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August 4, 2004

Laura Tarantino, Ph.D.
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

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FOOD ADDITIVE SAFETY

Dear Dr. Tarantino:

In accordance with proposed 21 CFR § 170.36 (notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18937-18964), I am submitting in triplicate, as the representative of the notifier, LycoRed Natural Products Industries, Ltd, P.O. Box 320, Hebron Road, Industrial Zone, Beer-Shiva 84102, Israel, a GRAS notification of Lyc-O-Mato® Oleoresin 6%, with the common name of "Tomato extract containing lycopene (6%)" for use as a dietary addition of lycopene, at levels up to 167 mg/kg (to give a lycopene concentration of 10 mg/kg) in baked goods, breakfast cereals, condiments and relishes, confections, dairy product analogs, frozen dairy desserts, gelatins, puddings and fillings, grain products, gravies, jams and jellies, meat products, milk products, processed vegetables and vegetable juices, snack foods, soft candies and soups and soup mixes. A GRAS panel report, setting forth the basis for the GRAS determination, as well as CVs of the members of the GRAS panel for review by the agency, are also enclosed.

Best regards,

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition

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1. GRAS Exemption Claim

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36 (c) (1)

Lyc-O-Mato® Oleoresin 6% has been determined to be generally recognized as safe (GRAS) and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

Date 4 Aug 04

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
Burdock Group
780 U.S. Highway 1, Suite 300
Vero Beach, FL 32962

(i) Name and Address of the Notifier

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
Burdock Group
780 U.S. Highway 1, Suite 300
Vero Beach, FL 32962

Telephone: 772-562-3900
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(ii) Common Name of the Notified Substance

Tomato extract containing lycopene (6%)

(iii) Conditions of Use

Lyc-O-Mato® Oleoresin 6% is intended to be used as an ingredient to provide consumers with a supplementary source of lycopene in their diets. Lyc-O-Mato® Oleoresin 6% will be used at levels up to 167 mg/kg as a nutrient supplement in baked goods, breakfast cereals, condiments and relishes, confections, dairy product analogs, frozen dairy desserts, gelatins, puddings and fillings, grain products, gravies, jams and jellies, meat products, milk products, processed vegetables and vegetable juices, snack foods, soft candies and soups and soup mixes. This would add a maximum of 10 mg/kg lycopene to the above foods. The estimated mean and 90th percentile intake of lycopene (the main functional ingredient of Lyc-O-Mato® Oleoresin 6%) by the total population from all proposed uses at the maximum use levels in the United States was determined to be 53.88 and 102.6 mg *per* person *per* day, respectively.

(iv) Basis of GRAS Determination

Pursuant to 21 CFR § 170.3, Lyc-O-Mato® Oleoresin 6% has been determined GRAS by scientific procedures for its intended conditions of use. The safety of Lyc-O-Mato® Oleoresin 6% is supported by use of its components in tomato-based foodstuffs for millennia, as well as animal and clinical studies. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of substances used as ingredients in food.

(v) Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at a reasonable time at the office of:

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Alternatively, copies of data and information can be provided to FDA upon request, by contacting Dr. Burdock.

2. Detailed Information About the Identity of the Notified Substance

A. Identity

Lyc-O-Mato® Oleoresin 6% is prepared from a naturally-selected, non-genetically modified, hybrid, high lycopene content (150-250 ppm) variety of tomato (*Lycopersicon esculentum* (L.) Karst Ex. Farwell; tradenames Lycogold™, or LRT 90™; and Lycorich™ or LRT 89™), by an ethyl acetate extraction process. The product contains only the fat-soluble solids from the fruit.

Common or Usual Name: Tomato extract containing lycopene (6%)

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Table 1. General description and analytical information of Lyc-O-Mato® Oleoresin 6%

Botanical Source	*Lycopersicon esculentum* (L.) Karst Ex. Farwell
Physical description	Viscous, dark red liquid.
Packaging	One, 10 and 25 kg aliquots packed under nitrogen in aluminum, HDPE or plastic coated metal containers.
Storage	Store in a cool, dry environment at 4°C.
Labeling	Tomato extract containing lycopene (6%).
Functional Use in Food	Source of supplemental lycopene.

B. Composition

Chemical composition of the tomato extract containing lycopene (6%) is summarized in Table 2. Lyc-O-Mato Oleoresin 6% is an extract of tomatoes that contains a high lycopene content, with lower levels of other carotenoids, phytosterols and tocopherols.

Table 2. Chemical analysis of Lyc-O-Mato® Oleoresin 6%*

Chemical Analysis	Value
Total lycopene	6.0 ± 0.1%
Total tocopherols	1.9 ± 0.3%
Total fatty acids	69 ± 4.8%
Total phytosterols	0.5%
Unsaponifiable matter	16 ± 3.2%
Phytoene	0.5 to 0.75%
Phytofluene	0.4 to 0.65%
ß-carotene	0.2 to 0.35%
Water content	0.15 ± 0.05%

*Further information can be found in Table 3.

C. Method of Manufacture of Lyc-O-Mato® Oleoresin 6%

Production of the tomato extract containing lycopene (6%) starts with the preparation of tomato pulp from naturally selected, non-genetically-modified, hybrid, high lycopene content tomatoes. The tomatoes are selected, crushed and screened and the resulting tomato juice is passed through a heat exchanger and centrifuged to produce the tomato pulp. Pulp with lycopene content greater than 1200 mg/kg is then extracted with ethyl acetate in a three-stage process. All traces of the pulp are removed from the extract, then the ethyl acetate in the extract is removed under vacuum in a three stage stripping process. Only those lots that meet rigorous specifications are packaged and adjusted to achieve the final, 6% lycopene concentration. Lots not meeting specifications are reprocessed (see Figure 1).

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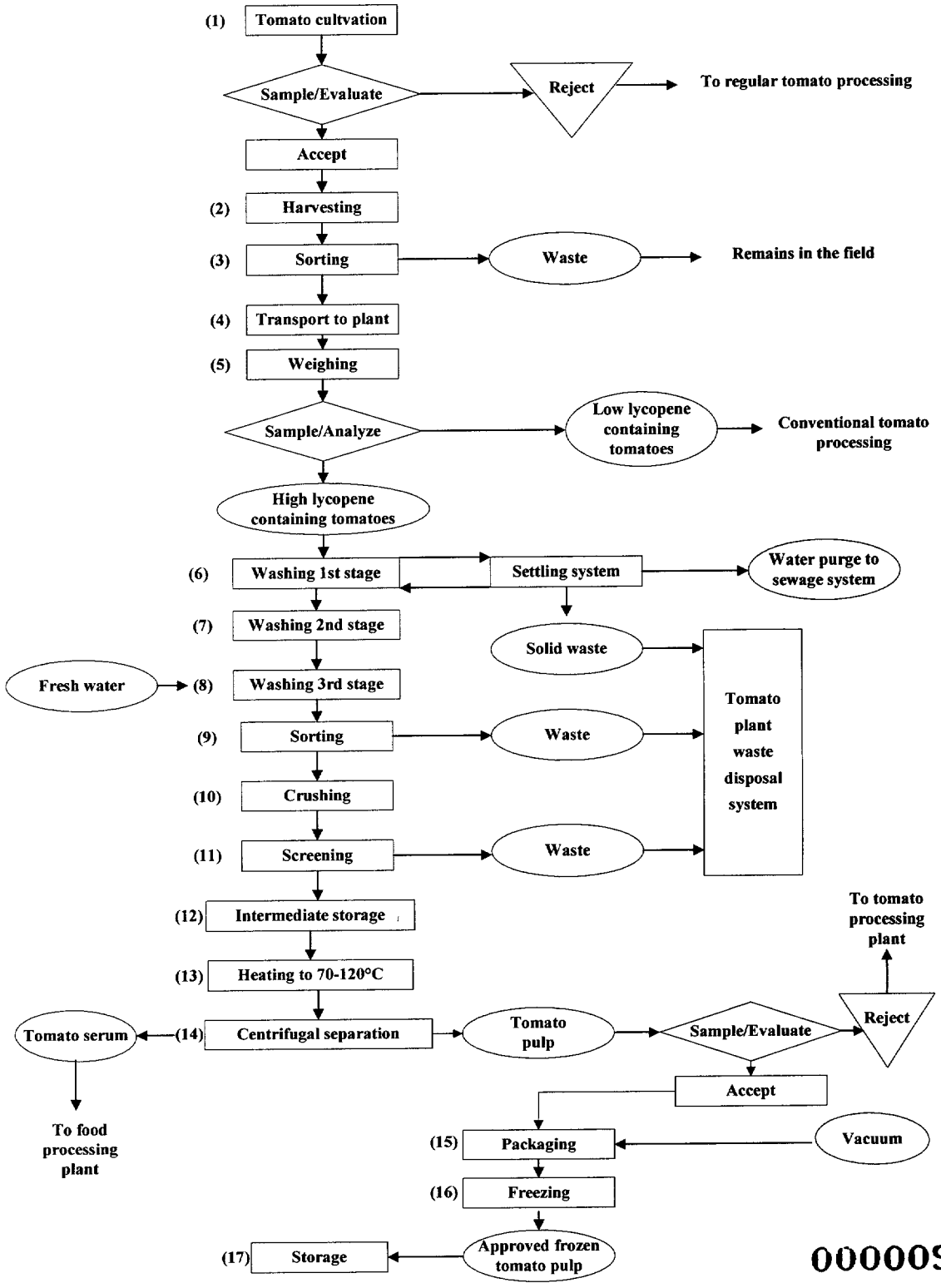
Figure 1. Lyc-O-Mato® Oleoresin 6% production scheme.



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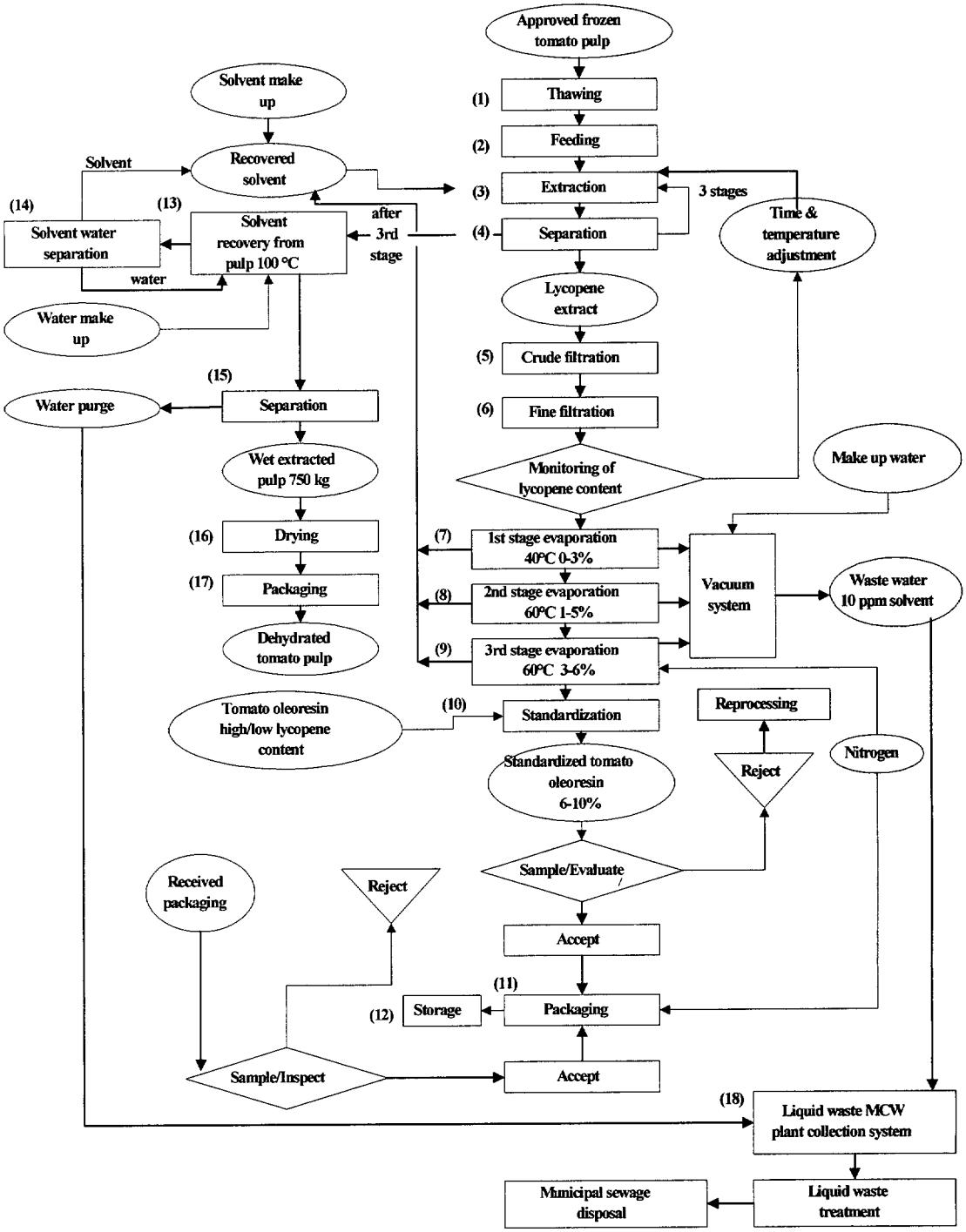

Figure 1, continued. Lyc-O-Mato® Oleoresin 6% production scheme.

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D. Specifications for Food Grade Material

Table 3. Specifications and Analytical Methods of Lyc-O-Mato® Oleoresin 6%.

Analysis	Specification	Method
Clearness	Clear solution	LAB/123/01[a]
Lycopene identity	HPLC retention time	LAB/109/01[a]
Total lycopene[b]	5.0 to 8.0%	LAB/109/01[a]
% *trans*-Lycopene	90 to 95%	LAB/109/01[a]
Total carotenoids	6.5 to 9.0%	LAB/102/02[a]
Other carotenoids	Phytoene: 0.5 to 0.75% Phytofluene: 0.4 to 0.65% ß-carotene: 0.2 to 0.35%	LAB/118/01[a]
Total tocopherols	1.5 to 3.0%	LAB/118/01[a]
Unsaponifiable matter	13 to 20%	Study 98/021[a]
Total fatty acids	60 to 75%	Study 98/021[a]
Phytosterols	0.5 to 2.5%	Study 98/021[a]
Lycopene crystal particle size	90% < 5μ; 99% < 10μ	Microscopic
Water	0.5% max	Karl Fisher
Sulphated ash	0.5 to 1.5 %	AOAC 34.104[d]
Residual solvent (ethyl acetate)	50 ppm max	LAB/114/01[a]
Pesticides	Meets USP 24 NF 19/561	DFG-S19[c]
Heavy metals	Pb < 2ppm Ag, Mo, Cd, Ni, Hg all <1ppm	I.C.P.[c]
Arsenic	As < 2ppm	I.C.P.[c]
Microbiology	Total count < 1000/g Mold, Yeast < 100/g each *Escherichia coli*: 0/10g *Salmonella* sp.: 0/10g *Pseudomonas aeruginosa* 0/10g *Staphylococcus aureus* 0/10g	USP 24 NF 19/<61>

[a]LycoRed method, SOP available on request; [b]Combined *cis*- and *trans*-lycopenes; [c]Analysis method SOP available on request; [d]Official Methods of Analysis of the AOAC International; HPLC = High Performance Liquid Chromatography; ppm = parts per million; USP = United States Pharmacopoeia; NF = National Formulary

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III. Self Limiting Levels of Use

At high levels (in excess of 800 mg/kg), certain food items may acquire an undesirable taste.

IV. Basis of GRAS Determination

The determination that Lyc-O-Mato® Oleoresin 6% is GRAS is on the basis of scientific procedures. See attached- DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® OLEORESIN 6% AS A FOOD INGREDIENT.

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® OLEORESIN 6% AS A FOOD INGREDIENT

March 12, 2004

Panel Members

George A. Burdock, Ph.D., D.A.B.T.

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® OLEORESIN 6% AS A FOOD INGREDIENT

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® OLEORESIN 6% AS A FOOD INGREDIENT

1. SUMMARY

The undersigned, an independent panel of recognized experts (hereinafter referred to as the Expert Panel)[1], qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, was requested by LycoRed Natural Product Industries Ltd. (hereafter referred to as LycoRed) to determine the Generally Recognized As Safe (GRAS) status, based on scientific procedures, of Lyc-O-Mato® Oleoresin 6%. Lyc-O-Mato® Oleoresin 6% is to be used as an ingredient to provide consumers with a supplementary source of lycopene in their diets, so that total daily consumption of lycopene from all sources does not exceed 120 mg *per* day of lycopene. In particular, the Expert Panel has evaluated the proposed use of Lyc-O-Mato® Oleoresin 6% at specified levels in the foods listed in Table 4 of this document. A comprehensive search of the scientific literature was conducted for safety and toxicity information on lycopene and related compounds and, along with supporting documentation, was made available to the Expert Panel. In addition, the Expert Panel independently evaluated materials submitted by LycoRed and other materials deemed appropriate and necessary. Following an independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein.

2. INTRODUCTION

Lyc-O-Mato® Oleoresin 6% is an extract of tomatoes that contains a high lycopene content. Lycopene (ψ,ψ-carotene), the predominant colorant in tomatoes, is an acyclic carotenoid with 11 linear conjugated double bonds (Figure 1). Lycopene is increasingly the subject of intense study because of its potential ability to help maintain the healthy structure and function of the body. Humans do not synthesize lycopene and depend entirely on dietary sources of lycopene such as red and pink colored vegetables and fruits. Lyc-O-Mato® Oleoresin 6% is a good source of lycopene that can be used as an ingredient to provide consumers with a supplementary source of lycopene in their diets. This dossier is a summary of the scientific evidence that supports the general recognition that Lyc-O-Mato® Oleoresin 6% is safe for human consumption as a food ingredient.

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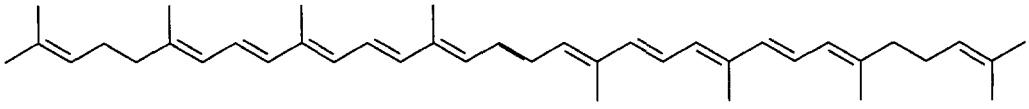
[1] Modeled after that described in Section 201(s) of the Federal Food, Drug, and Cosmetic Act, as amended. See also attachments (*curriculum vitae*) documenting the expertise of the Panel members.

A.



