Curricula vitae* evidencing the qualifications of the Panel for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel was requested to evaluate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil from *T. erecta* for use as a food ingredient in infant formulas in the United States (U.S.) so that the total lutein content in finished infant formula product would not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal[1]. The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled from the literature and other published sources. The data evaluated by the Panel comprises information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in infant formula, consumption estimates for the intended use, bioavailability studies in animals and infants, safety studies conducted with FloraGLO Crystalline Lutein, growth and safety studies conducted with FloraGLO Lutein 20% Liquid in Safflower Oil in infants, and other relevant data on the safety of lutein and zeaxanthin obtained from the literature.

Following independent critical evaluation of the data and information, the Panel participated in two conference calls on February 23 and March 2, 2007. During the conference call on March 2, 2007, the Panel concluded that FloraGLO Lutein 20% Liquid in Safflower Oil meets appropriate food grade specifications, is manufactured in compliance with current Good Manufacturing Practices (cGMP), and is GRAS based on scientific procedures under the conditions of use. A summary of the basis for our conclusion is set forth below.

MANUFACTURING AND SPECIFICATIONS

FloraGLO Lutein 20% Liquid in Safflower Oil is produced in accordance with current good manufacturing practice. FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured using FloraGLO Crystalline Lutein, which is considered to be GRAS. Specifications for FloraGLO Crystalline Lutein and FloraGLO Lutein 20% Liquid in Safflower Oil meet acceptable food grade specifications, and are presented in Tables 1 and 2, respectively. The panel reviewed the results of analysis of several non-consecutive representative lots of FloraGLO Crystalline Lutein and concluded the product complies with final product specifications.

Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein

Parameters	Specification	Method Reference
Principal Constituents		
Total Carotenoids (Pigment)	Minimum 80.0% wt	KHM-005-904
Lutein	Minimum 74.0% wt	KHM-009-904
Zeaxanthin	Minimum 4.0% wt Maximum 9.0% wt	KHM-005-904
Aggregate Constituents & Properties		

[1] Conversion factor of 6.72 Kcal/100mL

Table 1 Specifications for Food-Grade FloraGLO Crystalline Lutein		
Parameters	**Specification**	**Method Reference**
Moisture	Maximum 1.0% wt	KHM-005-913
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Protein	Maximum 100 mg/kg	KHM-005-921
Waxes	Maximum 14.0 % wt	Alturas 12/27/00
Metals		
Lead (Pb)	Maximum 0.65 ppm	AOAC993.14
Cadmium (Cd)	Maximum 1.25 ppm	AOAC 993.14
Arsenic (As)	Maximum 2.5 ppm	AOAC 993.14
Mercury (Hg)	Maximum 0.15 ppm	Analyst 86.608, Analytical Chem. 40:2085
Other Constituents		
Hexane	Maximum 50 ppm	KHM-005-023
Propylene glycol	Maximum 1,000 mg/kg	KHM-005-033
Thiophenes	Maximum 300 mg/kg	Alturas Analytics TM01-105
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 27, NF 22, 2004
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 27, NF 22, 2004
Staph enrichment	Negative/10 g	USP 27, NF 22, 2004
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

Table 2 Specifications for Food-Grade FloraGLO Lutein 20% Liquid in Safflower Oil		
Parameters	**Specification**	**Method Reference**
Principal Constituents		
Lutein	Minimum 20.0% wt	KHM-005-905
Zeaxanthin	Minimum 0.8% wt	KHM-005-905
Aggregate Constituents & Properties		
Moisture	Maximum 1% wt	KHM-005-035
Ash	Maximum 1.0% wt	AOAC 900.02A, 920.153, 923.03
Microbiological Assays		
Aerobic plate count	Maximum 100 cfu/g	AOAC 966.23
E. coli enrichment	Negative/10 g	USP 29, NF 24, 2006

Table 2 Specifications for Food-Grade FloraGLO Lutein 20% Liquid in Safflower Oil		
Parameters	**Specification**	**Method Reference**
Listeria monocytogenes	Negative/25 g	AOAC 999.06
Salmonella	Negative/10 g	USP 29, NF 24, 2006
Staph enrichment	Negative/10 g	USP 29, NF 24, 2006
Coliform enrichment	Negative/25 g	CMMEF 4th Ed.
Yeast count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.
Mold count	Maximum 100 cfu/g	BAM-FDA, 7th Ed.