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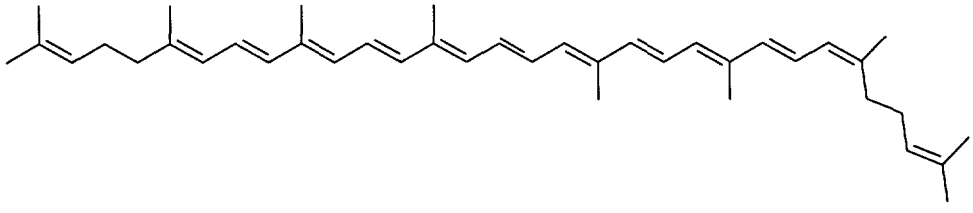

Figure 1 Structures of all-*trans*-Lycopene (A) and 5-*cis*-Lycopene (B)

2.1. Mechanism of Action: Antioxidant

Similar to other carotenoids, lycopene acts as an anti-oxidant, giving rise to the hypothesis that it protects cells against the damaging effects of free radicals. The anti-oxidant properties of lycopene rely on the conjugated double bond system (Figure 1). This system allows the establishment of a resonance condition and stabilizes carbon-centered radicals {Burton, 1984 #211}(Burton and Ingold, 1984). *In vitro*, carotenoids quench singlet oxygen-induced lipid peroxidation and intercept the propagation step of lipid peroxidation {Rice-Evans, 1997 #212;Burton, 1984 #211}(Burton and Ingold, 1984; Rice-Evans *et al.*, 1997). Some *in vitro* studies have reported that the antioxidant activity of β-carotene and possibly other carotenoids, may have shifted into pro-oxidant activity, however, the conditions used to demonstrate this pro-oxidant activity appear non-physiological and require artificially high oxygen concentrations (Burton and Ingold, 1984; Palozza *et al.*, 1997). Thus, it is unlikely that carotenoids are pro-oxidants *in vivo* under normal physiological conditions. An important distinction between lycopene and other carotenoids, such as β-carotene, is that lycopene is not a Vitamin A precursor. This and other differences between lycopene and β-carotene are discussed in greater detail below (see β-carotene human intervention trials).

2.2. Regulatory Status

The European Union's Scientific Committee on Food has ruled that the use of lycopene (Natural Yellow 27) prepared from natural foods (such as tomatoes) by physical processes (*i.e.*, solvent extraction) and containing not less than 5% lycopene is acceptable for use as a colorant in foods including tomato products, confectionery products, and beverages (EU, 1995; EUSCF, 1975). The Committee did not establish an Acceptable Daily Intake (ADI) for lycopene in humans. Lycopene extracted from tomato is also an allowed food colorant in Japan, where it is used in processed vegetable products, soft drinks and confectionery products at levels from 50 to

200 parts per million (ppm). The FDA has recently been notified of a GRAS self-affirmation determination for synthetic lycopene as a food ingredient (BASF, 2002).

Lyc-O-Mato® Oleoresin 6% is currently under final review by the FDA's Division of Petition Review, Office of Food Additive Safety as a food color additive (Color Additive Petition #1C0273) submitted 4 September 2001 (Orstan, A., 2002). The proposed use of tomato lycopene at concentrations up to 50 ppm in foods has received preliminary approval and a regulation concerning its use is currently in preparation. It will be released for public comment in the near future.

Table 1. Physical and chemical properties of *all-trans*-lycopene (Budavari *et al.*, 1996).

Characteristic	Value
CAS No.	all-trans: 502-65-8 all-*cis* : 4418-71-7 15-*cis* : 59092-07-8 13-*cis* : 13018-46-7 9-*cis* : 64727-64-6
Mol. Wt.	536.85
Chemical formula	$C_{40}H_{56}$
Percent Composition	C = 89.5%, H = 10.5%
Melting Point	172-173°C; mp approximately 105°C then solidifies again
Appearance	Long, deep red needles from carbon disulfide + ethanol, from methylene chloride + methanol
Physical form	Solid
Assay	Absorption max, *trans*-form (petroleum ether): 446, 472, 505 nm ($E_{1cm}^{1\%}$ 2250, 3450, 3150). 15,15'-*cis*-Form: mp approximately 105°C then solidifies again; absorption max (petroleum ether): 361, 444, 470, 502 nm ($E_{1cm}^{1\%}$ 1110, 1280, 1660, 1280).
Solubility	One gram dissolves in 50 ml carbon disulfide, in 3 ltr boiling ether, in 12 ltr boiling petr ether, in 14 ltr hexane at 0°C. Sol in chloroform, benzene. Almost insol in methanol, ethanol.

3. MANUFACTURING PROCESS, DESCRIPTION AND SPECIFICATIONS

3.1. Description

The large family of carotenoids is based upon the same C_{40} isoprenoid skeleton. The vast arrays of different structures are brought about through cyclization, addition, elimination, rearrangement and substitution of the isoprenoid skeleton (Rice-Evans *et al.*, 1997). The carotenoids are classified into two major categories: the oxygen-containing xanthophylls (*e.g.* lutein, zeaxanthin, β-cryptoxanthin) and the non-oxygen containing carotenoid hydrocarbons (*e.g.* β-carotene, lycopene). The subject substance of this GRAS monograph is Lyc-O-Mato® Oleoresin 6%, which consists of lycopene, the predominant colorant and antioxidant in the tomato oleoresin, and natural tomato lipid. Lycopene is a hydrocarbon carotenoid composed solely of carbon and hydrogen. Lycopene has 11 conjugated double bonds, which account for its spectral absorbance maximum of approximately 472 nm and its intensely red-orange to red color in concentrated forms (Figure 1). The physical and chemical properties of lycopene and specifications for Lyc-O-Mato® Oleoresin 6% are provided in Table 1 and Table 2, respectively.

3.2. Manufacturing Process and Specifications

Lyc-O-Mato® Oleoresin 6% is manufactured by a patented process (United States Patent, #5,837,311) involving solvent extraction of naturally-selected, non-genetically modified, hybrid, high lycopene content (150-250 ppm) variety of tomato (*Lycopersicon esculentum* (L.) Karst. Ex. Farwell; tradenames Lycogold™, or LRT 90™; and Lycorich™ or LRT 89™). The extract (oleoresin) contains 6% lycopene on average, with the balance made up of other tomato lipids and carotenoids (Table 2).

Production of the tomato lycopene oleoresin is done in two steps. In the first step, high lycopene content tomatoes are used to prepare tomato pulp (Figure 2). After sorting and washing, the tomatoes are crushed and screened. The resulting tomato juice is passed through a heat exchanger at 80 to 90°C and centrifuged to produce the tomato pulp. Pulp with a satisfactory lycopene content (>1200 ppm lycopene) is cooled, packed into laminate bags under nitrogen, then into drums, and stored at -18°C until extracted. The production process introduces no exogenous substances to the tomato pulp.

In the second step, lycopene is extracted from the tomato pulp (Figure 3). The tomato pulp is crushed and extracted with ethyl acetate in a three-stage extraction process. After each stage, the pulp is separated from the lycopene extract and the extract filtered twice to remove all traces of pulp from the extract. The ethyl acetate in the extract is then removed under vacuum at 40 to 60°C in a three stage stripping process. The resulting oleoresin is then analyzed for lycopene content as well as for solvent residues, pesticides, water content, microbiological contamination, and metals (Table 2). Only those lots meeting specifications are packaged. Lots not meeting specifications are reprocessed. Lots may be mixed to achieve the final, 6% lycopene concentration.

The final product, Lyc-O-Mato® Oleoresin 6%, is available in 1, 10 and 25 kg aliquots packed under nitrogen in aluminum, HDPE, or plastic coated metal containers and stored at 4°C.

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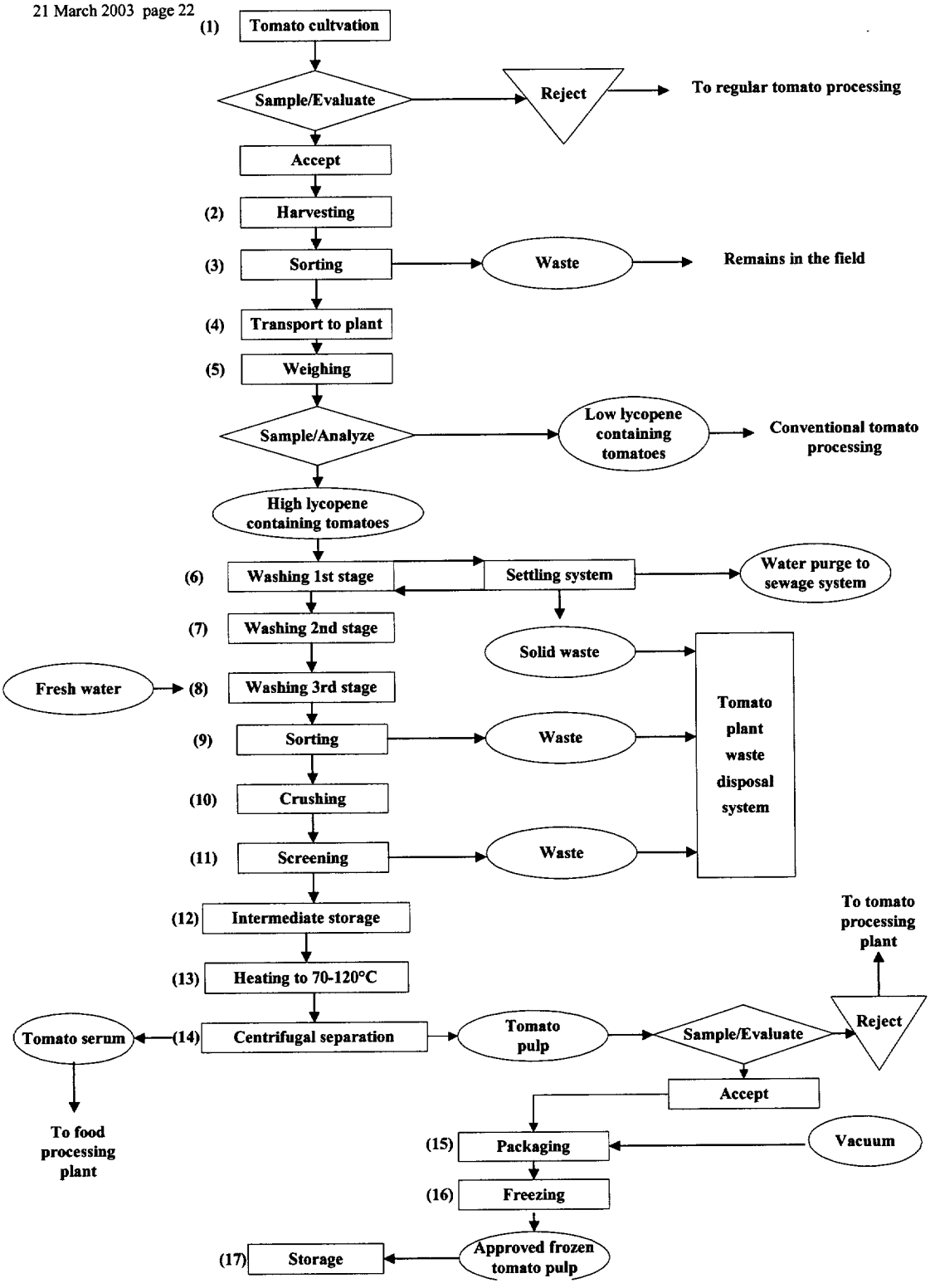

Figure 2. Pulp production scheme

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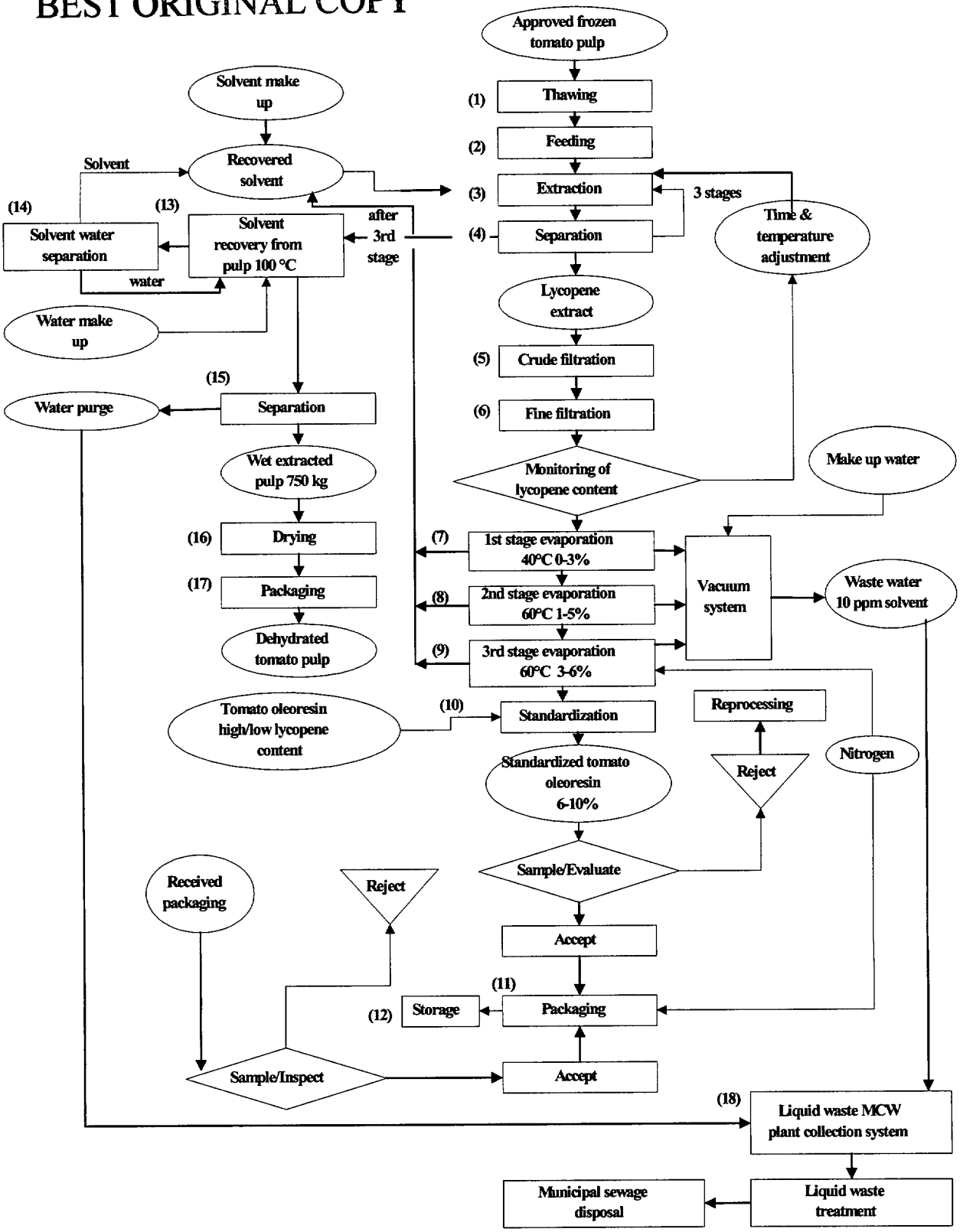

Figure 3. Lyc-O-Mato® Oleoresin 6% production scheme.

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Table 2. Specifications of Lyc-O-Mato® Oleoresin 6%.

Analysis	Method	Specification	Batch Analysis Results (N=3-12) Range	Average
Clearness	LAB/123/01	Clear solution	Passes	Passes
Lycopene identity	LAB/109/01[a]	HPLC retention time	24 to 25.2 min	24.8 ± 0.6 min (N=10)
Total lycopene[b]	LAB/109/01[a]	5.0 to 8.0%	5.8 to 6.2%	6.0 ± 0.1% (N=12)
% *trans*-Lycopene	LAB/109/01[a]	90 to 95%	90-91%	90.4 ± 0.11% (N=4)
Total carotenoids[c]	LAB/102/02[a]	6.5 to 9.0%	6.6 to 7.0%	6.8 ± 0.2% (N=12)
Other carotenoids	LAB/118/01[a]	Phytoene: 0.5 to 0.75% Phytofluene: 0.4 to 0.65% ß-carotene: 0.2 to 0.35%	0.5 to 0.7% 0.4 to 0.61% 0.2 to 0.31%	0.59 ± 0.05% (N=12) 0.53 ± 0.06% (N=12) 0.27 ± 0.03% (N=12)
Total tocopherols	LAB/118/01	1.5 to 3.0%	1.5 to 2.5%	1.9 ± 0.3% (N=12)
Unsaponifiable matter	Study 98/021[a]	13 to 20%	13 to 19%	16 ± 3.2% (N=3)
Total fatty acids[d]	Study 98/021	60 to 75%	64 to 74%	69 ± 4.8% (N=3)
Phytosterols	Study 98/021	0.5 to 2.5%	0.5 to 2.5%	0.5%
Lycopene crystal particle size	Microscopic	90% < 5μ 99% < 10μ	Passes	Passes
Water	Karl Fisher	0.5% max	0 to 0.5%	0.15 ± 0.05%
Sulphated ash	AOAC 34.104	0.5 to 1.5 %	0.7 to 0.9 %	0.8 ± 0.1 %
Residual solvent (ethyl acetate)	LAB/114/01[a]	50 ppm max	10 to 50 ppm	30 ± 20 ppm
Pesticides	DFG-S19[e]	Meets USP 24 NF 19/561	Meets USP	Total ≤ 3 ppm
Heavy metals	I.C.P.[e]	Pb < 2ppm Ag,Mo,Cd,Ni,Hg all <1ppm	Meets limits	Each < 1ppm
Arsenic	I.C.P.[e]	As < 2ppm	Meets limit	≤ 0.5 ppm
Microbiology	USP 24 NF 19/<61>	Total count < 1000/g Mold, Yeast < 100/g each *Escherichia coli*: 0/10g *Salmonella* sp.: 0/10g *Pseudomonas aeruginosa* 0/10g *Staphylococcus aureus* 0/10g	Meets limits	All less than limits

[a]LycoRed Method, SOP available on request.
[b]Combined *cis*- and *trans*-lycopenes.
[c]Calculated as lycopene.
[d]Free fatty acids (myristic acid (14:0); palmitic acid (16:0); stearic acid (18:0); oleic acid (18:1); linoleic acid (18:2); linolenic acid (18:3); arachidic acid (20:0); behenic acid (22:0)); mono-, di- and tri-glycerides
[e]Analysis method SOP available on request.

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3.3. Stability

Lyc-O-Mato® Oleoresin 6%, is very stable for at least two years at 4°C with some minimal degradation occurring after storage for 2 years at room temperature (LycoRed, 2003a).

Lyc-O-Mato® Oleoresin 6% was evaluated for its use in foods by assessing the stability of lycopene at concentrations in food ranging from 3 to 60 ppm (Table 3). Equivalent commercial products or foods formulated with β-carotene were used as controls if appropriate.