INTENDED USE AND ESTIMATED INTAKE

Lutein and zeaxanthin are among the most prevalent carotenoids in the North American diet (IOM, 2000), occurring in high concentrations in green leafy vegetables, such as spinach and kale (Khachik *et al*., 1995; Omaye *et al.*, 1997), and in chicken egg yolks (Handelman *et al.*, 1999). In the U.S., the daily intake of lutein and zeaxanthin from food, across the entire population sampled (aged 2 months and over), is estimated to range from 0.58 to 5.40 mg (IOM, 2001). In addition to their natural occurrence in various foods, lutein and zeaxanthin are available as dietary supplements (IOM, 2000); however, there are no consumption data from which to reliably estimate the intake of lutein and zeaxanthin by supplement users. Market share data indicate that lutein use in dietary supplements occurs predominantly from multi-vitamin type supplements.

The U.S. national survey data from the National Health and Nutrition Examination Survey (NHANES 2001-2, released 2004) and the food composition data from USDA National Nutrient Database for Standard Reference (Release 17, 2004) provide an adequate database for estimating lutein + zeaxanthin intake in U.S. children from 2 months through 8 years of age. Kemin Health (Des Moines, Iowa) commissioned an analysis of these databases to estimate lutein + zeaxanthin dietary intakes for the U.S. population (Sun, 2005 [Unpublished]). The mean and 90th percentile intakes of lutein and zeaxanthin for children from 2 through 6 months of age were 200 and 820 µg/day and were 460 and 1,100 µg/day for children from 7 through 11 months of age.

Lutein and zeaxanthin are present in human breast milk. Schweigert *et al.* (2000) extracted lipids from human milk and determined that the predominant form of lutein in human milk is free lutein. Exposure to lutein from human breast milk varies widely based on stage of lactation, geographical location, and individual diets, and has been demonstrated to range from 3 to 232 µg/L in individual mothers from around the world (Canfield *et al.*, 2003). Mean concentrations at individual sites ranged from 15 µg/L in Australia, Canada, the UK, and the US to 43 µg/L in China and Japan. The average lutein and zeaxanthin concentration across all of the sites

investigated was 25 ± 19 µg/L (Canfield *et al.*, 2003). A survey of commercial infant formulas not currently fortified with lutein demonstrates the presence of low amounts of lutein in current infant formula products worldwide. Infant formula products were analyzed using a method that extracts free lutein and zeaxanthin without saponification. Using this methodology, the mean innate concentration of lutein in different infant formulas, representing unfortified ready to feed (RTF) formulas and powder formulas from Ireland, Singapore, and the Philippines (n=74) was 17 ± 4.6 µg/L with a range of 6.1 to 26.0 µg/L.

FloraGLO Lutein 20% Liquid in Safflower Oil is intended for use as a food ingredient in infant formulas. An overage will be used to account for losses during manufacture and shelf life. Furthermore, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37 µg/100 kcal, and which is approximately the level tested in the infant clinical studies. The proposed maximum total lutein content in finished infant formula product of 250 µg/L is approximately the upper end of the range of the lutein concentrations present naturally in human breast milk as demonstrated by Canfield *et al.* (2003). FloraGLO Lutein 20% Liquid in Safflower Oil provides the optimal source for use in infant formulas, as the chemical form of lutein is the same as in human milk.

To provide a conservative estimate of potential lutein exposure (µg/kg/day), the 90th percentile of dietary lutein intake and the highest potential intake from the proposed products were used. For term infant formula, an estimated daily intake of 780 mL for term infants was used, per Codex and NAS estimated mean intake, and combined with the upper limit of lutein concentration (250 µg/L) to result in a daily intake of 195 µg/day. In contrast, reference weight was based on a female child at the 10th percentile of weight-for-age at the first age increment referenced (generally one half month older than the bottom of the range) using data from the U.S. Centers for Disease Control Growth Charts.

Under the intended conditions of use of FloraGLO Lutein 20% Liquid in Safflower Oil, a low weight-for-age child (10th percentile) who is a heavy consumer (90th percentile) of lutein from other dietary sources and consumes the highest recommended intake of proposed product will take in approximately 230 µg/kg body weight/day. This is equivalent to approximately 10 % of the Joint FAO/WHO Expert Committee on Food Additives' (JECFA) acceptable daily intake (ADI) for lutein, which is set at 2,000 µg/kg/day (JECFA, 2006) and provides approximately a 1,000-fold safety factor compared to the NOAEL of 200 mg/kg body weight/day from the rat study used to establish the JECFA ADI (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002). Whereas lutein exposure attributable solely from the proposed fortification of infant formula is equal to 44 µg/kg body weight/day, or approximately 2.2% of the JECFA ADI for lutein (providing an approximately 5,000-fold safety factor in comparison to the same NOAEL).

DATA PERTAINING TO SAFETY

FloraGLO Crystalline Lutein was previously determined to be GRAS based on its safety, which has been established in toxicological studies in rats, mutagenicity studies conducted with *Salmonella typhimurium*, and is further supported by intervention studies conducted with healthy subjects designed to measure metabolic endpoints. The safety of FloraGLO Crystalline Lutein is also corroborated by additional animal and human studies conducted with other sources of lutein, lutein-rich foods, and lutein supplements. In addition, the safety of lutein and zeaxanthin is well established in the literature based on the historical consumption of eggs and fruits and vegetables where these carotenoids predominate (*e.g.*, green leafy vegetables, such as spinach and kale). Additional studies published subsequent to the determination of the GRAS status of FloraGLO Crystalline Lutein continue to support its safety as a food ingredient.

The safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas has been further demonstrated in two clinical studies conducted in healthy term infants, corroborating the safety of lutein for infant formula use.

Lutein is the major xanthophyll found in human serum, with smaller amounts of zeaxanthin and cryptoxanthin also present (Williams *et al.*, 1998; Boileau *et al.*, 1999). Lutein is also present in breast milk (Gossage *et al.*, 2002), and, together with zeaxanthin, are the only carotenoids found in the macular region of the human retina (Bone *et al.*, 1985, 1988, 1993; Omaye *et al.*, 1997). In general, carotenoids in foods are not known to be toxic, even when ingested in large amounts (*e.g.*, >30 mg carotenoid) (Olson, 1996; Omaye *et al.*, 1997). The safety of lutein and zeaxanthin was addressed by the Institute of Medicine (IOM, 2000) following a review of the available data regarding β-carotene and other carotenoids. The IOM concluded that no adverse effects, other than carotenodermia, have been reported from the consumption of carotenoids, including lutein and zeaxanthin, in foods. Carotenodermia, characterized by a yellowish discoloration of the skin, is a harmless and reversible biological effect of high carotenoid intake (IOM, 2000). No tolerable upper intake levels were established for lutein or zeaxanthin, or for any other carotenoid (β-carotene, α-carotene, lycopene, and β-cryptoxanthin) considered by the IOM (2000).

JECFA completed a safety evaluation of lutein from *Tagetes erecta* L. and assigned a group ADI of 0 to 2 mg lutein and zeaxanthin/kg body weight (JECFA, 2006). The ADI was established based on a no observed adverse effect level (NOAEL) of 200 mg lutein/kg body weight/day (the highest dose tested) reported in a 90-day rat study (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002), to which a safety factor of 100 was applied. This safety factor was considered appropriate given the lack of adverse effects reported at much higher doses than 200 mg/kg body weight/day [up to 1,000 mg/kg body weight/day in a study of developmental toxicity (Edwards *et al.*, 2002)]. The committee noted that there were no adverse effects

documented in any of the studies of toxicity in animals, including mice, rats, and monkeys, or in humans.

Studies of Absorption and Bioavailability

The absorption and bioavailability of lutein and zeaxanthin was previously reviewed while determining the GRAS status of FloraGLO Crystalline Lutein. The bioavailability of FloraGLO Lutein 20% Liquid in Safflower Oil from a commercial infant formula matrix has likewise been demonstrated in neonatal pigs and infant rhesus monkeys (Kullen, 2006; Kullen and Ramanujam, 2006). Data from both studies indicate a dose-dependent response in the maximal plasma lutein concentration and the lutein area under the curve. The time course of absorption appears to be rapid and is similar to that of other carotenoids (Schweigert *et al.*, 1995). Lower doses may reach peak serum concentrations more rapidly than higher doses and less complete absorption may occur with higher doses. Additionally, there were no significant differences in the serum parameters of the other carotenoids, including β-carotene, when assessed in neonatal pigs.