Table 3. Levels of Lyc-O-Mato® Oleoresin 6% tested for stability in the indicated foods.

Food	Lyc-O-Mato® Oleoresin 6% (ppm)[a]	Control Colorant
Orange gelatin	10-30	Yellow 6/Red 40[b]
Yellow cake	20-30	β-Carotene (80)
Lemon beverage	3-60	NC[c]
Orange hard candy	5-20	NC
Ice cream	10-20	NC
Salad dressing	20-50	NC
Margarine	0.5-1.0	β-Carotene (2)

[a]ppm=part per million; [b]Commercial formulation; [c]No control

After formulation and processing, the foods were analyzed for color using Hunter Colorimetry and samples taken for HPLC analysis of lycopene content. The foods were then stored for 5 days at normal storage temperatures (room temperature, 4°C, or frozen, as appropriate) under fluorescent light to assess lycopene stability. After storage, the foods were again analyzed by Hunter Colorimetry and HPLC.

No obvious color changes were seen in the foods by visual inspection and Hunter Colorimetry showed no significant changes in total color. HPLC analysis and recovery studies showed little loss of lycopene in the foods in storage (LycoRed, 2003b). Ninety five percent of the added lycopene was recovered at the time of formulation and ninety percent five days after formulation, which are very high levels when considering normal losses with chemical extraction methodology. Thus, the chemical stability of lycopene under these food processing conditions demonstrates that Lyc-O-Mato® Oleoresin 6% is a stable food ingredient in a variety of foods.

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4. ESTIMATED DAILY INTAKE

Table 4. Food groups selected for Lyc-o-Mato® Oleoresin 6% supplementation*.

Food Category	Intended use level (mg/kg) Lyc-O-Mato® Oleoresin 6%	Lycopene
Baked goods and baking mixes, including all ready-to-eat and ready-to-bake products, flours, and mixes requiring preparation before serving (1)	167	10
Breakfast cereals, including ready-to-eat and instant and regular hot cereals (4)	167	10
Cheeses, including curd and whey cheeses, cream, natural, grating, processed, spread, dip, and miscellaneous cheeses (5)	167	10
Condiments and relishes, including plain seasoning sauces and spreads, olives, pickles, and relishes, but not spices or herbs (8)	167	10
Confections and frostings, including candy and flavored frostings (9)	167	10
Dairy product analog, including nondairy milk, frozen or liquid creamers, coffee whiteners, toppings, and other nondairy products (10)	167	10
Frozen dairy desserts and mixes, including ice cream, ice milks, sherbets, and other frozen dairy desserts and specialties (20)	167	10
Gelatins, puddings, and fillings, including flavored gelatin desserts, puddings and custards, parfaits, pie fillings, and gelatin base salads (22)	167	10
Grain products and pastas, including macaroni and noodle products, rice dishes, and frozen multi-course meals, without meat or vegetables (23)	167	10
Gravies and sauces, including all meat sauces and gravies, and tomato, milk, buttery, and specially sauces (24)	167	10
Jams and jellies, commercial, including only commercially processed jams, jellies, fruit butters, preserves, and sweet spreads (28)	167	10
Meat products, including all meats and meat containing dishes, salads, appetizers, frozen multi-course meat meals, and sandwich ingredients prepared by commercial processing or using commercially processed meats with home preparation (29)	167	10
Milk products, including toppings, snacks dips, spreads, weight control milk beverages, and other milk origin products (31)	167	10
Processed vegetables and vegetable juices, including all commercially processed vegetable, vegetable dishes, frozen multi-course vegetable meals, and vegetable juices and blends (36)	167	10
Snack foods, including chips, pretzels, and other novelty snacks (37)	167	10
Soft candy, including candy bars (38)	167	10
Soups and soup mixes, including commercially prepared meat, fish, poultry, vegetable, and combination soups and soup mixes (40)	167	10

*The food categories correspond to those listed in 21 CFR 170.3(n). The number in parenthesis following each food category is the paragraph listing in 21 CFR 170.3(n) for that food category.
ppm=parts *per* million.

The intake profile (amount and frequency) by individuals in USDA's Continuing Survey of Food Intakes by Individuals 1994-96, 98 (CSFII 1994-96, 2000) was used to calculate the estimated daily intake (EDI) of Lyc-O-Mato® Oleoresin 6% and lycopene for individuals consuming the food groups selected for the addition of Lyc-O-Mato® Oleoresin 6% *per* this GRAS evaluation. The reference to lycopene in this GRAS review is due to its biological significance. The food groups as defined by the FDA (21 CFR 170.3(n)) are listed in Table 4.

The means and 90th percentile EDIs were calculated (as indicated in Table 5) for: (1) current lycopene intake from natural sources (line 'A'); (2) lycopene intake following addition of Lyc-O-Mato® Oleoresin 6% to the selected food groups (line 'B'); (3) lycopene intake following addition of Lyc-O-Mato® Oleoresin 6% to the selected food groups as a color additive (line 'C') and; (4) total estimated EDI from natural sources combined with levels from addition to the foods (line 'D').

Foods in which lycopene is a known constituent were identified using the USDA-NCC[2] carotenoid database as reported by Holden *et al* (1999). The USDA-NCC database also provided the concentration of lycopene in these foods. A total of 26 foods and food products were selected that included fruits, vegetable products, meat products, as well as tomato and tomato products. Food and lycopene consumption were estimated by (1) weighting of the data for estimation of consumption by individuals in the entire United States population and (2) multiplying the estimated food consumption (grams food/day) with the lycopene concentration (mg lycopene/g food). The current consumption analysis done presently of all individuals that consume lycopene-containing foods indicates that the mean daily intake for lycopene is estimated to be 8.2 mg/day, with a 90th percentile intake of 15.7 mg/day (Table 5, line A). If Lyc-O-Mato® Oleoresin 6% is added to the selected foods at the levels specified in Table 4, the added mean and 90th percentile lycopene consumption will be 10.4 mg/day and 17.7 mg/day, respectively (Table 5, line B).

A Color Additive Petition for Lyc-O-Mato® Oleoresin 6% was recently submitted with the FDA (Color Additive Petition #1C0273). This may add to the consumption of lycopene and Lyc-O-Mato® Oleoresin 6% in the diet. The stated use level of Lyc-O-Mato® Oleoresin 6% as a color additive is not to exceed 50 ppm, which would equate to a mean of 5.28 mg/day and a 90th percentile 9.20 mg/day intake of lycopene, in the foods found in Table 4 (Table 5, line C).

Combining the current and added intake levels (added lycopene consumption from Lyc-O-Mato® Oleoresin 6% as both a food ingredient and as a color additive) gives the total lycopene consumption level. The estimated total mean consumption of lycopene, if Lyc-O-Mato® Oleoresin 6% were added to the selected foods at the levels specified in Table 4 (as a food ingredient summed with that added as a color additive) would be 23.88 mg/day, while the 90th percentile consumption of lycopene would be 42.6 mg/day, (Table 5, line D).

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[2] United States Department of Agriculture-Nutrition Coordinating Center

A possible source of lycopene and Lyc-O-Mato® Oleoresin 6% in the diet is from consumption of dietary supplements. Lyc-O-Mato® Oleoresin 6% consumption from dietary supplements is difficult to determine from currently available data. The 1987 National Health Interview Survey identified that 51.1% of the adults aged 19-99 years in the US consumed a vitamin/mineral supplement in the past year, but that only 23.1% did so daily (Subar and Block, 1990). Multivitamins were the most commonly consumed supplement at that time. Lyc-O-Mato® Oleoresin 6% is available as a dietary supplement (Lyc-O-Mato® Lycopene Softgels™, Healthy Origins, Pittsburgh, PA), with one 250 mg Lyc-O-Mato® Oleoresin 6% capsule providing 15 mg lycopene. Since there are no available statistical data on consumption of dietary supplements that are a source of lycopene, we have used the levels reported in labeling as a basis for estimating consumption ranges (Healthy Origins, 2003). Thus, the potential theoretical lycopene consumption from dietary supplements may equal 30 mg[3] (Table 5, line E) from 500 mg Lyc-O-Mato® Oleoresin 6%. These estimates need to be added to those in Table 5 to arrive at the total potential theoretical background consumption of lycopene from both conventional food and dietary supplements (Table 5, line F).

Table 5. Current lycopene intake, predicted lycopene intake following supplementation of selected foods at the indicated levels (Table 4) and potential total lycopene intake (predicted + current) for individuals consuming selected supplemented foods and dietary supplements.

	Per User (mg/day)	
Lycopene intake from:	**Mean**	**90th Percentile**
A. Current consumption from food	8.2[a]	15.7
B. Possible maximum consumption with Lyc-O-Mato® Oleoresin 6% as an added ingredient to food [b]	10.4	17.7
C. Amount consumed as a color additive	5.28	9.20
D. Total from conventional food (current + added)	23.88	42.6
E. Potential dietary supplement use	30.0	60.0
F. Potential total lycopene from all sources (food + dietary supplements)	53.88	102.6

[a] Levels calculated using consumption values from CSFII 1994-1996, 1998 (CSFII 1994-96, 2000) and food lycopene concentrations from Holden *et al.*, 1999.
[b] Levels calculated using consumption values from CSFII 1994-1996, 1998 (CSFII 1994-96, 2000) and lycopene levels from Table 4 (See text for details).

[3] The website recommends two 15 mg capsules *per* day.

It should be noted, however, that the Color Additive Petition for Lyc-O-Mato® Oleoresin 6% addition to foods is set at a maximum addition of 50 ppm of liquid, solid or semisolid food. Assuming Lyc-O-Mato® Oleoresin 6% was added to all foods eaten (3000 grams/person/day, liquid and solids) at 50 ppm, the total amount of lycopene that could be consumed as a color additive would be 150 mg/day.[4] In reality, the addition of lycopene as a color additive at this maximal level of 150 mg/day would be very difficult to achieve.

5. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION (ADME)

Lyc-O-Mato® Oleoresin 6% is a food ingredient source of lycopene, which is the most abundant carotenoid in Lyc-O-Mato® Oleoresin 6%. There were numerous studies identified in the public literature that reported on the ADME of lycopene from various sources.

Carotenoids, which are fat-soluble compounds, are absorbed in parallel with fat digestion and absorption. Chylomicrons are the main intestinal lipoprotein particles responsible for the transport of carotenoids, retinyl esters and other fat-soluble vitamins in the lymphatic system. Thus, the carotenoid pattern in chylomicrons is an early indicator for carotenoid composition of these compounds after absorption from the gut, before liver-dependent modifications will occur. Lipoproteins are structured such that the more polar constituents are situated toward the outside of the lipoprotein, whereas the more non-polar compounds, such as lycopene, are located toward the inner core (Bierer *et al.*, 1995). In the systemic circulation, chylomicrons are processed to chylomicron remnants, which are taken up primarily by the liver (Wingerath *et al.*, 1995). Once in the liver, the internalized hydrocarbon carotenoids (*e.g.*. lycopene) are then assembled into very low-density lipoproteins (VLDL) and released into the blood circulation, or in the case of β-carotene, are also utilized to produce retinoids (Wingerath *et al.*, 1995).

Interactions between carotenoids exist that can affect the bioavailability of other carotenoids (reviewed in van den Berg, 1999). The best evidence of this occurring is between the hydrocarbon carotenoid β-carotene and the oxycarotenoids lutein and canthaxanthin. Evidence demonstrating interactions between lycopene and other carotenoids is not well understood

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[4] This is an extremely conservative assumption as (1) the 3000 gms/day includes foods which would not be colored (*e.g.*, water; fresh vegetables, meat, poultry and dairy products and; other products whose standard of identity would preclude addition of a color additive); (2) there are certain technical limitations of Lyc-O-Mato Oleoresin 6% as a food color (*e.g.*, it is not compatible with aqueous systems and the development of a strong tomato flavor at higher use levels) and; (3) all foods consumed (solid and liquid) would be colored red; in reality, few foods are colored red (exposure to citrus red color was 0.00008474 mg/kg; carmine color was 0.03686 mg/kg; grape skin extract was 0.06398 mg/kg, canthaxanthin was 0.001483 mg/kg, cochineal was 0.002683 mg/kg); as compared to foods colored brown, *e.g.*, caramel color, which is consumed at a level of 132 mg/kg (~8000 mg/day) (Clydesdale, 1997a; 1997b; 1997c; 1997d; 1997e; 1997f). However, because addition of lycopene as a color additive to all foods is technically impossible, if it is assumed that half of the liquid consumed (1500/2 = 750 grams) and half of the solid/semi-solid food consumed (1500/2 = 750 grams) is either fresh or standardized, precluding the addition of color and, of the remaining 1500 grams, one half is technically incompatible with the addition of lycopene, the remaining 750 grams is colored with lycopene (to the exclusion of all ~125 color additives/adjuncts), at 50 ppm, approximately 38 mg could be consumed.

because of many discrepancies between studies. Thus, at this time it is unknown whether lycopene can affect the bioavailability or biological effects of other carotenoids.

The predominant form of lycopene in foods is all-*trans*-lycopene, including Lyc-O-Mato® Oleoresin 6% (90-95%), but the predominant forms of lycopene identified in human serum and tissues are the *cis*-isoforms. Some investigators have suggested that the *cis*-lycopene isomers that are in food are preferentially absorbed (Boileau *et al.*, 2002). While others have suggested -and provided evidence- that the *trans*-isomer is isomerized to the *cis*-isomers by the gastric milieu prior to absorption (Holloway *et al.*, 2000; Re *et al.*, 2001). The proportions of the *cis/trans* isomers in serum appear constant regardless of the isomer distribution in the supplement/diet, thus serum isomer distribution appears to be independent of that in the supplement/diet. The majority (>50%) of tissue and serum lycopene consists as the 9-*cis*-, 13-*cis*- and 15-*cis*-isomers, while the 5-*cis*- and 9-*cis* are the main *cis*-isomers in plasma.

Lycopene is found predominantly in the testes and adrenals with significant amounts found in the liver, adipose tissue, prostate, kidney and ovary. Elimination of lycopene is by first-order kinetics providing a plasma half-life of 2 to 33 days (Brown *et al.*, 1989; Burri *et al.*, 2001; Rock *et al.*, 1992; Stahl and Sies, 1992). Human studies on the absorption and bioavailability, distribution, metabolism and elimination of lycopene are summarized below.

5.1. Absorption and Bioavailability

In men and women on self-selected diets, 43% and 35% of the total carotenoids measured in plasma were lycopene, respectively (Micozzi *et al.*, 1992; Yong *et al.*, 1994).

Olmedilla *et al.* (2002) reported the results from a multicenter, placebo-controlled intervention study in healthy male and female volunteers (N=400) recruited from five European regions designed to study the serum response of carotenoids and tocopherols. Subjects given ~222 mg/day Lyc-O-Mato® Oleoresin 6% (containing 13.3 mg/day lycopene) for 20 weeks had a 2-fold increase in serum lycopene. In addition, the isomer distribution of lycopene in the serum remained constant, regardless of the lycopene isomer composition in various natural extracts in the capsules from the different treatment groups. In Spanish volunteers, additional data showed that the serum response to lycopene supplementation reached a plateau after 4 weeks.

In a crossover study, volunteers (N=15F/9M; 5F/3M/group), after a 2-week lycopene depletion period, were given 4-weeks of lycopene (5 mg/day) in the form of capsules containing processed tomato oleoresins or processed tomato oleoresin formulations or synthetic lycopene (Böhm, 2002). Plasma lycopene levels at the end of the study period relative to week 1 of supplementation were elevated in all groups. The greatest absorption of lycopene was observed in subjects consuming capsules containing tomato lipids combined with lycopene crystal sizes < 10 μm in diameter.

A double-blind, randomized, crossover study was conducted in healthy men (N=10) who received either all-*trans* β-carotene (0.11 mmol; 60 mg) or all-*trans* lycopene (0.11 mmol; 60 mg) or by a combined oral dose of 0.11 mmol each (Johnson *et al.*, 1997). Serum lycopene concentrations significantly increased from baseline at 5 hours after the lycopene dose and returned to baseline thereafter with significant increase in serum concentrations still observed at 24 hours. The 24-hour area under the curve (AUC) for lycopene was significantly greater when

lycopene was ingested with β-carotene than when ingested alone. Thus, ingestion of a combined dose of β-carotene and lycopene possibly improved the absorption of lycopene in men.

Lycopene bioavailability from a single dose of fresh tomatoes or tomato paste (23 mg lycopene) was studied in healthy subjects (N=5) (Gartner *et al.*, 1997). The lycopene isomer pattern was the same in both fresh tomatoes and tomato paste. Compared to fresh tomatoes, ingestion of tomato paste was found to yield 2.5-fold higher total and all-*trans*-lycopene peak concentrations and 3.8-fold higher area under the curve (AUC) responses. Only the AUC response for the *cis*-isomers was significantly higher after ingestion of tomato paste compared to fresh tomatoes.

Stahl and Sies (1992) studied the absorption of lycopene from processed (boiled with 1% corn oil for 1 hour) and unprocessed tomato juice in humans. Serum lycopene concentrations increased only when processed tomato juice was consumed. Peak serum lycopene concentrations were reached between 24 and 48 hours. Absorption was dose-dependent, but not linear, as there was greater absorption at lower doses. Absorption of 9-*cis* and 13-*cis* isomers was somewhat better than the all-*trans* form.

Men (N=30) on a controlled diet were fed defined daily doses of carotenoids, including lycopene, from foods (broccoli, carrots, or tomato juice) for 6 weeks (Micozzi *et al.*, 1992). Compared with baseline, lycopene declined in all groups except the tomato-juice group.

In a randomized, crossover study design, the bioavailability of lycopene from tomato juice and 2 dietary supplements, each containing 70-75 mg lycopene, was studied in healthy volunteers (N=15) (Paetau *et al.*, 1998). Subjects ingested lycopene-rich tomato juice, Lyc-O-Mato® Oleoresin 5% (the same as Lyc-O-Mato® Oleoresin 6%, but with average lycopene concentration of 5%), lycopene beadlets, and a placebo for 4 weeks each while consuming self-selected diets. Compared to the placebo group, plasma lycopene concentrations were significantly higher in subjects consuming all forms of lycopene sources with no differences in mean lycopene levels (~0.24 μmol/L) between the treatment groups. Subjects in the three treatment groups also had increased plasma concentrations of phytofluene and phytoene, which were present in small amounts in tomato juice, Lyc-O-Mato® Oleoresin 5% and lycopene beadlets. Beta-carotene, zeta-carotene, and 2,6-cyclolycopene-1,5-diol (a metabolite of lycopene), also present in tomato juice and supplements, were significantly increased with consumption of the tomato juice and lycopene beadlets, but not with Lyc-O-Mato® Oleoresin 5% consumption. Thus, lycopene appears to be equally bioavailable from tomato juice and the supplements used in this study.