Data from a prospective, randomized, double-blinded clinical trial conducted in accordance with GCP/ICH guidelines and all applicable regulations indicate that lutein provided from FloraGLO Lutein 20% Liquid in Safflower Oil is also bioavailable in healthy term infants, as was demonstrated by a linear relationship between the log plasma concentration and the log dose of lutein delivered (Wyeth Nutrition, 2006a). A total of 63 infants were randomized to receive the control infant formula (S-26 Gold), S-26 Gold plus 25 µg lutein/L or S-26 Gold plus 200 µg lutein/L *ad libitum* for a period of 5 weeks. In the manufacturing of the formula, an innate amount of lutein, 20 µg/L, was present. To accommodate for manufacturing and shelf life loss, lutein was fortified at 150% of the test label claim, *i.e.* S-26 Gold plus 25 µg lutein/L was fortified with 38 µg lutein/L and S-26 Gold plus 200 µg lutein/L was fortified with 300 µg lutein/L. The final lutein content of each test formula by analysis was 20, 47, and 289 µg lutein/L for S-26 Gold, S-26 Gold plus 25 µg lutein/L, and S-26 Gold plus 200 µg lutein/L, respectively. Statistically significant increases in plasma zeaxanthin, cis-lutein/zeaxanthin, and cis-beta-carotene were observed in the Gold plus 200 µg lutein/L treatment-group when compared to the control group. Treatment with Gold plus 25 µg lutein/L did not result in significant increases in any of the plasma carotenoids when compared to the control.

These data demonstrate that lutein from FloraGLO Lutein 20% Liquid in Safflower Oil is available from the commercial infant formula matrix, and at a fortification level of 200 µg lutein/L, lutein was absorbed into the plasma of healthy term infants.

Toxicological Studies

The Panel reviewed toxicological studies conducted with FloraGLO Crystalline Lutein, as well as safety studies of lutein and zeaxanthin, in general, from other sources (*e.g.*, other marigold

extracts) that were utilized in the previous determination of the GRAS status of FloraGLO Crystalline Lutein. An additional developmental/reproductive toxicity study of lutein from marigold extract conducted to GLP standards in Sprague-Dawley rats was also reviewed.

In 4-week and 13-week toxicological studies conducted with FloraGLO Crystalline Lutein, no adverse effects were reported in terms of body weight gain, organ weights, feed intake, clinical chemistry, or histopathology in Wistar rats (Kruger *et al*., 2002). Animals were exposed to FloraGLO® Crystalline Lutein in the diet at levels up to 770 mg/kg body weight/day (delivering 640 mg lutein plus zeaxanthin/kg body weight/day) for 4 weeks, or up to 260 mg/kg body weight/day (delivering 210 mg lutein plus zeaxanthin/kg body weight/day) for 13 weeks. The no-adverse-effect levels (NOAELs) for FloraGLO Crystalline Lutein in Wistar rats corresponded to the highest doses tested in each toxicology study; 770 mg/kg body weight/day following 4 weeks of exposure, and 260 mg/kg body weight/day following 13 weeks of exposure.

Additional supportive toxicological studies conducted with rodents have investigated the effects of dietary exposure to lutein and zeaxanthin, from other sources (*e.g*., marigold extract), for 2 to 8 weeks on body weight, feed intake, and organ weights. No changes in body weight gain, feed intake, liver weight, or spleen weight, and no external signs of toxicity were reported in BALB/c mice following 2 to 4 weeks of dietary exposure to up to 800 mg lutein/kg body weight/day and 11 mg zeaxanthin/kg body weight/day (Chew *et al*., 1996; Park *et al*., 1998, 1999). Similarly, no changes in body weights, feed intake, or organ weights were reported in Wistar rats following 16 days of dietary exposure to up to 45 mg lutein/kg body weight/day (Gradelet *et al*., 1996; Jewell and O'Brien, 1999), and 8 weeks of dietary exposure to 500 mg lutein/kg body weight/day was well tolerated in experimental mice models of atherosclerosis (Dwyer *et al*., 2001).

Female Sprague-Dawley rats mated between the ages of 10 to 13 weeks were given lutein supplements from Day 6 to 20 of gestation (Edwards *et al.*, 2002; JECFA, 2006). Beadlets containing 10% lutein (from marigold extract, 79% lutein, 5% zeaxanthin) were mixed into the rats' diets to result in doses of 250, 530, and 1,100 mg lutein/kg body weight/day. No effects on pre- or postimplantation, embryo-fetal survival, or sex ratios were reported. In the offspring, there were no adverse effects on the incidence of external or skeletal abnormalities due to treatment with lutein in any of the dose-groups. A few minor visceral abnormalities in each treatment group were reported, but these were not considered to be treatment-related as their incidence was similar to that for historical controls. A slight dose-related increase in the incidence of rudimentary extra lumbar ribs was reported in the intermediate- and high-dose groups; however, this was not considered to be of toxicological significance due to the reversibility of this minor skeletal finding. Based on the above results, it was determined that the NOAEL for embryotoxicity/teratogenicity in Sprague-Dawley rats was 1,000 mg/kg body weight/day, the highest dose tested.

Human Safety Data

The Panel reviewed the clinical data from safety/tolerance studies that were used to determine the GRAS status of FloraGLO Crystalline Lutein. To confirm the safety of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formulas, the Panel reviewed two additional studies conducted in healthy term infants. The Panel also reviewed several studies conducted with FloraGLO Crystalline Lutein or lutein from other dietary sources published since the determination of the GRAS status of FloraGLO Crystalline Lutein to corroborate the safety of FloraGLO Lutein 20% Liquid in Safflower Oil.

Wyeth Nutrition (2006b) conducted a prospective, randomized, controlled, double-blind clinical trial with parallel groups of healthy term infants to compare infant growth and the incidence of adverse events, blood chemistry, and eye health in relation to the consumption of control formula *vs.* formula fortified with lutein (Capeding *et al.*, 2006; Wyeth Nutrition, 2006b). Infants (230) aged 0 to 14 days were randomized to receive S-26 Gold or S-26 Gold with 200 µg lutein/L for a period of 16 weeks. Ten infants were withdrawn from the study, 3 by the request of a parent/guardian, and 7 due to adverse events (4 in the S-26 Gold treatment group and 3 in the S-26 Gold with lutein treatment group), leaving 220 infants to complete the study. Lutein intake from the S-26 Gold with lutein formula ranged from a mean intake of 190 µg/day in week 4 to a mean intake of 250 µg/day in Week 12. There were no differences in average daily weight gain, mean rate of change in length, or mean rate of increase in head circumference between the treatment groups at any measurement point. A total of 103 adverse events occurred throughout the course of the study [54 in the S-26 Gold treatment group (52.4%) and 49 in the S-26 Gold with lutein treatment group (47.6%)]. Of these, 10 in the S-26 Gold and 8 in the S-26 Gold with lutein treatment groups were reported to be possibly due to the study formula. Of the 10 possibly treatment-related adverse events in the S-26 Gold group, 4 were rashes, 1 was an incident of irritability, 1 was a food intolerance, and 4 were GI disorders (1 occurrence of abdominal pain, 2 occurrences of loose stools, and 1 occurrence of vomiting). Similarly, of the 8 possibly treatment-related adverse events in the S-26 Gold with lutein group, 3 were rashes, 1 was an incident of irritability, 1 was a food intolerance, and 3 were GI disorders (1 occurrence of abdominal pain, 2 occurrences of vomiting). All adverse events but 2 were considered mild to moderate. Two serious adverse events were reported in the S-26 Gold with lutein treatment group (acute gastroenteritis and bronchopneumonia); however, both were considered unrelated to formula administration and were resolved after infant hospitalization. There were no clinically relevant differences in the mean values between the treatment groups for measures of albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, glucose, phosphorus, or total protein. All mean values fell within the range of laboratory values from Soldin *et al.* (1999), a range that was considered representative of an infant population. The Panel concluded that the infant growth and safety study corroborated the safety of FloraGLO Lutein 20% Liquid in Safflower Oil that was established through the preclinical toxicity studies.