Following seven days of a lycopene-free diet, plasma lycopene concentrations were measured in healthy female subjects (N=11) that consumed 25 g tomato puree daily (containing 7.0 mg lycopene) for 14 consecutive days (Pellegrini *et al.*, 2000). The mean plasma lycopene levels increased approximately 3-fold by day 14 (0.57 μmol/L) when compared with baseline plasma levels (0.13 μmol/L).

Plasma lycopene concentrations increased by 3-fold in adult women (N=9) that consumed 25 g tomato puree (containing 7 mg lycopene) for 14 consecutive days, after a 7-day

washout period (Porrini and Riso, 2000). The mean plasma lycopene concentrations were 0.13 μmol/L and 0.55 μmol/L at day 0 and day 14, respectively.

Porrini *et al.* (1998) studied the relationship between duration of lycopene intake and food matrix on plasma lycopene concentrations in healthy female subjects. Following a one-week lycopene-free washout period, subjects were given 16.5 mg/day total lycopene in tomato purée or fresh raw tomato for a single day (N=9) or seven consecutive days (N=10). In subjects consuming tomato products for a single day, the plasma area under the curve (AUC) (calculated from time 0 to 104 hours after consumption) for total lycopene and all-*trans*-lycopene, but not *cis*-lycopene, was significantly increased in the tomato purée group compared with the raw tomato group. In subjects consuming tomato products for seven consecutive days, the AUC (calculated from day 0 to day 11 after first consumption) for total-, *trans*- and *cis*-lycopene was significantly higher in the tomato purée group compared with the raw tomato group. Thus, there is a significant effect of food matrix on lycopene bioavailability.

After a 3-week lycopene-restricted washout period, healthy subjects ingested 25 mg lycopene/day for 8 weeks from Lyc-O-Mato® Oleoresin 6% in whey protein (lactolycopene; N=4M/6F), tomato paste (positive control; N=5M/7F) or a placebo of whey proteins (N=4M/7F) while consuming their self-selected diets (Richelle *et al.*, 2002). Plasma lycopene concentrations reached a maximum after 2 weeks of supplementation in both lycopene-treated groups and then a plateau was maintained until the end of the treatment. The mean plasma lycopene at week 8 were significantly increased in the treatment groups compared with placebo controls, but they were not different from each other (lactolycopene group=0.58 μmol/L; tomato paste group=0.47 μmol/L). Although lycopene was present mainly as all-*trans* isomers (>90%) in lactolycopene and tomato paste, plasma lycopene enrichment consisted of 40% as all-*trans* and 60% as *cis*-isomers. These results indicate that the lactolycopene formulation and tomato paste exhibited similar lycopene bioavailability in plasma.

In a crossover study, renal transplant patients (N=15) were randomized to daily consumption (400 ml/day) of either tomato juice or synthetic orange drink for 4 weeks (Sutherland *et al.*, 1999). At week 4, plasma lycopene levels were significantly higher in patients that consumed tomato juice (1.57 μmol/L) compared with baseline levels (0.86 μmol/L) and in patients that consumed orange drink (0.91 μmol/L).

In a crossover study designed to measure the interactions of carotenoids during absorption, a study group of males (N=20) on a carotenoid-restricted diet received a single oral dose of 15 mg lycopene (Lyc-O-Mato® Oleoresin 5%) plus 15 mg β-carotene (palm oil carotenoids) (van den Berg and van Vliet, 1998). The areas under the curve (AUCs) for the lycopene plus β-carotene group was similar to the AUC for the β-carotene only group. Therefore, ingestion of a combined dose of β-carotene and lycopene (from (Lyc-O-Mato® Oleoresin 5%) did not interfere with each others absorption.

In a split plot design, men and women consumed whole tomatoes, mildly homogenized tomatoes or severely homogenized tomatoes that were either minimally heated or extensively heated (N=33/group) (van het Hof *et al.*, 2000). The tomato products were consumed daily (22 mg/day lycopene) for 4 days. Plasma lycopene levels were measured at day 0 and day 4. The greatest lycopene absorption was observed in extensively heated, severely homogenized

tomatoes. Thus, the intactness of the cellular matrix of tomatoes determines the bioavailability of carotenoids and matrix disruption by mechanical homogenization and/or heat treatment enhances the bioavailability.

Following two weeks on a low-carotenoid diet, female adults (N=22) were randomized into three groups that received a 5 mg/day lycopene for 6-weeks provided through a daily portion of tomatoes (N=6), tomato juice or Lyc-O-Mato® Oleoresin 6% in soft gel capsules (Böhm and Bitsch, 1999). Plasma lycopene levels increased to a similar level in subjects consuming Lyc-O-Mato® Oleoresin 6% and tomato juice, but no increase in plasma lycopene was observed in those consuming raw tomatoes. Thus, lycopene from Lyc-O-Mato® Oleoresin 6% capsules and tomato juice (processed tomatoes) was better absorbed from the intestine than lycopene from raw tomatoes.

In a crossover study, Lee *et al.* (2000) compared the effect of consumption of tomato products with extra-virgin olive oil vs. tomato products plus sunflower oil on plasma lycopene levels. Subjects (N=3M/5F) consumed tomato products (canned tomatoes (230 g) and tomato soup (200 g); ~ 46 mg lycopene) prepared with the same oil daily for 7 days. Results showed that the oil composition does not affect the absorption of lycopene from tomato products because similar mean levels of plasma lycopene were obtained on feeding tomatoes with either olive oil (1.2 μmol/L) or sunflower oil (1.14 μmol/L).

Following a two week carotenoid-depletion period, healthy male volunteers (N=23) consumed successively for two weeks each, 330 mL tomato juice (40 mg lycopene), 330 mL carrot juice (15.7 mg α-carotene and 22.3 mg β-carotene) and 10 g spinach powder preparation (11.3 mg lutein and 3.1 mg β-carotene) served with main meals (Müller *et al.*, 1999). During the tomato juice intervention, plasma concentrations of *trans*- and *cis*-lycopene increased 2.4-fold, compared to the depletion period, with no differences found in the *trans*-to-*cis* isomer ratios. Lycopene oxidation products (*e.g.*, lycopene epoxides) could also be demonstrated in plasma and, were significantly elevated after tomato juice supplementation, compared to control.

After an overnight fast, subjects (N=3M/3F) received a single dose of lycopene (38 mg) with β-carotene (40 mg) in a standard meal containing 43 g of fat (O'Neill and Thurnham, 1998). The lycopene was isolated from tomatoes. Plasma carotenoid levels were tracked for 8 hours after dosing. Approximately 1.0 mg of the 38 mg lycopene dose (~2.6%) was absorbed. A two- to three-fold inter-individual variation in lycopene was observed, but was not sex-dependent.

In a controlled intervention study, male and female subjects consumed 330 ml/day tomato juice (47.1 mg/day lycopene; N=29) or mineral water (N=21) for 8 weeks (Watzl *et al.*, 2000). Tomato juice consumption resulted in significantly increased plasma lycopene concentrations over time with no significant differences in the levels of the *trans*- and *cis*-isomers at week 8.

In a controlled 4-week study, female students (N=16-17/group) were given 1, 2 or 3 cans of tomato juice *per* day and a control group received apple juice (Sakamoto *et al.*, 1994). Compared with their baseline levels, serum lycopene levels were significantly elevated in the groups receiving 2 or 3 cans *per* day. All three tomato juice groups had significantly elevated

serum lycopene levels compared with the apple juice group. A large amount of the serum lycopene was identified as the *cis*-isomer.

Tyssandier *et al.* (2002) studied the short-term (24 hours) and long-term (3-weeks) interactive effects of carotenoids, including lycopene, on absorption in women (N=20). The lycopene groups received: (a) 96 g tomato puree/day (14.98 mg lycopene + 1.50 mg β-carotene); (b) 1 Lyc-O-Mato® Oleoresin 6% pill/day (15 mg lycopene) + 92 g chopped spinach/day (11.93 mg lutein + 7.96 mg β-carotene), or; (c) 96 g tomato puree/day (14.98 mg lycopene + 1.50 mg β-carotene) + 2 lutein pills (12 mg lutein). Plasma carotenoid levels in chylomicrons were measured on the day before the supplementation period, the first day of each supplementation period and the day after the supplementation period ended. In the short-term (24 hours) consumption of β-carotene and/or lutein with lycopene decreased serum lycopene levels (AUC) relative to consumption of lycopene (tomato puree) alone. However, there were no interactive effects on lycopene levels (nmol/L) observed following 3-weeks combined consumption of the carotenoids.

5.2. Distribution

Healthy Japanese female subjects were randomized to one of three treatment groups that consumed a control drink (control group; 0 mg lycopene; N=10), 160 g of tomato juice (low dose group; 15 mg lycopene; N=11) or 480 g of tomato juice (high dose group; 45 mg lycopene; N=10) for one menstrual cycle (Maruyama *et al.*, 2001). Plasma lycopene increased in the low and high dose groups relative to the control group. Sixty-nine percent of lycopene in plasma was distributed in the low-density-lipoprotein (LDL) fraction and 24% in the high-density-lipoprotein (HDL) fraction. In the low dose group, the lycopene concentration increased 160% each in the very-low-density-lipoprotein (VLDL) + intermediate-density-lipoprotein (IDL), LDL and HDL fractions. In the high dose group, the lycopene concentration increased 270% each in the VLDL+IDL and LDL fractions, and 330% in the HDL fraction.

Concentrations of carotenoids, including lycopene were determined in liver, kidney and lung tissue from autopsies of subjects (N=20; 4 months to 86 years) (Schmitz *et al.*, 1991). Within the same patient, total mean carotenoid concentrations in liver (21.0 nmol/g tissue) were always greater than in kidney (3.1 nmol/g tissue) or lung (1.9 nmol/g tissue. Lycopene concentrations ranged from 0.2 to 20.7 nmol/g tissue in the liver, 0.1 to 2.4 nmol/g tissue in the kidney and less than 0.1 to 4.2 nmol/g tissue in the lung.

Kaplan *et al.* (1990) determined the carotenoid content, including lycopene, in 10 different human organs obtained at autopsy (N=16). The median levels of lycopene varied disproportionately between organs with the highest levels in the adrenal and testes. Much lower lycopene levels (1% of adrenal levels) were identified in subcutaneous fat, pancreas, kidneys, heart, thyroid, ovary and spleen.

The isomeric composition of lycopene was measured in serum and seven human tissues (Stahl *et al.*, 1992). all-*trans*-, 9-*cis*-, 13-*cis*- and 15-*cis*-Lycopene combined accounted for more than 50% of total lycopene identified. The highest levels of lycopene were observed in the adrenals and testes with levels 3.4 and 1.5 times higher than in the liver, respectively. Lycopene was also present in ovary, fat and kidneys.

Concentrations of lycopene were quantitated in serum and prostate tissue from men (N=25; ages 53 to 74 years) undergoing prostatectomy for localized prostate cancer (Clinton *et al.*, 1996). Lycopene concentrations ranged from 0 to 2.58 nmol/g prostate tissue with a mean of 0.80 nmol/g tissue. all-*trans* Lycopene accounted for 12 to 21% and *cis* isomers for 79 to 88% of total lycopene in prostate tissues. Lycopene concentrations in the serum ranged between 0.60 and 1.9 nmol/ml, with 27 to 42% all-*trans* lycopene and 58 to 73% *cis*-isomers.

Plasma concentrations of lycopene were measured in men (N=121) and women (N=186) participating in two prospective investigations of dietary etiologies of chronic diseases (Ascherio *et al.*, 1992). The bioavailability of lycopene from these varied diets was evidenced by the detectable serum lycopene levels. Mean lycopene concentrations were 0.82 μmole/L in men and 0.76 μmole/L in women.

Paetau *et al* (1999) reported significantly increased lycopene concentrations in buccal mucosa cells (BMCs) in subjects (N=15) consuming Lyc-O-Mato® Oleoresin 5% (the same as Lyc-O-Mato® Oleoresin 6%, but with average lycopene concentration of 5%) or lycopene beadlets, but not lycopene-rich tomato juice. There was only a weak correlation between BMC lycopene levels and plasma lycopene levels. Alternatively, Richelle *et al.* (2002) reported a good correlation between increased plasma lycopene concentrations and increased lycopene concentrations in BMCs in subjects that consumed 25 mg lycopene/day for 8 weeks from Lyc-O-Mato® Oleoresin 6% in whey protein (lactolycopene) or tomato paste.

Lymphocyte lycopene concentrations increased by 80% in adult women (N=9) that consumed 25 g tomato puree (containing 7 mg lycopene) for 14 consecutive days, after a 7-day washout period (Porrini and Riso, 2000).

5.3. Metabolism

In human serum, a metabolite of lycopene was identified (5,6-dihydroxy-5, 6-dihydrolycopene), which apparently resulted from oxidation of lycopene to a lycopene epoxide intermediate, which then underwent metabolic reduction (Khachik *et al.*, 1995). Lycopene epoxide was identified in the plasma of men that consumed lycopene (Müller *et al.*, 1999). In breast milk and serum of lactating mothers (N=3), an oxidative metabolite of lycopene was identified (epimeric 2,6-cyclolycopene-1, 5-diol) that contained a novel five-membered-ring end group (Bertram *et al.*, 2000; Khachik *et al.*, 1997).

5.4. Elimination

In a study conducted to determine the effects of processing food on lycopene absorption in humans, the estimated serum half-life of lycopene was 2-3 days (Stahl and Sies, 1992).

In a controlled, crossover study, men (N=30) on a low carotenoid diet were fed single dose of carotenoids, including lycopene, from foods (broccoli (600 g), carrots (270 g), or tomato juice (180 g)) (Brown *et al.*, 1989). The estimated plasma half-life for lycopene was approximately 14 days.

To investigate the effect of a low carotenoid diet on plasma carotenoid levels, including lycopene, healthy male subjects (N=12) housed in a live-in metabolic unit were fed a low

carotenoid diet for 13 weeks (Rock *et al.*, 1992). Blood samples were drawn on days 2-3, 14-15, 35-36 and 63-64. The estimated mean plasma half-life of lycopene was between 12 and 33 days.

As part of two carotenoid isotopic studies, Burri *et al.* (2001) measured serum concentrations of carotenoids, including lycopene, in healthy young adult women (N=19) that were fed controlled low carotenoid diets for approximately 10 weeks. Serum lycopene concentration decreased during depletion and followed first-order kinetics with a half-life of 26 days. Half-life was unrelated to physical or demographic characteristics such as body mass, body fat, racial background or age in the relatively homogeneous groups.

In a study designed to measure the lycopene absorbance of various tomato oleoresin preparations, plasma lycopene levels significantly decreased 21 to 52 % of the basal values after volunteers (N=24) consumed a diet low in lycopene for 2 weeks (Böhm, 2002).

6. SAFETY EVALUATION

6.1. Acute Studies

Acute lethality studies were conducted on two batches of Lyc-O-Mato® Oleoresin 5% (Dreher, 1994a, b). Sprague-Dawley rats (N=5/sex; 124 to 162 g) received a single 5000 mg/kg dose of undiluted Lyc-O-Mato® Oleoresin 6% by gavage and were observed for 14 days. No signs of systemic toxicity were noted for 14 days after administration of the oleoresin. The animals were sacrificed and necropsy showed no macroscopic abnormalities in the abdominal and thoracic cavities. One female died 4 hours after dosing; this rat demonstrated signs of distress 2 hours after dosing and at necropsy showed hemorrhagic lungs, dark liver and dark kidney. It was concluded that the death of this single animal was inconsistent with the lack of any symptoms in the other animals and may have been due to maldosing. These studies demonstrated that the LD_{50} for Lyc-O-Mato® Oleoresin 5% was greater than 5000 mg/kg bodyweight.

Lyc-O-Mato® Oleoresin 5% was applied with semi-occlusion for 24 hours at 2000 mg/kg to a shaved area of intact skin on Sprague-Dawley rats (N=5/sex) (Dreher, 1994d). After 24 hours, the bandage was removed and the animals were observed for 14 days for evidence of toxicity. No deaths or signs of systemic toxicity were observed during this period. After the 14 days, necropsy macroscopic examination of the abdominal and thoracic cavities showed no abnormalities. It was concluded that the acute dermal LD_{50} of Lyc-O-Mato® Oleoresin 5% is greater than 2000 mg/kg in rats.

In male Wistar rats (N=8/group) fed 300 mg/kg lycopene in their diet for 16 days, no adverse effects were observed on growth, liver weight, lung weight, kidney weight or small intestine cytochrome P450 expression and activity (Jewell and O'Brien, 1999).

Mice (N=30/group) fed a diet containing 700 ppm lycopene (approximately 90 mg/kg body weight *per* day) for 2 weeks had no reported adverse effects or changes in liver weight (Black, 1998).

Milani *et al.* (1970) reported lycopene to be non-toxic to: (1) rats at 50 mg/kg orally and subcutaneously at 50 mg/kg and 100 mg/kg; (2) guinea pigs at 20 mg/kg subcutaneously and; (3) mice at 3 g/kg administered orally, subcutaneously or intraperitoneally.

6.2. Subchronic Studies

CD rats (N=20/sex/group; 96-132 g) were given 0, 45, 450 or 4500 mg/kg/day Lyc-O-Mato® Oleoresin 5% by gavage for 13 weeks (East, 1995). No deaths occurred during the treatment period. There were no differences in bodyweight gain, food intake, or food conversion efficiency between test and control animals. Test animals had no ocular lesions, changes in hematology, urinalysis changes, changes in organ weights, or macroscopic or microscopic differences from control animals. Test animals did exhibit low alkaline phosphatase blood levels in comparison to controls, but the toxicological significance of this finding is unclear. Plasma levels of lycopene did not increase for the 450 mg/kg/day dosage over those found with the 45 mg/kg/day indicating lycopene absorption was saturated at higher doses. Thus, oral administration of Lyc-O-Mato® Oleoresin 5% was well tolerated with no evidence of toxicity at doses of 45, 450 or 4500 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) of Lyc-O-Mato® Oleoresin 5% was 4500 mg/kg/day.

In an extensive carotenoid feeding study, carotenoids, including lycopene, were fed to rats, rabbits and dogs (Zbinden and Studer, 1957). The lycopene studies had four groups:

(1) Rat (N=10F/10M), 1000 mg/kg body weight/day, direct feeding, 100 days---authors stated that the animals ate about 10 g lycopene total (each)

(2) Rat (N=15F/15M), 1000 mg/kg diet/day, feed additive, 200 days---authors reported that the animals ate about 2.5 g lycopene total (each)

(3) Rat (N=18F/13M, second generation), 1000 mg/kg diet/day, feed additive---authors stated that the animals ate approx. 0.8 g lycopene total (each)

(4) Dog (N=1F), 100 mg/kg body weight/day, direct feeding, 192 days---authors reported that the animal ate approx. 272 g lycopene total

During the first weeks of the study, two spontaneous deaths occurred in group #1 that were reported not to be treatment related. Otherwise, all rats grew at same pace as controls. No significant changes were observed in hematology; or in histopathology on liver, kidneys, adrenal glands, spleen, pancreas, testis, ovaries, skin, bone and bone marrow.