Wyeth conducted a second prospective, randomized, double-blind clinical trial with parallel groups of healthy term infants to compare the effect of feeding S-26 Gold with or without added lutein on infant plasma lutein concentrations (Wyeth Nutrition, 2006a). The study was conducted in accordance with GCP/ICH guidelines and all applicable regulations and also included information regarding the growth and safety of the infants. A total of 63 infants were randomized to receive the control formula (S-26 Gold), S-26 Gold plus 25 µg lutein/L or S-26 Gold plus 200 µg lutein/L *ad libitum* for a period of 5 weeks. In the manufacturing of the formula, an innate amount of lutein, 20 µg/L, was present. To accommodate for manufacturing and shelf life loss, lutein was fortified at 150% of the test label claim, *i.e.* S-26 Gold plus 25 µg lutein/L was fortified with 38 µg lutein/L and S-26 Gold plus 200 µg lutein/L was fortified with 300 µg lutein/L. The final lutein content of each test formula by analysis was 20, 47, and 289 µg lutein/L for S-26 Gold, S-26 Gold plus 25 µg lutein/L, and S-26 Gold plus 200 µg lutein/L, respectively. Infant body weight and weight gain, length and length increase, and head circumference and head circumference increase were not statistically different between the treatment groups after 5 weeks of treatment. When compared to the U.S. Centers for Disease Control (CDC) reference population, values for weight-for-age, weight-for-length, and head circumference-for-age indicated that the infants in the study population had appropriate growth. Nineteen adverse events occurred in 15 infants: 10 in the control group, 6 in the Gold plus 25 treatment group, and 3 in the Gold plus 200 treatment group. None of the adverse events was considered to be serious, all resolved during the study, and none was the cause of discontinuation of formula consumption or removal of the infant from the study. While some of the infants withdrew from the study, this was not considered to be associated with the consumption of the study formula containing lutein.

Human safety data published since the GRAS determination of FloraGLO Crystalline Lutein also continues to support its safety at higher levels than is the subject of this notification. A dietary intervention study conducted in patients with age-related macular degeneration using FloraGLO capsules supports the safety of 10 mg lutein/day for a period of 12 months (Richer *et al.*, 2004). Recently published intervention studies conducted with healthy subjects also support the safety of lutein supplementation at levels up to 6 mg lutein/day for periods of up to 60 days (Kiokias and Gordon, 2003; Morganti *et al.*, 2004; Zhao *et al.*, 2006). There were no adverse effects due to lutein supplementation reported in any of the studies. In addition, Shao and Hathcock (2006) conducted a risk assessment for orally administered lutein and concluded that 20 mg *all-trans* lutein/day should be designated as the observed safe level (OSL). Shao and Hathcock (2006) utilized the methodology from the Council for Responsible Nutrition (CRN) Vitamin and Mineral Safety (Hathcock, 2004) and human clinical trial data to determine the OSL for lutein. Of note in their evaluation of the data was the complete absence of any reports of adverse effects, at any of the doses investigated (which ranged to up to 40 mg/day) in all of the published human clinical trials that were evaluated. The authors also noted that in the U.S., the average background consumption of lutein from food sources is low, and therefore, the OSL need not be corrected for background exposure to lutein from the diet.

In addition, studies investigating the relationship of lutein and zeaxanthin to chronic disease published since the GRAS determination for FloraGLO Crystalline Lutein have reported no adverse relationships between increased serum levels of lutein and zeaxanthin, or dietary intake of lutein and zeaxanthin, and eye health (*i.e*., risk of AMD, risk of cataracts) (Gale *et al.*, 2003; Kang *et al.*, 2003; Cardinault *et al.*, 2005; Delcourt *et al.*, 2006; Vu *et al.*, 2006), and no adverse relationships were reported between increased serum or plasma levels of lutein and zeaxanthin and the risk for subsequent myocardial infarction (Hak *et al.*, 2003), progression of intima-media thickness of the common carotid arteries (Dwyer *et al.*, 2004), or generalized cardiovascular disease (Sesso *et al.*, 2005), while an inverse relationship was reported between dietary intake of lutein and zeaxanthin and risk for coronary heart disease mortality (Connor *et al.*, 2004) and coronary artery disease (Osganian *et al.*, 2003). Only 1 epidemiological study reported a positive relationship between dietary intake of lutein and zeaxanthin and the risk for myocardial infarction (Kabagambe *et al.*, 2005). This study also reported an increased risk for myocardial infarction with increased levels of lutein and zeaxanthin in adipose tissue; however, the increased risk was only significant in the 5th quintile for both measures of lutein and zeaxanthin (dietary intake and levels in adipose tissue).