For groups #2 and #3, the authors observed no significant differences between test and control animals with respect to food intake or body weight. There were neither spontaneous deaths nor the need to sacrifice any animals due to disease in either group. Hematology was normal in both test and control groups. No significant differences were observed in reproduction (gestation period, litter size, average pup weight, *etc.*). Histopathology showed that females (but not males) stored lycopene in the liver as coarse-granulated pigment; otherwise, the liver was normal. Also, no significant changes were observed in the kidneys, adrenal glands, spleen, pancreas, testes, epididymis, ovaries, lungs, heart, bones and bone marrow. No pigment storage (outside of the liver) was observed. The authors noted that based on consumption of lycopene, the rats ate about 50 mg/kg *per* day which translates to a daily dose of 3 g/day of lycopene in a 60 kg human or about the amount found in 20 kg of concentrated tomato paste.

For the single dog in group #4, lycopene was administered in gelatin capsules, orally. No intolerance symptoms were observed. Body weight increased normally during the experiment. No significant change in blood chemistry was observed. All organs appeared normal at termination. The authors noted that liver contained 22.6 mg/g tissue and kidneys 0.6 mg/g tissue of lycopene at termination of the experiment. They also noted that in the 192 day test, the dog ate a lycopene amount equivalent to that found in 10,000 to 15,000 kg of tomatoes.

6.3. Eye Studies

Two separate eye irritation studies using different batches of Lyc-O-Mato® Oleoresin 5% (0.1 mL, approximately 5% lycopene by weight) were conducted (Dreher, 1994c). Lyc-O-Mato® Oleoresin 5% (0.1 mL, approximately 5% lycopene by weight) was applied into the conjunctival sac of the right eye of New Zealand white rabbits (N=6) pretreated with a local anesthetic (Ophthaine) to minimize pain (Dreher, 1994c). Ocular damage/irritation was assessed at 1, 24, 28 and 72 hours; and 7 days following treatment using Draize evaluation criteria. In both studies, Lyc-O-Mato® Oleoresin 5% was scored as a Moderate Eye Irritant (class 5 on a 1 to 8 scale).

6.4. Skin Studies

Two separate skin irritation studies using different batches (Nos. 620106, 620207) of Lyc-O-Mato® Oleoresin 5%, were conducted (Dreher, 1994e, f). In each test, Lyc-O-Mato® Oleoresin 5% was applied directly to the shaved skin (dorsal/flank area; 0.5 mL oleoresin under a 2.5 x 2.5 cm gauze patch) of New Zealand white rabbits (N=6). The patch was removed four hours after oleoresin application and any residual material was removed by swabbing with diethyl ether. Test sites were examined and scored for irritation at 1, 24, 48 and 72 hours after patch removal using the Draize system for erythema and edema formation. Both batches of Lyc-O-Mato® Oleoresin 5% produced very slight to well-defined erythema and slight to moderate edema in all animals. An averaging of the scores for the six animals in each test resulted in a primary irritation index of 4.3 (on a scale of 0 to 8). The two tested batches of Lyc-O-Mato® Oleoresin 5% were classified as "Moderate Irritants" according to the Draize classification scheme.

A skin irritation study was repeated using the same protocol as the earlier studies, but with a different batch (No. 511008) of tomato oleoresin, Lyc-O-Mato® Oleoresin 6%, that was produced at a later date than the earlier batches (Rees, 1996). However, unlike the earlier studies, application of 0.5 ml of the tested batch of Lyc-O-Mato® Oleoresin 6% did not produce any effects and was classified as a "Non-Irritant" to skin.

In an acute dermal toxicity study, Lyc-O-Mato® Oleoresin 5% (batch No. 620207) was applied with semi-occlusion for 24 hours at 2000 mg/kg to a shaved area of intact skin on Sprague-Dawley rats (N=5/sex) (Dreher, 1994d). After 24 hours, the bandage was removed and the animals were observed for 14 days for evidence of primary irritation according to the standard Draize scale. Incidents of hemorrhage of the dermal capillaries were noted in one male and one female animal, two to four days after treatment, however no erythema or edema formation was observed in any animal. It was concluded that the Lyc-O-Mato® Oleoresin 5% tested was not a skin irritant.

The results from these skin irritation studies are inconsistent and suggest that irritation may be species specific with irritation in the rabbit, but not in the rat. Alternatively, irritation in

rabbits from application of the earlier batches of Lyc-O-Mato® Oleoresin might have been due to the adventitious presence of lactic acid, which was not present in the latter material[5] that was tested in rats.

The skin contact sensitization potential of Lyc-O-Mato® Oleoresin 5% (Batch No. 620207) was evaluated in the albino guinea pig (N=20/test group; N=10 controls) (Dreher, 1994g). Shaved shoulder regions areas of the animals received three intradermal injections (0.1 mL each) of Freund's Complete Adjuvant, a 5% (wt/vol) dilution of oleoresin in arachis oil, and a 5% (wt/vol) dilution of the oleoresin in a 1:1 mixture of Freund's Complete Adjuvant plus arachis oil. On day 7, the same area on each animal was treated with a topical application of 25% (wt/wt) Lyc-O-Mato® Oleoresin 5% in petroleum jelly and a dressing was applied for 48 hours. Observations for erythema and edema were made at 1 and 24 hours following removal of the dressing. Control animals were injected with carriers only and challenged with 5% (wt/wt) Lyc-O-Mato® Oleoresin 5% in petroleum jelly. Animals were scored according to reactions of test *vs* control animals. The Lyc-O-Mato® Oleoresin 5% produced a 35% (7 out of 20 test animals) sensitization rate and was classified as a "Moderate Sensitizer" to guinea pig skin in these studies. This effect might have been due to the lactic acid present in the batch of oleoresin used in the study.

6.5. Genotoxicity

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and *Escherichia coli* strain WP2uvrA$^-$ were treated with five dilutions of Lyc-O-Mato® Oleoresin 5% (up to 250 µg lycopene *per* plate) (Batch No. 620207) with and without metabolic activation according to the Ames plate incorporation method (Thompson, 1994). Lyc-O-Mato® Oleoresin 5% was found to be non-mutagenic under the conditions of the test.

6.6. Carcinogenesis

Animal studies have reported anti-carcinogenic effects from lycopene. For example, feeding tomato juice containing up to 17 ppm lycopene to rats for up to 35 weeks significantly protected the animals from nitrosamine-induced bladder cancer and N-methylnitrosourea-induced colon cancer (Narisawa *et al.*, 1998; Okajima *et al.*, 1998). In another study, addition of 50 ppm lycopene in the drinking water of mice for 21 weeks resulted in a significant reduction in nitrosourea-induced lung adenomas and carcinomas in male mice (Kim *et al.*, 1997).

6.7. *In vitro* studies

In vitro studies have shown that lycopene can inhibit cell proliferation in human mammary cancer cells (Prakash *et al.*, 2001) and the production of transformed loci in methylchloranthrene-treated C3H/10T1/2 mouse embryo fibroblasts (Araujo *et al.*, 1995; Bertram *et al.*, 1991; Levy *et al.*, 1995). Lycopene caused a concentration-dependent reduction in HL-60 promyelocytic leukemia cell growth accompanied by inhibition of cell cycle progression in the GO/G1 growth phase (Amir *et al.*, 1999). The lycopene effect was enhanced, synergistically, by 1,25-dihydroxyvitamin D3, a known anticancer agent. In a related study, the lycopene inhibition of MCF7 mammary cancer cells appears due to lycopene interference with

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[5] LycoRed Natural Product Industries Ltd., personal communication.

IGF-I (insulin-like growth factor I) receptor signaling and cell growth cycle progression (Karas *et al.*, 2000).

6.8. Observations in Humans

Fruits and vegetables that contain lycopene have been a normal part of the human diet since antiquity. Moreover, numerous clinical studies using tomato products have demonstrated that consumption of these tomato products and lycopene is safe and well tolerated. A reported side effect from excessive lycopene consumption is lycopenemia, which is when an excess of lycopene in the blood leads to deposition in the liver forming "fatty cysts". The skin takes on the red color found in tomatoes. It is considered harmless and is readily reversible when lycopene ingestion is discontinued. The following is a summary of two clinical studies that carefully documented the safety of Lyc-O-Mato® Oleoresin 6% and two case reports of lycopenemia.

No lycopene-induced toxicity was observed in Spanish volunteers that were enrolled in a multicenter, placebo-controlled intervention study in healthy male and female volunteers (N=400) recruited from five European regions designed to study the serum response of carotenoids and tocopherols (Olmedilla *et al.*, 2002). Subjects were given ~222 mg/day Lyc-O-Mato® Oleoresin 6% (containing 13.3 mg/day lycopene) for 20 weeks. Plasma lycopene levels increased 2-fold (~1.2 μmol/L) compared with placebo controls. No significant changes in biochemical (plasma glucose, cholesterol, triacylglycerol, uric acid, albumin, aspartate aminotransferase (AST), total bilirubin, calcium, creatinine, alkaline phosphatase, low density lipoprotein (LDL), total protein, urea, iron) or hematological indices (hemoglobin concentration, red cell (RBC Count, HGB, HCT, MCV, MCH, MCHC)[6], white cell (number and % of neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count and mean platelet volume) were observed throughout the study[7]. Carotenodermia[8] developed in 25% of the subjects, but this is considered harmless and is readily reversible when carotene ingestion is discontinued.

Lyc-O-Mato® Oleoresin 6% was given to prostate cancer patients as part of an ongoing National Institutes of Health funded dose escalating phase II trial of lycopene for biochemical relapse of prostate cancer (Hall, 2003). Patients (N=6/group) will be given 250, 500, 750, 1000, 1500 or 2000 mg/day Lyc-O-Mato® Oleoresin 6% (15, 30, 45, 60, 90, or 120 mg/day lycopene) for one year. Patients will be evaluated monthly and every three months laboratory studies will be conducted on electrolytes, liver function and complete blood count. To date, patients in the high dose group have completed between 4 and 10 months of treatment. Results from the high dose group indicate that Lyc-O-Mato® Oleoresin 6% was well tolerated and no clinically significant toxicity was observed. One subject given an unreported dose of Lyc-O-Mato®

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[6] RBC=red blood cell; HGB=hemoglobin; HCT=hematocrit; MCV= mean corpuscular volume; MCH= mean corpuscular HGB; MCHC=mean corpuscular HGB concentration.

[7] These specific endpoints were not published with the article, but were provided in response to an inquiry in an e-mail from Begoña Olmedilla (bolmedilla.hpth@salud.madrid.org).

[8] The authors of this study used the term carotenodermia, however this was in all likelihood lycopenemia.

Oleoresin 6% developed treatment-related diarrhea that subsided after the Lyc-O-Mato® Oleoresin 6% supplementation was stopped.

Reich *et al.*(1960) reported a case of lycopenemia in a woman who consumed 2 liters of tomato juice daily for "several years," equivalent to a daily dosage of up to 160 mg of lycopene. She had a previous history of the same condition. The woman was admitted to the hospital with chest pains and apparent jaundice, but an examination showed no indication of jaundice, so the physicians looked to carotenoid intake to explain the coloration of the skin.

After three weeks on a diet free of tomato juice, total blood carotenoid levels were 3.7 mg/mL (α- and β-carotene=1.5 mg/mL; lycopene=1.1 mg/mL; lutein=1.1 mg/mL). The expected total carotenoid levels were ~1 mg/mL. It was estimated that the total carotenoid levels had dropped about 19% during the 3 weeks of tomato juice deprivation. Thus, the approximate level of the four carotenoids in the serum at the time of admission was approx. 4.4 mg/mL, or approximately 4X the expected level in normal serum.

The woman was also diagnosed with choelithiasas and a cholecystectomy was performed. During this process, there was an opportunity to examine the patient's bile for carotenoid content. By colorimetry, the bile contained 191 units/100mL or approximately 7.6 mg carotenoids/mL. The patient's liver was enlarged and had a "strange" orange-yellow color. A biopsy for found indications of carotenoid (lycopene) accumulation as masses of butter-yellow, non-doubly refractile material within the liver cells.

The authors of this study distinguish this first reported case of lycopenemia from carotenemia by the much deeper orange skin hue observed in the patient; and due to the fact that, unlike cases of carotenemia reported to date, the patient did not have diabetes, hypothyroidism, nephrosis or lipemia---conditions which have been associated with carotenemia in other cases. In addition, the liver from the lycopenemic patient was orange yellow and gave histologic evidence of storage of carotenoid pigments (the livers of patients with carotenemia have been reported as normal in color).

Reich *et al.* (1960) concluded that, in spite of the observations made, lycopene was neither toxic nor beneficial to the patient, and they characterized lycopene as simply an "adventitious visitor" to her body.

Lycopenemia was reported in a 19-year old Italian woman that sought medical attention after developing a cutaneous discoloration lasting 3 months (La Placa *et al.*, 2000). Her diet for the past 3 years consisted of four to five big red tomatoes and pasta with tomato sauce daily. A "yellow-orange" pigmentation was observed on the forehead, nasolabial folds, palms and soles. She reported recurrent abdominal pain. Hepatic echographia revealed a digitate area relatively hypoechogenic, measuring 2 cm in diameter, in the upper portion of the parenchyma, which the authors suggested consisted of deposits of lycopene. Blood cell count and laboratory tests, including liver enzymes, were normal. Restricting the diet of tomatoes resulted in a complete regression of pigmentation within 6 weeks and disappearance of the abdominal pain.

7. β-CAROTENE HUMAN INTERVENTION TRIALS

The Expert Panel considered whether reported results of studies of β-carotene have any relevance to the safety of lycopene. Randomized clinical trials of β-carotene supplementation as a chemopreventive agent have reported contradictory results. In two of four intervention trials (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) 1994; U.S. Beta Carotene and Retinol Efficacy Trial (CARET) Omenn *et al.*, 1996a; Omenn *et al.*, 1996b), increased lung cancer risk was measured among heavy smokers who received pharmacologic doses of β-carotene either alone (20 mg/day; ATBC) or β-carotene (30 mg/day) plus retinyl palmitate (25,000 IU/day; CARET). No increased risk for other types of cancers was observed. In contrast, no increases in lung cancer or any other cancer incidences were observed in any subjects, including smokers, consuming high doses of β-carotene (50 mg on alternate days; ~25 mg/day) from the U.S. Physician's Health Study (Hennekens *et al.*, 1996). Moreover, a large study conducted in a high-risk population in Linxian, China found that supplementation with 15 mg β-carotene, 50 μg selenium and 30 mg vitamin E daily for 5 years reduced the number of deaths from gastric cancer (Blot *et al.*, 1993). The results from these human intervention studies are difficult to interpret given their different designs and study populations, but one possible explanation is that physiological doses (<20 mg/day) of β-carotene have no adverse effects, whereas pharmacological doses (>20 mg/day) may cause a slight increase in lung cancer risk in heavy smokers. At this time, however, the data are inconclusive and the risk, if any, from β-carotene consumption will require further study.

The specific molecular and cellular mechanism(s) underlying the reported effects of β-carotene in these studies has not been identified. While several hypotheses have been put forward, the most credible of these relates to β-carotene's pro-vitamin A activity and altered retinoid signaling. Because lutein is not a pro-vitamin A carotenoid, lycopene will not affect these retinoid pathways.

7.1. Hypothesis for β-Carotene Effects: Altered Retinoid Signaling

Wang *et al.* (1999) studied ferrets that were given a β-carotene supplement (at a dose equivalent to those used in the clinical trials) or exposed to cigarette smoke, or both for 6 months. They chose ferrets as a model because ferrets metabolize β-carotene in much the same way as humans (Wang and Krinsky, 1997). The results showed a proliferative response in lung tissue in all β-carotene-supplemented animals and this response was enhanced by exposure to tobacco smoke. Histological analysis revealed localized keratinized squamous metaplasia (a precancerous lesion) in all of the ferrets in the high-dose groups of β-carotene, with or without exposure to smoke. The β-carotene treated groups had significantly lower concentrations of retinoic acid in lung tissue and they exhibited 18% to 73% reductions in retinoic acid receptor beta (RARβ) gene expression. The authors proposed that the increased production of β-apocarotenals (from eccentric cleavage of β-carotene) in the ferret lung might promote lung tumorigenesis through interference with retinoid signaling *via* depression of retinoic acid levels (required for normal cell growth and regulation) and down regulation of RARβ (a tumor suppressor gene).

A subsequent study using the same ferret model reported that the β-carotene effects were dose-dependent (Liu *et al.*, 2000). Physiological doses of β-carotene (equivalent to 6 mg/day in

humans) were not harmful, and instead protected against lung damage induced by cigarette smoke. No protection from smoke-induced lung tissue damage was observed in the ferrets given high doses of β-carotene (equivalent to 30 mg/day in humans). At the end of the study, β-carotene levels in lung tissue increased 25-fold in the low-dose group, and 202-fold in the high-dose group. Thus, it appears that the most plausible explanation for the results of these studies is that β-carotene may interfere with retinoid signaling at high doses.

7.2. β-Carotene *vs.* Lycopene

It is apparent from the studies summarized above that there are significant differences between β-carotene and lycopene. Whereas β-carotene alters retinoid signaling, this activity has not been reported for lycopene, a non-provitamin A carotenoid. Therefore, it is the Expert Panel's view that the data described above with respect to β-carotene are not relevant to a safety assessment of lycopene.

8. EVALUATION

Lyc-O-Mato® Oleoresin 6% is a tomato concentrate that contains an average of 6% lycopene. Lycopene is a non-provitamin A carotenoid, which does not alter retinoid signaling like the provitamin A carotenoid, β-carotene. Tomatoes are a normal component of the American diet with an estimated average annual consumption of processed tomato products equal to nine million metric tons. Tomato lycopene extracts are approved food colorants in the EU and Japan. In the US, all of the major constituents in Lyc-O-Mato® Oleoresin 6% are either approved food ingredients (food additives, GRAS) or are normal constituents found in commonly consumed foods at similar concentrations.

Lyc-O-Mato® Oleoresin 6% is stable at ambient temperatures for up to two (2) years and is stable as an added ingredient to a variety of foods.

Topical application of Lyc-O-Mato® Oleoresin 6% produced equivocal results. Initial tests indicated that Lyc-O-Mato® Oleoresin 6% was moderately irritating to rabbit skin and eyes and was a moderate sensitizer to guinea pig skin. A later study on a new batch of Lyc-O-Mato® Oleoresin 6% indicated that it was not a skin irritant to rabbits. The earlier results were most likely due to the adventitious presence of lactic acid in that batch of Lyc-O-Mato® Oleoresin 6%. The current method of manufacturing described in this document produces Lyc-O-Mato® Oleoresin 6% without lactic acid.

Lyc-O-Mato® Oleoresin 6% was found to be non-toxic in acute and subchronic animal studies. In separate tests, a single oral administration of 5000 mg/kg Lyc-O-Mato® Oleoresin 6% (containing 300 mg/kg lycopene) or single dermal application of 2000 mg/kg Lyc-O-Mato® Oleoresin 6% (containing 120 mg/kg lycopene) to rats resulted in no lethality or toxicity by two weeks. A ninety-day subchronic study in rats identified the NOAEL from oral exposure to Lyc-O-Mato® Oleoresin 6% to be the highest dose tested, 4500 mg/kg/day (containing 270 mg/kg/day lycopene). Lyc-O-Mato® Oleoresin 6% was not mutagenic in an Ames assay and reports indicate that lycopene–rich tomato extracts are anti-carcinogenic in animal studies.

Lycopene is fat-soluble and absorbed in parallel with over-all fat digestion and absorption. Lyc-O-Mato® Oleoresin 6% contains predominantly all-*trans* lycopene (90-95% of

the lycopene present). However, the proportions of the *cis/trans* isomers in serum appear constant regardless of the isomer distribution in the supplement/diet, thus serum isomer distribution appears to be independent of that in the supplement/diet. Serum steady-state levels following lycopene supplementation are reached at about four weeks. Lycopene is found predominantly in the testes and adrenals with significant amounts found in the liver, adipose tissue, prostate, kidney and ovary. The majority (>50%) of tissue and serum lycopene consist of the 9-*cis*-, 13-*cis*- and 15-*cis*-isomers, while the 5-*cis*- and 9-*cis* are the main *cis*-isomers in plasma. Lycopene is eliminated by first-order kinetics with a plasma half-life of 2 to 33 days.

Human clinical intervention studies indicate that long-term consumption of Lyc-O-Mato® Oleoresin 6% is well tolerated. No clinically significant toxicity was observed in an ongoing clinical intervention study in which subjects consumed up to 2000 mg/day Lyc-O-Mato® Oleoresin 6% (containing 120 mg/day lycopene) supplements for 4 to 10 months, although one subject developed treatment-related diarrhea that subsided after the Lyc-O-Mato® Oleoresin 6% supplementation was stopped. In a multicenter, placebo-controlled intervention study, no clinically significant toxicity was reported following 20 weeks consumption of ~222 mg/day Lyc-O-Mato® Oleoresin 6% (containing 13.3 mg/day lycopene).

Reported side effects from excessive consumption of lycopene are carotenodermia[9] and lycopenemia[10], which are not considered health hazards and are reversible conditions. Carotenodermia[11] was observed in 25% of the subjects in one arm of the multicenter study. However, there were no reports of carotenodermia developing in subjects from the other arms of this study nor was carotenodermia reported in the ongoing study in which subjects consumed 2000 mg/day Lyc-O-Mato® Oleoresin 6% (containing 120 mg/day lycopene) supplements for up to ten months. Case reports of lycopenemia indicate that the condition was not considered adverse and was reversed upon reduction of excessive lycopene from the diet.

The NOAEL for Lyc-O-Mato® Oleoresin 6% in rats is 4500 mg/kg/day (equivalent to 270,000 mg/day in a 60 kg human) and the highest tolerable intake of Lyc-O-Mato® Oleoresin 6% in humans identified is at least 2000 mg/day. Thus, based on the generally available data establishing the Lyc-O-Mato® Oleoresin 6% NOAEL at 4500 mg/kg/day (containing 270 mg/kg/day lycopene), the Panel has used a safety factor of 135 and established a conservative acceptable daily intake (ADI) of Lyc-O-Mato® Oleoresin 6% of 33 mg/kg/day or 2000 mg/day for a 60 kg individual, which provides for a safe intake of 120 mg/day lycopene.

Combining the 90th percentile lycopene consumption levels from foods supplemented with Lyc-O-Mato® Oleoresin 6% (17.7 mg/day) with the 90th percentile current consumption level of lycopene from conventional foods (15.7 mg/day), the estimated daily intake of lycopene from conventional foods is 33.4 mg/day. The 90th percentile consumption of lycopene as a color additive (in the foods reported here) is proposed to be 9.20 mg/day. In addition, the potential

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[9] Carotenodermia is characterized by a yellowish discoloration of the skin. It is considered harmless and is readily reversible when carotene ingestion is discontinued.

[10] A similar condition as carotenodermia – an excess of lycopene in the blood leads to deposition in the liver forming "fatty cysts". The skin takes on the red color found in tomatoes. It is considered harmless and is readily reversible when lycopene ingestion is discontinued.

[11] The authors of this study used the term carotenodermia, however this was in all likelihood lycopenemia.

lycopene consumption from dietary supplements may add an additional maximum intake of 60[12] mg/day. Thus, the potential theoretical maximum lycopene consumption at the 90th percentile may reach 102.6 mg/day (1.71 mg/kg/day). This theoretical intake level represents a conservative estimate because it is unlikely that an individual would consume lycopene from both conventional foods and dietary supplements at the 90th percentile level. Even this conservative estimate, however, is well within the 120 mg/day lycopene levels at the ADI for Lyc-O-Mato® Oleoresin 6%, 2000 mg/day.

A color additive petition has been submitted for Lyc-O-Mato® Oleoresin 6% and may have an additive effect to Lyc-O-Mato® Oleoresin 6% consumption. In realistic terms however, saturation of the diet with lycopene could not be achieved for a number of technical and esthetic reasons (see section on consumption) and, as a result, the use of Lyc-O-Mato® Oleoresin 6%, is largely self-limiting. This self-limiting nature of Lyc-O-Mato® Oleoresin 6% provides some realistic boundaries for a still conservative estimate for lycopene ingestion (as a color) at as much as 38 mg. The addition of 38 mg/day as a color to the 90th percentile 102.6 mg/day for all other purposes, would yield a total exposure of approximately 140 mg/day (2.33 mg/kg/day) – an amount 16% greater than the ADI (120 mg/day or 2 mg/kg/day) and well within the NOAEL (270 mg/kg/day), still allowing a safety factor >100. Lastly, and importantly, the only adverse events that have been reported from high intakes of lycopene (*i.e.*, one case study reported a calculated dose of 160 mg/day lycopene for several years) were skin discoloration and deposits of lycopene in the liver, both of which are reversible upon cessation of lycopene-containing foods. Therefore, even at high doses of lycopene consumption, toxicity would not be expected.

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[12] The Healthy Origins website says 15 mg twice daily.

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9. CONCLUSION

After critically evaluating the information available, the Expert Panel has determined that, based on common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food, there is reasonable certainty that Lyc-O-Mato® Oleoresin 6%, as currently described and produced in accordance with current Good Manufacturing Practice (cGMP), will not be harmful under the intended conditions of use. Lyc-O-Mato Oleoresin® 6% is therefore Generally Recognized As Safe (GRAS), by scientific procedures, when used as an ingredient to provide consumers with a supplementary source of lycopene in their diets, so that total daily consumption of lycopene from all sources does not exceed 120 mg lycopene. In particular, the Expert Panel has evaluated the proposed use of Lyc-O-Mato® Oleoresin 6% at specified levels in the foods listed in Table 4 of this document and has concluded that such use results in an estimated intake that is below 120 mg/day lycopene and 2000 mg/day Lyc-O-Mato® Oleoresin 6% and is therefore Generally Recognized As Safe (GRAS).

10. SIGNATURES

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Burdock Group

19 July 04
Date

Walter H. Glinsmann, M.D.
Glinsmann Incorporated

22 July 2004
Date

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Date

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REFERENCES

Amir, H.; Karas, M.; Giat, J.; Danilenko, M.; Levy, R.; Yermiahu, T.; Levy, J. and Sharoni, Y. (1999) Lycopene and 1,25-dihydroxyvitamin D3 cooperate in the inhibition of cell cycle progression and induction of differentiation in HL-60 leukemic cells. *Nutrition and Cancer* 33:105-112.

Araujo, F. B.; Barbosa, D. S.; Hsin, C. Y.; Maranhao, R. C. and Abdalla, D. S. (1995) Evaluation of oxidative stress in patients with hyperlipidemia. *Atherosclerosis* 117:61-71.

Ascherio, A.; Stampfer, M. J.; Colditz, G. A.; Rimm, E. B.; Litin, L. and Willett, W. C. (1992) Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. *Journal of Nutrition* 122:1792-1801.

ATBC (1994) The effect of vitamin E and *beta* carotene on the incidence of lung cancer and other cancers in male smokers. The *Alpha*-Tocopherol, *Beta* Carotene Cancer Prevention Study Group. *New England Journal of Medicine* 330:1029-1035.

BASF (2002) *GRAS Notification Number 119: Synthetic Lycopene as an Ingredient in Food in General, Except Meat and Poultry Products*. BASF Corporation, Mount Olive, NJ. (visited on March 21, 2003), URL: http://www.cfsan.fda.gov/~rdb/opa-gn02.html.

Bertram, J.; King, T.; Fukishima, L. and Khachik, F. (2000) Enhanced activity of an oxidation product of lycopene found in tomato products and human serum relevant to cancer provention. In *Antioxidant and Redox Regulation of Genes*, (C. K. Sen, H. Sies and P. A. Baeuerle, Eds.), Academic Press, San Diego, CA, pp. 409-425.

Bertram, J. S.; Pung, A.; Churley, M.; Kappock, T. D.; Wilkins, L. R. and Cooney, R. V. (1991) Diverse carotenoids protect against chemically induced neoplastic transformation. *Carcinogenesis* 12:671-678.

Bierer, T. L.; Merchen, N. R. and Erdman, J. W., Jr. (1995) Comparative absorption and transport of five common carotenoids in preruminant calves. *Journal of Nutrition* 125:1569-1577.

Black, H. S. (1998) Radical interception by carotenoids and effects on UV carcinogenesis. *Nutrition and Cancer* 31:212-217.

Blot, W. J.; Li, J. Y.; Taylor, P. R.; Guo, W.; Dawsey, S.; Wang, G. Q.; Yang, C. S.; Zheng, S. F.; Gail, M.; Li, G. Y.; Yu, Y.; Lin, B.-Q.; Tangrea, J.; Sun, Y.-H.; Liu, F.; Fraumeni, J. F., Jr.; Zhang, Y.-H. and Li, B. (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *Journal of the National Cancer Institute* 85:1483-1492.

Böhm, V. and Bitsch, R. (1999) Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. *European Journal of Nutrition* 38:118-125.

Böhm, V. (2002) Intestinal absorption of lycopene from different types of oleoresin capsules. *Journal of Food Science* 67:1910-1913.

Boileau, T. W.; Boileau, A. C. and Erdman, J. W., Jr. (2002) Bioavailability of all-*trans* and *cis*-isomers of lycopene. *Experimental Biology and Medicine* 227:914-919.

Brown, E. D.; Micozzi, M. S.; Craft, N. E.; Bieri, J. G.; Beecher, G.; Edwards, B. K.; Rose, A.; Taylor, P. R. and Smith, J. C., Jr. (1989) Plasma carotenoids in normal men after a single ingestion of vegetables or purified beta-carotene. *American Journal of Clinical Nutrition* 49:1258-1265.

Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E. and Kinneary, J. F. (1996) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.* 12th Edition, Merck & Co., Inc., Whitehouse Station, NJ.

Burri, B. J.; Neidlinger, T. R. and Clifford, A. J. (2001) Serum carotenoid depletion follows first-order kinetics in healthy adult women fed naturally low carotenoid diets. *Journal of Nutrition* 131:2096-2100.

Burton, G. W. and Ingold, K. U. (1984) *beta*-Carotene: an unusual type of lipid antioxidant. *Science* 224:569-573.

Chug-Ahuja, J. K.; Holden, J. M.; Forman, M. R.; Mangels, A. R.; Beecher, G. R. and Lanza, E. (1993) The development and application of a carotenoid database for fruits, vegetables, and selected multicomponent foods. *Journal of the American Dietetic Association* 93:318-323.

Clinton, S. K.; Emenhiser, C.; Schwartz, S. J.; Bostwick, D. G.; Williams, A. W.; Moore, B. J. and Erdman, J. W., Jr. (1996) *cis-trans* Lycopene isomers, carotenoids, and retinol in the human prostate. *Cancer Epidemiology, Biomarkers and Prevention* 5:823-833.

Clydesdale, F.M. (1997a) Canthaxanthin. *Food Additives: Toxicology, Regulation, and Properties*. CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997b) Caramel. *Food Additives: Toxicology, Regulation, and Properties*. CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997c) Carmine (*Coccus Cacti* L.). *Food Additives: Toxicology, Regulation, and Properties*. CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997d) Citrus Red No. 2. *Food Additives: Toxicology, Regulation, and Properties*. CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997e) Cochineal Extract (*Coccus Cacti* L.). *Food Additives: Toxicology, Regulation, and Properties*. CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997f) Grape Skin Extract. *Food Additives: Toxicology, Regulation, and Properties*. CRC Press, Boca Raton, FL. CD-ROM.

CSFII 1994-96 (2000) *Continuing Survey of Food Intakes by Individuals (CSFII) 1994-96, 1998*, Agricultural Research Service, U.S. Department of Agriculture, Washington, D.C, CD-ROM.

Dreher, D. (1994a) *Lycopene Batch No. 620207: Acute Oral Toxicity (Limit Test) in the Rat.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/203.

Dreher, D. (1994b) *Lycopene Batch No. 620106: Acute Oral Toxicity (Limit Test) in the Rat.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/209.

Dreher, D. (1994c) *Lycopene Batch No. 620207: Acute Eye Irritation Test in the Rabbit.* Safepharm Laboratories Limited, Derby, UK, May 16, 1994, Project Number: 306/206.

Dreher, D. (1994d) *Lycopene Batch No. 620207: Acute Dermal Toxicity (Limit Test) in the Rat.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/204.

Dreher, D. (1994e) *Lycopene Batch No. 620207: Acute Dermal Toxicity (Limit Test) in the Rabbit.* Safepharm Laboratories Limited, Derby, UK, May 16, 1994, Project Number: 306/205.

Dreher, D. (1994f) *Lycopene Batch No. 620106: Acute Dermal Toxicity (Limit Test) in the Rabbit.* Safepharm Laboratories Limited, Derby, UK, May 16, 1994, Project Number: 306/210.

Dreher, D. (1994g) *Lycopene Batch No. 620207: Magnusson & Kligman Maximisation Study in the Guinea Pig.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/207.

East, P. (1995) *Lycopene: Toxicity Study by Oral (gavage) Administration to CD Rats for 13 Weeks*. Pharmaco LSR Ltd., Suffolk, UK, March 8, 1995, Report No. 94/MAK288/1290.

EU (1995) *EU Commission Directive 95/45/EC*. Official Journal of the European Communities, pp. 1-3, 32 and 33.

EUSCF (1975) *Report of the Committee for Food on the Revision of the Directive on Colouring Matters Authorized for Use in Foodstuffs Intended for Human Consumption*. First Series, Brussels, Belgium, pp. 17-29.

Gartner, C.; Stahl, W. and Sies, H. (1997) Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *American Journal of Clinical Nutrition* 66:116-122.

Hall, M. (2003) *Letter dated April 9, 2003 from M. Craig Hall, M.D. (Wake Forest School of Medicine) to Dr. Zohar Nir (LycoRed Natural Products Industries, Ltd)*. Personal Communication.

Healthy Origins (2003) *Lyc-O-Mato® Lycopene Softgels Product Overview*. Healthy Origins, Pittsburgh, PA. (visited on May 21, 2003), URL: http://www.healthyorigins.com/lycomato.htm.

Hennekens, C. H.; Buring, J. E.; Manson, J. E.; Stampfer, M.; Rosner, B.; Cook, N. R.; Belanger, C.; LaMotte, F.; Gaziano, J. M.; Ridker, P. M.; Willett, W. and Peto, R. (1996) Lack of effect of long-term supplementation with *beta* carotene on the incidence of malignant neoplasms and cardiovascular disease. *New England Journal of Medicine* 334:1145-1149.

Holden, J. M.; Eldridge, A. L.; Beecher, G. R.; Buzzard, I. M.; Bhagwat, S. A.; Davis, C. S.; Douglass, L. W.; Gebhardt, S. E.; Haytowitz, D. B. and Schakel, S. (1999) Carotinoid content of US foods: An update of the database. *Journal of Food Composition and Analysis* 12:169-196.

Holloway, D. E.; Yang, M.; Paganga, G.; Rice-Evans, C. A. and Bramley, P. M. (2000) Isomerization of dietary lycopene during assimilation and transport in plasma. *Free Radical Research* 32:93-102.

Jewell, C. and O'Brien, N. M. (1999) Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of the rat. *British Journal of Nutrition* 81:235-242.

Johnson, E. J.; Qin, J.; Krinsky, N. I. and Russell, R. M. (1997) Ingestion by men of a combined dose of beta-carotene and lycopene does not affect the absorption of beta-carotene but improves that of lycopene. *Journal of Nutrition* 127:1833-1837.

Kaplan, L. A.; Lau, J. M. and Stein, E. A. (1990) Carotenoid composition, concentrations, and relationships in various human organs. *Clinical Physiology and Biochemistry* 8:1-10.

Karas, M.; Amir, H.; Fishman, D.; Danilenko, M.; Segal, S.; Nahum, A.; Koifmann, A.; Giat, Y.; Levy, J. and Sharoni, Y. (2000) Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. *Nutrition and Cancer* 36:101-111.

Khachik, F.; Beecher, G. R. and Smith, J. C., Jr. (1995) Lutein, lycopene, and their oxidative metabolites in chemoprevention of cancer. *Journal of Cellular Biochemistry. Supplement* 22:236-246.

Khachik, F.; Spangler, C. J.; Smith, J. C., Jr.; Canfield, L. M.; Steck, A. and Pfander, H. (1997) Identification, quantification, and relative concentrations of carotenoids and their metabolites in human milk and serum. *Analytical Chemistry* 69:1873-1881.

Kim, D. J.; Takasuka, N.; Kim, J. M.; Sekine, K.; Ota, T.; Asamoto, M.; Murakoshi, M.; Nishino, H.; Nir, Z. and Tsuda, H. (1997) Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH. *Cancer Letters* 120:15-22.