Since the GRAS determination for FloraGLO Crystalline Lutein, lutein and zeaxanthin have also been investigated in several other epidemiological studies examining their relationship to such health concerns as Alzheimer's disease, preeclampsia, respiratory infections, osteoporosis, prelabor rupture of the membranes preterm (PPROM), and inflammatory poly arthritis (Rinaldi *et al.*, 2003; Semba *et al.*, 2003; Williams *et al.*, 2003; van der Horst-Graat *et al.*, 2004; van Herpen-Broekmans *et al.*, 2004; Mathews and Neil, 2005; Pattison *et al.*, 2005; Maggio *et al.*, 2006). There were no adverse relationships between plasma levels, serum levels, or dietary intake of lutein and zeaxanthin and risk for adverse health effects except for risk for PPROM. A positive relationship was reported between serum levels of lutein and risk for PPROM (Mathews and Neil, 2005); however, epidemiological studies provide only correlational data and no other reports of an association between increased serum lutein and increased risk for PPROM were identified in the literature. Thus, the Panel considers this correlation to be of little toxicological significance.

SUMMARY

FloraGLO Crystalline lutein has previously been considered GRAS by an Expert Panel of independent scientists for use in food and has been the subject of a successful GRAS notification, GRAS Notice No. GRN 000140. Subsequent to the GRAS notification, JECFA has completed a safety evaluation of lutein from *Tagetes erecta* L. and assigned an ADI of 0 to 2 mg lutein and zeaxanthin/kg body weight (JECFA, 2006). FloraGLO Lutein 20% Liquid in Safflower Oil is currently intended for use as a food ingredient in infant formulas in the U.S. Furthermore, if lutein is added to infant formulas from this source, the total lutein content in finished infant formula product should not exceed 250 µg/L, which is equivalent to 37.2 µg/ 100 kcal.

Under the intended conditions use of FloraGLO Lutein 20% Liquid in Safflower Oil, a low weight-for-age child (10th percentile) who is a heavy consumer (90th percentile) of lutein from other dietary sources and consumes the highest recommended intake of proposed product will take in approximately 230 µg/kg body weight/day. This is approximately 10% of the JECFA ADI for lutein (JECFA, 2006) and provides approximately a 1,000-fold safety factor compared to the NOAEL of 200 mg/kg body weight/day from the rat study used to establish the JECFA ADI (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002). Whereas lutein exposure attributable solely from the proposed fortification of infant formula is equal to 44 µg/kg body weight/day, or approximately 2.2% of the JECFA ADI for lutein (providing an approximately 5,000-fold safety factor in comparison to the same NOAEL).

Lutein and zeaxanthin are present in human breast milk. In the largest survey to date of breast milk carotenoids, exposure to lutein from human breast milk was demonstrated to range from 3 to 232 µg/L in individual mothers from around the world (Canfield *et al.*, 2003). The proposed maximum total lutein content in finished infant formula product, 250 µg/L, is approximately the upper end of this range and allows for endogenous lutein and overages to compensate for losses during manufacture and shelf life. . FloraGLO Lutein 20% Liquid in Safflower Oil provides the optimal source for use in infant formulas, as the chemical form of lutein is the same as in human milk.

The Panel reviewed preclinical data and concluded that the 13-week toxicity conducted in Wistar rats at doses up to 260 mg FloraGLO Crystalline Lutein/kg body weight/day (corresponding to 210 mg lutein+zeaxanthin/kg body weight/day) (Pfannkuch *et al.*, 2000, 2001; Kruger *et al.*, 2002) and the developmental toxicity study conducted in Sprague-Dawley rats at doses up to 1,100 mg lutein/kg body weight/day (Edwards *et al.*, 2002; JECFA, 2006) were central to the GRAS determination of FloraGLO Lutein 20% Liquid in Safflower Oil for use in infant formula. The Panel also acknowledged that the safety of FloraGLO Lutein 20% Liquid in Safflower Oil was supported by studies conducted using FloraGLO Crystalline Lutein in Fischer 344 rats, tabby cats, and beagle dogs at doses up to 120 mg lutein/kg body weight/day for periods ranging from 8 to 12 weeks (Jenkins *et al.*, 2000; Kim *et al.*, 2000a,b). Additional studies conducted with other sources of lutein and zeaxanthin in mice, rats, and Cynomolgus monkeys at doses ranging from 20 to 800 mg/kg body weight/day for periods of 2 to 52 weeks further support the safety of FloraGLO Lutein 20% Liquid in Safflower Oil (Chew *et al.*, 1996; Gradelet *et al*., 1996; Park *et al.*, 1998, 1999; Jewell and O'Brien, 1999; Dwyer *et al.*, 2001; Schierle *et al.*, 2002).