La Placa, M.; Pazzaglia, M. and Tosti, A. (2000) Lycopenaemia. *Journal of the European Academy of Dermatology and Venereology* 14:311-312.

Lee, A.; Thurnham, D. I. and Chopra, M. (2000) Consumption of tomato products with olive oil but not sunflower oil increases the antioxidant activity of plasma. *Free Radical Biology and Medicine* 29:1051-1055.

Levy, J.; Bosin, E.; Feldman, B.; Giat, Y.; Miinster, A.; Danilenko, M. and Sharoni, Y. (1995) Lycopene is a more potent inhibitor of human cancer cell proliferation than either α-carotene or β-carotene. *Nutrition and Cancer* 24:257-266.

Liu, C.; Wang, X. D.; Bronson, R. T.; Smith, D. E.; Krinsky, N. I. and Russell, R. M. (2000) Effects of physiological versus pharmacological *beta*-carotene supplementation on cell proliferation and histopathological changes in the lungs of cigarette smoke-exposed ferrets. *Carcinogenesis* 21:2245-2253.

LycoRed (2003a) *Stability of the 6% Lycopene Oleoresin at 4°C and Room Temperature.* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

LycoRed (2003b) *Recovery of Lycopene from Foods Formulated with Lycopene 6% Oleoresin.* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

Maruyama, C.; Imamura, K.; Oshima, S.; Suzukawa, M.; Egami, S.; Tonomoto, M.; Baba, N.; Harada, M.; Ayaori, M.; Inakuma, T. and Ishikawa, T. (2001) Effects of tomato juice consumption on plasma and lipoprotein carotenoid concentrations and the susceptibility of low density lipoprotein to oxidative modification. *Journal of Nutritional Science and Vitaminology* 47:213-221.

Micozzi, M. S.; Brown, E. D.; Edwards, B. K.; Bieri, J. G.; Taylor, P. R.; Khachik, F.; Beecher, G. R. and Smith, J. C., Jr. (1992) Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. *American Journal of Clinical Nutrition* 55:1120-1125.

Milani, C.; Maccari, M. and Mosconi, P. (1970) Action of lycopene in the experimental gastric ulcer. *Pharmacology* 4:334-340.

Müller, H.; Bub, A.; Watzl, B. and Rechkemmer, G. (1999) Plasma concentrations of carotenoids in healthy volunteers after intervention with carotenoid-rich foods. *European Journal of Nutrition* 38:35-44.

Narisawa, T.; Fukaura, Y.; Hasebe, M.; Nomura, S.; Oshima, S.; Sakamoto, H.; Inakuma, T.; Ishiguro, Y.; Takayasu, J. and Nishino, H. (1998) Prevention of N-methylnitrosourea-induced colon carcinogenesis in F344 rats by lycopene and tomato juice rich in lycopene. *Japanese Journal of Cancer Research* 89:1003-1008.

Okajima, E.; Tsutsumi, M.; Ozono, S.; Akai, H.; Denda, A.; Nishino, H.; Oshima, S.; Sakamoto, H. and Konishi, Y. (1998) Inhibitory effect of tomato juice on rat urinary bladder carcinogenesis after N-butyl-N-(4-hydroxybutyl)nitrosamine initiation. *Japanese Journal of Cancer Research* 89:22-26.

Olmedilla, B.; Granado, F.; Southon, S.; Wright, A. J.; Blanco, I.; Gil-Martinez, E.; van den Berg, H.; Thurnham, D.; Corridan, B.; Chopra, M. and Hininger, I. (2002) A European multicentre, placebo-controlled supplementation study with alpha-tocopherol, carotene-rich palm oil, lutein or lycopene: analysis of serum responses. *Clinical Science (London)* 102:447-456.

Omenn, G. S.; Goodman, G. E.; Thornquist, M. D.; Balmes, J.; Cullen, M. R.; Glass, A.; Keogh, J. P.; Meyskens, F. L., Jr.; Valanis, B.; Williams, J. H., Jr.; Barnhart, S.; Cherniack, M. G.; Brodkin, C. A. and Hammar, S. (1996a) Risk factors for lung cancer and for intervention effects in CARET, the *Beta*-Carotene and Retinol Efficacy Trial. *Journal of the National Cancer Institute* 88:1550-1559.

Omenn, G. S.; Goodman, G. E.; Thornquist, M. D.; Balmes, J.; Cullen, M. R.; Glass, A.; Keogh, J. P.; Meyskens, F. L.; Valanis, B.; Williams, J. H.; Barnhart, S. and Hammar, S. (1996b) Effects of a combination of *beta* carotene and vitamin A on lung cancer and cardiovascular disease. *New England Journal of Medicine* 334:1150-1155.

O'Neill, M. E. and Thurnham, D. I. (1998) Intestinal absorption of *beta*-carotene, lycopene and lutein in men and women following a standard meal: response curves in the triacylglycerol-rich lipoprotein fraction. *British Journal of Nutrition* 79:149-159.

Orstan, A. (2002) Tomato Lycopene Extract. FDA, Office of Food Additive Safety. Color Additive Petition #1C0273. 3-4. LycoRed, personal communication.

Paetau, I.; Khachik, F.; Brown, E. D.; Beecher, G. R.; Kramer, T. R.; Chittams, J. and Clevidence, B. A. (1998) Chronic ingestion of lycopene-rich tomato juice or lycopene supplements significantly increases plasma concentrations of lycopene and related tomato carotenoids in humans. *American Journal of Clinical Nutrition* 68:1187-1195.

Paetau, I.; Rao, D.; Wiley, E. R.; Brown, E. D. and Clevidence, B. A. (1999) Carotenoids in human buccal mucosa cells after 4 wk of supplementation with tomato juice or lycopene supplements. *American Journal of Clinical Nutrition* 70:490-494.

Palozza, P.; Luberto, C.; Calviello, G.; Ricci, P. and Bartoli, G. M. (1997) Antioxidant and prooxidant role of *beta*-carotene in murine normal and tumor thymocytes: effects of oxygen partial pressure. *Free Radical Biology and Medicine* 22:1065-1073.

Pellegrini, N.; Riso, P. and Porrini, M. (2000) Tomato consumption does not affect the total antioxidant capacity of plasma. *Nutrition* 16:268-271.

Porrini, M.; Riso, P. and Testolin, G. (1998) Absorption of lycopene from single or daily portions of raw and processed tomato. *British Journal of Nutrition* 80:353-361.

Porrini, M. and Riso, P. (2000) Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. *Journal of Nutrition* 130:189-192.

Prakash, P., Russell, R., M. and Krinsky, N.I. (2001) *In vitro* inhibition of proliferation of estrogen-dependent and estrogen-independent human breast cancer cells treated with carotenoids or retinoids. *Journal of Nutrition* 131:1574-1580.

Re, R.; Fraser, P. D.; Long, M.; Bramley, P. M. and Rice-Evans, C. (2001) Isomerization of lycopene in the gastric milieu. *Biochemical and Biophysical Research Communications* 281:576-581.

Rees, P. (1996) *Lyc-O-Pen™: Acute Dermal Irritation Test in the Rabbit.* Huntington Lifr Sciences Ltd., Suffolk, UK, May 2, 1996, Report No. 96/LYN002/0274.

Reich, P.; Shwachman, H. and Craig, J. (1960) Lycopenemia: A variant of carotenemia. *New England Journal of Medicine* 262:263-269.

Rice-Evans, C. A.; Sampson, J.; Bramley, P. M. and Holloway, D. E. (1997) Why do we expect carotenoids to be antioxidants *in vivo*? *Free Radical Research* 26:381-398.

Richelle, M.; Bortlik, K.; Liardet, S.; Hager, C.; Lambelet, P.; Baur, M.; Applegate, L. A. and Offord, E. A. (2002) A food-based formulation provides lycopene with the same bioavailability to humans as that from tomato paste. *Journal of Nutrition* 132:404-408.

Rock, C. L.; Swendseid, M. E.; Jacob, R. A. and McKee, R. W. (1992) Plasma carotenoid levels in human subjects fed a low carotenoid diet. *Journal of Nutrition* 122:96-100.

Sakamoto, H.; Mori, H.; Ojima, F.; Ishiguro, Y.; Arimoto, S.; Imae, Y.; Nanba, T.; Ogawa, M. and Fukuba, H. (1994) Elevation of serum carotenoids after continual ingestion of tomato juice. *Journal of the Japanese Society of Nutrition and Food Science* 47:93-99.

Schmitz, H. H.; Poor, C. L.; Wellman, R. B. and Erdman, J. W., Jr. (1991) Concentrations of selected carotenoids and vitamin A in human liver, kidney and lung tissue. *Journal of Nutrition* 121:1613-1621.

Stahl, W.; Schwarz, W.; Sundquist, A. R. and Sies, H. (1992) *cis-trans* Isomers of lycopene and *beta*-carotene in human serum and tissues. *Archives of Biochemistry and Biophysics* 294:173-177.

Stahl, W. and Sies, H. (1992) Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. *Journal of Nutrition* 122:2161-2166.

Subar, A. F. and Block, G. (1990) Use of vitamin and mineral supplements: demographics and amounts of nutrients consumed. The 1987 Health Interview Survey. *American Journal of Epidemiology* 132:1091-1101.

Sutherland, W. H.; Walker, R. J.; De Jong, S. A. and Upritchard, J. E. (1999) Supplementation with tomato juice increases plasma lycopene but does not alter susceptibility to oxidation of low-density lipoproteins from renal transplant recipients. *Clinical Nephrology* 52:30-36.

Thompson, P. (1994) *Lycopene: Six Strain Reverse Mutation Assay "Ames Test" using Salmonella typhimurium and Escherichia coli*. Safepharm Laboratories Limited, Derby, UK, May 3, 1994, Project Number: 306/208.

Tyssandier, V.; Cardinault, N.; Caris-Veyrat, C.; Amiot, M. J.; Grolier, P.; Bouteloup, C.; Azais-Braesco, V. and Borel, P. (2002) Vegetable-borne lutein, lycopene, and *beta*-carotene compete for incorporation into chylomicrons, with no adverse effect on the medium-term (3-wk) plasma status of carotenoids in humans. *American Journal of Clinical Nutrition* 75:526-534.

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

van den Berg, H. (1999) Carotenoid interactions. *Nutrition Reviews* 57:1-10.

van het Hof, K. H.; de Boer, B. C.; Tijburg, L. B.; Lucius, B. R.; Zijp, I.; West, C. E.; Hautvast, J. G. and Weststrate, J. A. (2000) Carotenoid bioavailability in humans from tomatoes processed in different ways determined from the carotenoid response in the triglyceride-rich lipoprotein fraction of plasma after a single consumption and in plasma after four days of consumption. *Journal of Nutrition* 130:1189-1196.

Wang, X. D. and Krinsky, N. I. (1997) Identification and quantification of retinoic acid and other metabolites from *beta*-carotene excentric cleavage in human intestine in vitro and ferret intestine *in vivo*. *Methods in Enzymology* 282:117-130.

Wang, X. D.; Liu, C.; Bronson, R. T.; Smith, D. E.; Krinsky, N. I. and Russell, M. (1999) Retinoid signaling and activator protein-1 expression in ferrets given *beta*-carotene supplements and exposed to tobacco smoke. *Journal of the National Cancer Institute* 91:60-66.

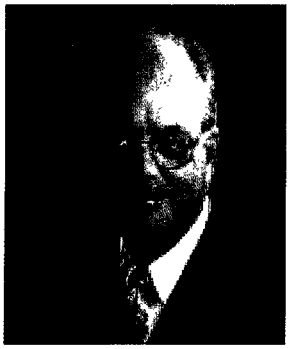
Watzl, B.; Bub, A.; Blockhaus, M.; Herbert, B. M.; Luhrmann, P. M.; Neuhauser-Berthold, M. and Rechkemmer, G. (2000) Prolonged tomato juice consumption has no effect on cell-mediated immunity of well-nourished elderly men and women. *Journal of Nutrition* 130:1719-1723.

Wingerath, T.; Stahl, W. and Sies, H. (1995) *beta*-Cryptoxanthin selectively increases in human chylomicrons upon ingestion of tangerine concentrate rich in *beta*-cryptoxanthin esters. *Archives of Biochemistry and Biophysics* 324:385-390.

Yong, L. C.; Forman, M. R.; Beecher, G. R.; Graubard, B. I.; Campbell, W. S.; Reichman, M. E.; Taylor, P. R.; Lanza, E.; Holden, J. M. and Judd, J. T. (1994) Relationship between dietary intake and plasma concentrations of carotenoids in premenopausal women: application of the

USDA-NCI carotenoid food-composition database. *American Journal of Clinical Nutrition* 60:223-230.

Zbinden, G. and Studer, F. (1957) *Animal Experimentation Investigations of Chronic Tolerance of beta-Carotene, Lycopene. 7,7'-Dihydro-B-Carotene, and Bixin.* Hoffmann-LaRoche & Co., Medical Research Dept., Basel, Switzerland, Report No. 46780.



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Consulting Toxicologist

Dr. Burdock provides safety and toxicity information on foods, food additives, dietary supplements and contaminants information to various clients including corporations, law firms and individuals for regulatory petitions, Generally Recognized As Safe (GRAS) petitions, GRAS notifications and litigation support. He has extensive experience searching and evaluating the scientific literature in a number of subject areas. He provides reviews of the literature on substances and advises clients on safety and regulatory matters concerning their products and procedures. He is also engaged, on an on-going basis, by a publisher to provide reference books on food additives, flavor ingredients and regulatory matters.

Flavor and Extract Manufacturers' Association (FEMA) **1986 - 1992**
Washington, D.C.
Flavor ingredient and food product trade association

Director of Scientific Affairs

Dr. Burdock assisted member companies in the preparation of materials for submission for FEMA Expert Panel for GRAS review, maintained awareness of the Expert Panel and Association of scientific developments in food and flavor arena and changes in regulatory policy as a result of these developments. He authored and edited comprehensive reviews of the literature on flavor additives. Dr. Burdock also managed the FEMA scientific program, coordinated activities of testing laboratories, consultants and allied industry committees and organizations.

Shulton Research Division, American Cyanamid Corporation **1984 - 1986**
Clifton, New Jersey
Consumer products manufacturer

Manager of Biological Services

As senior toxicologist, Dr. Burdock represented the Consumer Products Division on toxicology matters within the corporation with other divisions, outside vendors, government agencies and trade associations. Dr. Burdock was a member of the Pharmacology/Toxicology Committee and the Cosmetic Ingredient Review Subcommittee of the Cosmetic, Toiletries and Fragrance Association. In-house, Dr. Burdock managed Product Safety section, Microbiological Research Services, the Clinical Evaluation Laboratory and the Product Evaluation Center. Dr. Burdock was responsible for the toxicologic and microbiologic safety of products applied to the test groups in the clinical evaluation laboratories and those products released for public use.

Hazleton Laboratories America, Inc. **1979 - 1984**
Vienna, Virginia

Contract testing laboratory

Senior Staff Scientist

As a Study Director, Dr. Burdock designed and managed toxicological studies, reproduction and teratology studies in a variety of species. Dr. Burdock was also concerned with regulatory requirements, quality assurance, budgetary monitoring, and monitoring the performance of subcontractors. He negotiated program design and individual toxicity study requirements for registration of substances with regulatory agencies (FDA and EPA). Dr. Burdock also supervised two laboratory sections, Teratology/Reproduction and Subchronic Rodent Toxicology.

EDUCATION

Ph.D., Toxicology, School of Pharmacy, University of Mississippi, 1980

Master of Combined Sciences, Physiology and Biochemistry, University of Mississippi, 1973

Bachelor of Science, Biology, University of Mississippi, 1969

CERTIFICATION

Diplomate, American Board of Toxicology, 1983; Recertified, 1988, 1993, 1998
Fellow, American College of Nutrition

PROFESSIONAL MEMBERSHIPS

American Chemical Society
American College of Toxicology
American Oil Chemists Society
Institute of Food Technologists (Executive Committee of Toxicology and Safety Evaluation Division)
Society for Regulatory Toxicology and Pharmacology (Vice President & Councilor)
Society of Toxicology (Associate Member)
American Society for Clinical Nutrition

PUBLICATIONS

G.A. Burdock (2004). Handbook of Flavor Ingredients. 5th edition. CRC Press, Boca Raton, FL. (in press)

M.G. Soni, I.G. Carabin, J.C. Griffiths and G.A. Burdock (2004). B-Nitropropionic acid in the diet: toxicity aspects. Reviews in Food and Nutrition (in press).

M.G. Soni, G.A. Burdock, H.G. Preuss, S.J. Stohs, S.E. Ohia and D. Bagchi. (2004). Safety assessment of (-)-hydroxycitric acid and Super CitriMax®, a novel calcium/potassium salt. Food and Chemical Toxicology 42:1513-1529.

G.A. Burdock and I.G. Carabin (2004). Generally recognized as safe (GRAS): history and description. Toxicology Letters 150:3-18.

M.G. Soni, I.G. Carabin, J.C. Griffiths and G.A. Burdock (2004) Safety of Ephedra: lessons learned. Toxicology Letters 150:97-110.

G. A. Burdock (2003). The GRAS process. Food Technology 57:23.

G.A. Burdock (2002). Status and safety assessment of foods and food ingredients produced by genetically modified microorganisms In: Biotechnology & Safety Assessment, 3rd ed. Thomas, J.A. and Fuchs, R. (eds.). Elsevier Science (USA), pp. 39-83

M.G. Soni, G.A. Burdock, S.L. Taylor and N. Greenberg (2002). Safety assessment of methyl paraben. Food and Chemical Toxicology 40:1335-1373.

F. Kotsonis, G.A. Burdock and W.G. Flamm (2001). Chapter 31 - Food Toxicology. In: Toxicology: The Basic Science of Poisons. Klaassen, C.D. (ed). McGraw-Hill, Medical Publishing Division, New York pp. 1049-1088.

G.A. Burdock (2002). Regulation of Flavor Ingredients. In: Nutritional Toxicology. 2nd edition Target Organ Toxicology Series. Kotsonis, F and Mackey, M (eds.). Taylor and Frances, New York pp. 316-339

G.A. Burdock (2002). Handbook of Flavor Ingredients. 4th edition. CRC Press, Boca Raton, FL. 1834 pp.

G.A. Burdock, I.G. Carabin and M.G. Soni (2001). Safety assessment of β-nitropropionic acid: A monograph in support of an acceptable daily intake in humans. Food Chemistry 75 (1):1-27.

M.G. Soni, G.A. Burdock, S.L. Taylor and N. Greenberg (2001). Safety assessment of propyl paraben. Food and Chemical Toxicology 39:513-532.

G.A. Burdock, M.G. Soni and I.G. Carabin (2001). Evaluation of health aspects of kojic acid in food. Regulatory Toxicology and Pharmacology 33:80-101.