Intervention studies conducted in healthy adults indicate no adverse effects at doses of up to 20 mg FloraGLO Crystalline Lutein/day for 42 days (Schalch *et al.*, 2001). Additionally, no adverse effects were reported in patients with retinal degenerative diseases at doses of 10 to 30 mg lutein/day from unspecified sources for periods of 6 to 12 months (Aleman *et al.*, 2001; Duncan *et al.*, 2002; Richer *et al.*, 2004; Bahrami *et al.*, 2006). The absorption and bioavailability of

lutein, provided as FloraGLO Lutein 20% Liquid in Safflower Oil from a RTF commercial infant formula, was confirmed in neonatal pigs, rhesus monkeys, and healthy term infants (Kullen, 2006; Kullen and Ramanujam, 2006; Wyeth Nutrition, 2006a). Data from an intervention study demonstrated that oral exposure to FloraGLO Lutein 20% Liquid in Safflower Oil at a targeted concentration of 200 µg lutein/L in infant formula, resulting in a mean intake ranging from 190 to 250 µg lutein/day, for a period of 16 weeks did not result in any adverse health effects in healthy term infants (Capeding *et al.*, 2006; Wyeth Nutrition, 2006b). The Panel considered the results of the infant study to corroborate the safety of FloraGLO Lutein 20% Liquid in Safflower for use in infant formula.

FloraGLO Lutein 20% Liquid in Safflower Oil is manufactured to food grade specifications from the marigold plant, using the same manufacturing process as that for FloraGLO Crystalline Lutein, and there are no indications that the source of material or method of manufacture contribute to any adverse health effects under the intended conditions of use.

Overall, when viewed in its entirety, the scientific evidence presented herein provides no indication that FloraGLO Lutein 20% Liquid in Safflower Oil will produce adverse effects on human health when consumed under the intended conditions of use in infant formulas.

CONCLUSION

We, the Expert Panel, have independently and collectively critically evaluated the available pertinent scientific evidence, and conclude that FloraGLO Lutein 20% Liquid in Safflower Oil, meeting appropriate food grade specifications and manufactured in accordance with current Good Manufacturing Practice, is Generally Recognized as Safe (GRAS), based on scientific procedures, under the intended conditions of use in infant formulas, as specified herein.

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Ramos-Valle, Moraima

From: Debbie.Trinker@kemin.com
Sent: Monday, August 06, 2007 3:14 PM
To: Ramos-Valle, Moraima
Subject: Request for Expedited Review by FDA on GRAS Notification for Lutein in Infant Formula

Dear Moraima:

Last week I sent a letter to Dr. Taratino explaining why Kemin was renewing its request for expedited FDA review and notification on its GRAS notification for Lutein in Infant Formula. Hopefully you received a copy of the letter.

Any assistance that FDA can provide in reviewing the notification and advising Kemin of the results of its review by the end of August, in view of the upcoming CODEX meeting, would be greatly appreciated.

Thank you for your consideration of Kemin's request..
Debbie

Debbie Trinker, Esq.
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September 4, 2007

Via Email
And Courier, Return Receipt Requested

Ms. Moraima Ramos-Valle
Consumer Safety Officer
Office of Food Additive Safety
Division of Biotechnology and GRAS Notice Review
5100 Paint Branch Parkway
College Park, Maryland 20740-3835
Attn: Mail Code HFS-255

RE: GRAS Notification Number GRN 221 Lutein in Infant Formula:
Kemin Response on Request for Clarification

Dear Ms. Ramos-Valle:

This letter responds to your e-mail inquiry of August 31, 2007. With respect to the above-referenced GRAS Notification GRN 221 Lutein in Infant Formula, Kemin confirms that its crystalline lutein is not intended to impart color to the infant formula and does not constitute the use of a color additive under section 201(t)(1) of the Federal Food, Drug and Cosmetic Act, and FDA's implementing regulations in 21 C.F.R. Part 70.

Please feel free to contact me should you have any additional questions on this point of clarification.

Sincerely,

(b)(6)

Deborah Shur Trinker, Esq.
Vice President, Regulatory Affairs