M.G. Soni, S.A. White, W.G. Flamm and G.A. Burdock (2001). Safety evaluation of dietary aluminum. Regulatory Toxicology and Pharmacology 33:66-79.

M.G. Soni, H. Kimura and G.A. Burdock (2001). Chronic studies on diacylglycerol oil in rats. Food and Chemical Toxicology 39:317-329.

I.G. Carabin, G.A. Burdock and C. Chatzidakis (2000). Safety assessment of *Panax* ginseng. International Journal of Toxicology 19:293-301.

G.A. Burdock and W.G. Flamm (2000). Review article: Safety assessment of cyclopiazonic acid. International Journal of Toxicology 19:195-218.

G.A. Burdock, W.G. Flamm, I.G. Carabin (2000). Toxicity and mutagenicity studies of DN-50000® and RP-1® enzymes. Food and Chemical Toxicology. Food and Chemical Toxicology 38:429-442.

G.A. Burdock (2000). Dietary supplements and lessons to be learned from *GRAS*. Journal of Regulatory Toxicology and Pharmacology. 31:68-76.

G.A. Burdock (1999). The line between generally recognized as safe and dietary supplements. Proceedings of the 25th Annual Summer Meeting. The Toxicology Forum. Aspen, CO. July 12-16, 1999.

G.A. Burdock and W.G. Flamm (1999). A review of the studies of the safety of polydextrose in food. Food and Chemical Toxicology 37:233-264.

G.A. Burdock (1998). Review of the biologic properties and toxicity of bee propolis (propolis). Food and Chemical Toxicology 36:347-363.

G.A. Burdock (1997). Encyclopedia of Food and Color Additives. Volumes I-III. CRC Press, Boca Raton, FL. pp. 1-3153

F. Kotsonis, G.A. Burdock and W.G. Flamm (1995). Chapter 30 - Food Toxicology. In: Toxicology: The Basic Science of Poisons. Klaassen, C.D. (ed). Pergamon Press, New York. pp. 909-949.

G.A. Burdock (1995). Handbook of Flavor Ingredients. Volume I - Natural Flavoring Ingredients. 3rd edition. CRC Press, Boca Raton, FL. pp. 1-350

G.A. Burdock (1995). Handbook of Flavor Ingredients. Volume II - Synthetic Flavoring Ingredients. 3rd edition. CRC Press, Boca Raton, FL. pp. 1-990.

G.A. Burdock (1993). High Dose Irradiation of Food. A report submitted to the Food Safety Unit, World Health Organization. November, 1993.

W.G. Flamm, P. Lombardo, A. Forbes, W. Nichols, J.B. Little, G. Burdock and J.A. Flamm (1992). Review of the wholesomeness of irradiated food. A report submitted to the Food Safety Unit, World Health Organization. April, 1992.

G.A. Burdock and R.A. Ford (1992). Safety evaluation of dibenzyl ether as a flavoring ingredient. Food Chemical Toxicology 30(7):559-566.

G.A. Burdock, D.H. Pence and R.A. Ford (1992). Safety evaluation of benzophenone. Food Chemical Toxicology 29(11):741-750.

G.A. Burdock (ed.) (1991). Flavor and Fragrance Materials. 5th edition. Allured Publishing Corporation, Wheaton, IL pp.300.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with isobutyl 3-(2-furypropionate). Acute Toxic. Data 1(1): 1.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 3-benzyl-4-heptanone. Acute Toxic. Data 1(1): 2.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2-methyl-3-(2-furyl)acrolein. Acute Toxic. Data 1(1): 3.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2-mercaptomethylpyrazine. Acute Toxic. Data 1(1): 4.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2,5-diethyltetrahydrofuran. Acute Toxic. Data 1(1): 5.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2,5-dimethylpyrole. Acute Toxic. Data 1(1): 6.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with difurfuryl ether. Acute Toxic. Data 1(2): 93-94.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with phenoxyacetic acid. Acute Toxic. Data 1(2): 94-95.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 4,5-dimethylthiazole. Acute Toxic. Data 1(2): 95-96.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 3-methyl-4-phenyl-3-buten-2-one. Acute Toxic. Data 1(2): 96-97.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 3-(2-furylacrolein). Acute Toxic. Data 1(2): 97-98.

G.A. Burdock, B.M. Wagner, R.L. Smith, I.C. Munro and P.M. Newberne (1990). Recent progress in the consideration of flavoring ingredients under the food additives amendment. 15. GRAS substances. Food Technology 44(2):78, 80, 82, 84 & 86.

G.A. Burdock and R.L. Hall (1989). Pro-active flavor safety evaluation and management. In: Trends in food product development. Ghee et al (eds.) Presented at the Seventh World Congress of Food Science and Technology, Singapore, October, 1987. Singapore Institute of Food Science and Technology 1989, pp. 359-366.

G.A. Burdock, R.A. Ford, A.M. Bottomley, and D.M. John (1987). An Evaluation of the Teratogenic Potential of Orally Administered Phenylethyl Alcohol (PEA). The Toxicologist 7(1):176.

G.A. Burdock, R.H. Cox, S.L. Morseth, and L.W. Smith (1986). Teratogenicity Study of 4-Nitro-N-Methylphtalimide (4-NPI). The Toxicologist 6(1):94.

G.A. Burdock, B.A. Kulwich, R.D. Alsakar and P.M. Marshall (1984). 90-Day Dog Study - Caprolactam. In: Proceedings of a Symposium on An Industry Approach to Chemical Risk Assessment. Caprolactam and related compounds as a case study. May 15-17, 1984. Industrial Health Foundation, Pittsburgh, PA 15206.

J.A. Trutter, F.E. Reno, G.A. Burdock and D.W. Korte, Jr. (1984). Fertility Study with a Candidate Antimalarial Drug in the Rat. Journal of the American College of Toxicology 3:172.

G.A. Burdock (1983). Diethanolamine-Induced Changes in Liver and Kidney of the Neonatal Rat. The Toxicologist 4(1):491.

G.A. Burdock, R. B. Hackett and L.W. Masten (1980). A Comparison of Hepatic Microsomal Enzyme Induction by Methadone, Phenobarbital and 3-Methylcholanthrene in the Mouse. Biochemical Pharmacology 28:3476-3482.

J.C. Kapeghian, G.A. Burdock and L.W. Masten(1980). The Effect of the Route of Administration of Microsomal Enzyme Induction Following Repeated Methadone Administration in the Mouse. Biochemical Pharmacology 28:3021-3025.

G.A. Burdock (1980). Some Toxic Effects of Diethanolamine in the Neonatal Rat. Doctoral Dissertation, 1980.

G.A. Burdock and L.W. Masten (1979). Diethanolamine Induced Changes in the Neonatal Rat. Toxicology and Applied Pharmacology 48:A30.

J.C. Kapeghian, G.A. Burdock and L.W. Masten (1977). Effect of the Route of Administration on Microsomal Enzyme Induction Following Repeated Administration of Methadone in the Mouse. Toxicology and Applied Pharmacology 41:159.

G.A. Burdock, R. B. Hackett and L.W. Masten (1976). Dose-Response Relationship of Oral Methadone Administration and Liver Microsomal Enzyme Activity. Federation Proceedings 35:469.

J.D. Catravas, I.W. Waters, G.A. Burdock and W.M. Davis (1975). Haloperidol and Propanolol in the Treatment of Acute Amphetamine Intoxication in the Dog. Toxicology and Applied Pharmacology 33:185.

REPORTS

Dr. Burdock has been responsible for the generation of a number of technical reports as a consultant and as a scientist at the Flavor and Extract Manufacturers' Association, Hazleton Laboratories and American Cyanamid. The substance of these reports is proprietary to the clients sponsoring the research and to American Cyanamid and FEMA and is thus confidential and not available for publication.

WALTER H. GLINSMANN, M.D.

EDUCATION

1956	BA - Columbia College, New York, NY
1960	M.D. - Columbia College of Physicians and Surgeons, NY
1960-1965	Internship and Residency in Medicine - New York Hospital (Cornell Medical School), New York, NY - Training Dept, of Metabolism, Walter Read Army Medical Center and Army Institute of Research, Washington, DC

MEDICAL LICENSE

1961-Current

EMPLOYMENT HISTORY:

2002	As below with change in academic affiliation: Fellow and Adjunct Professor, Center for Food Safety and Nutrition and Ceres Forum®, Virginia Polytechnic Institute and State University (Virginia Tech), Arlington, VA.
1998-2000	President, Glinsmann, Inc. Evaluations of safety and health effects of foods, the development of nutritional products, and food-related claims. Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University. Member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc. Scientific Advisor to the Technical Committee on Food Components for Health Promotion ("Functional Foods"), International Life Sciences Institute, North America and to U.S. and International Food Companies.
1995-1997	President, Glinsmann, Inc. Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University. Advisor to the Committee on Revision (1995) and member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc. Scientific Advisor to the Technical Committee on Food Components for Health Promotion, International Life Sciences Institute, North America. Expert Consultant, Office of the Deputy Director for Programs, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration (FDA).
1993-1994	Expert in Nutrition, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services (DHHS)Health. Provided management/technical support for nutrition and dietary guidance-related activities.

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Visiting Fellow, Georgetown Center for Food and Nutrition Policy.

1992-1993 Director, Nutrition Policy Staff, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Public Health Service (PHS), DHHS, Provided leadership and coordination among DHHS agencies for Nutrition Policy Board functions; implementation of year 2000 nutrition objectives; development of dietary guidance with U.S. Department of Agriculture; and initiatives in food labeling, safety, and fortification: included program coordination for nutrition monitoring and related research; international nutrition conferences; interagency nutrition research initiatives; and preparation of nutrition and health reports and briefing materials.

1987-1991 Associate Director for Clinical Nutrition, Division of Nutrition, CFSAN, FDA. Provided program direction for human clinical and population-based research on: food safety; special dietary use and medical food products; novel food ingredients; health impacts of dietary behaviors of select populations; nutrient imbalances that relate to human morbidity and mortality; and techniques for assessing and monitoring nutritional status and adverse reactions to foods, food additives, and contaminants. Chaired the Center's Health Hazard Evaluation Board and Task Force for developing Guidelines for Clinical Testing for Food Additives and served as senior Center medical officer for developing Medical Foods Regulations. Represented Center or Agency interests and positions and provided guidance on human food safety evaluations to industry.

1983-1987 Chief, Clinical Nutrition Branch, Division of Nutrition, CFSAN, FDA. Developed and managed clinical nutrition activities, human food safety assessments, and the nutrition monitoring program. Special assignments included: FDA Research in Human Subjects Committee; CFSAN Health Hazards Evaluation Board; primary responsibility for Center programs dealing with Clinical Nutrition, Clinical Investigations, Foods for Special Dietary Use, and Health-and Injury-Related Surveillance; Chairperson, Task Forces on Medical Foods Regulation and Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners; and member Task Forces on Biotechnology, Food Monitoring Systems, and Nutrition and Toxicology Research Priorities.

1978-1983 Chief, Experimental Nutritional Branch and Director of Research, Division of Nutrition, CFSAN, FDA. Developed, managed, conducted research based on CFSAN priorities; Special assignments included: FDA Research Involving Human Subjects Committee; Center/FDA Science Liaison; Center Health Hazards Evaluation Committee; and Task Forces on Nitrates-Nitrosamines, Research and Research Facilities Plans, Medical Foods Regulations, and Coordinated Use of Databases to Estimate Exposures.

1965-1978 Chief, Section on Physiological Controls, Laboratory of Biomedical Sciences, National Institute of Child Health and Human Development (NICHHD), National Institutes of Health (NIH), Bethesda, Maryland. Developed and managed research; Chief Intramural Research Contracts Officer; Institute Safety Officer; Member/Chair of Clinical Research Review and Grants and Contracts Review Committees.

1967-1968 Senior Research Investigator, Laboratory of Biomedical Sciences, NICHHD, NIH.

1966-1967 Guest Investigator, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, NIH.

1965-1966 Medical Officer, Research Planning and Program Development, Growth and Development Program, NICHHD, NIH.

1962-1965 Assistant Chief, Department of Metabolism and Attending Physician in Medicine, Walter Reed Army Hospital, and Senior Investigator, Walter Reed Army Institute of Research, Washington, D.C.

PROFESSIONAL MEMBERSHIPS

American Institute of Nutrition, renamed American Society for Nutritional Sciences (Membership Committee, 1986-1991)
American Society for Clinical Nutrition (Membership Committee, 1986-1994: Chair, Publications Management Committee, American Journal of Clinical Nutrition, 1994-1996)
American Physiological Society
New York Academy of Sciences

AWARDS

Fellow, American Society for Nutritional Sciences, 2002.

FDA Commendable Service Award: assessing safety and labeling of monosodium glutamate, 1999.

DHHS Secretary's Award for Excellence in Public Service, Implementing the Food Labeling Initiative, 1993.

PHS Citation for exemplary and creative work as a management clinician in nutrition research and investigative matters, 1989

FDA Award of Merit for Leadership, Health Hazard Evaluations, 1988

PHS Unit Commendation, Food Irradiation Safety Evaluation, 1988

PHS Citations for Outstanding Management Performance in Clinical Nutrition and Food Safety Evaluations, 1986-91

PHS Meritorious Service Medal for sustained high quality leadership and outstanding contributions to Nutrition and Food Safety, 1986

FDA Award of Merit for Leadership, Aspartame Clinical Investigation Team, 1986

FDA Commissioner's Special Citation to the Research Involving Human Subjects Committee for unique and outstanding performance to the Food and Drug Administration by promoting research while ensuring the protection of the human subjects involved, 1984

PHS Commendation Medal for sustained high quality leadership and professional accomplishments in planning, implementing, and evaluating nutrition research at the FDA

SEMINARS, INVITED LECTURES

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June 12, 2001 *Is There a Need for Cyclical Third Party Reviews? An Affirmative Assessment*, 10th Annual Conference, Functional Foods for Health, Chicago, IL.

April 29, 2001	*Orientation to Functional Foods*, Pediatric Academic Societies' Annual Meeting, Baltimore, MD
April 3, 2001	*Safety Regulation for Dietary Supplements: The System Needs a Significant Change* - Toxicology Roundtable, Experimental Biology, Orlando, FL
August 3, 2000	*Communicating Benefits to the Consumer: FTC, FDA, and Claim Substantiation* Warner-Lambert-Pfizer Nutrition Symposium, Morris Plains, NJ
Jan. 27, 2000	*Concepts, Standards, and Substantiation of Effects of Functional Foods* Workshop on Functional Foods, Kappel am Albis, Switzerland
June 14, 1999	*Scientific Concepts, Standards, and Substantiation* American Association of Cereal Chemists Annual Meeting, Functional Foods – Strategies for the Food Industry, Newport Beach, CA
March 30,1999	*Distinguishing a Nutrient from a Drug* Ceres Forum® on What is a Nutrient? Georgetown University Conference Center, Washington, DC
June 19, 1998	*The Role of Clinical Investigations in Establishing Safety and Efficacy for Functional Foods* Course: A Global Perspective on Regulatory Approval for Food Ingredients, Nutraceuticals, and Dietary Supplements. Institute of Food Technologists Annual Meeting '98, Atlanta, GA
April 18, 1998	*Functional Foods: Regulatory Considerations* Symposium: Functional Foods for Health Promotion: A Public Health Opportunity? Experimental Biology '98, San Francisco, CA
Oct. 27, 1997	*Functional Foods: Regulatory Considerations* Panel: Are Consumers Ready for Functional Foods? American Dietetic Association Annual Meeting, Boston, MA
March 13, 1997	*Overview of Research on Health Benefits from Specific Phytochemicals* Panel on Demystifying Functional Foods, Public Voice 20th Annual National Food Policy Conference, Washington, DC
Nov. 28, 1996	*Dietary Guidance and the U.S. Food Supply: Focus on Infants and Young Children* Health Visitors Association Centenary Conference, Harrogate, England
Oct.17, 1996	*U.S. Health Claims: Rational and Lessons Learned* Symposium on Health Claims for Foods in Canada, U. Toronto, Ontario, Canada
Feb. 26, 1996	*Statements of Nutritional Support: Claim Substantiation* Symposium on the New Structure/Function Claims Frontier Under DSHEA, National Nutritional Foods Association, Washington, DC
Feb. 9, 1996	*Regulatory Framework: United States* Workshop on Antioxidants, ILSI-Europe, Brussels, Belgium

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Jan. 24, 1996	*Perspective on the Future of Designer and Functional Foods: Definitions, Regulatory Perspective, and Health Claims* Annual Meeting, ILSI, Cancun, Mexico
Oct. 2, 1995 Oct. 3	*Food Labeling and Food Safety Requirements in the United States and International Developments in Food Fortification, Foods for Special Dietary Use, and Functional Foods*, Doosan Technical Center, Seoul, Korea
Sept. 26, 1995 Sept. 28	*Functional Foods in North America* *Regulatory Aspects of Functional Foods* First International Conference on East-West Perspectives on Functional Foods, ILSI-Southeast Asia, Singapore

PUBLICATIONS

Carpenter, M.B., Glinsmann, W.H., Fabrega, H. Effects of secondary striatal lesions upon cerebella dyskinesia. Neurology. 8: 352, 1958.

Carpenter, M.D., Fabrega, H., Glinsmann, W.H. Physiological deficits occurring with lesions of labyrinth and fastigial nuclei. J. Neurosphysiol. 22: 22, 1959.

Fiala, S., Glinsmann, W.H., Fiala, A.E. Deoxyribonucleotidase activity during carcinogenesis in rat liver. Naturwiss. 46: 635, 1959.

Swank, R.L., Glinsmann, W.H., Sloop, P. The production of fat embolism in rabbits by feeding high fat meals. Surgery, Gynecology and Obstetrics 110: 9, 1960.

Fiala, S., Fiala, A.E., Glinsmann, W.H. Deoxycytidylic deaminase in carcinogenic rat liver. Naturwiss, 47: 45, 1960.

Fiala, S., Glinsmann, W.H. Acid soluble ribonucleotides in adrenal tissue after hormonal stimulation. Endocrinology 68: 479, 1961.

Fiala, S., Fiala, A., Glinsmann, W.H. Mechanism of carcinogenesis and proliferation of tumor cells in rat liver. Pathologie-Biologie 9: 613, 1961.

Fiala, S., Glinsmann, W.H. A unified concept of cancerogenesis. Neoplasma 10: 1, 1963.

Glinsmann, W.H. Renal micropuncture studies during exsanguination hypotension. Clin. Res. 12: 252, 1964.

Ericsson, J.L.E., Glinsmann, W.H. Focal degenerative cytoplasmic alterations in liver cells induced by hypoxia. Electron microscopic observations. Acta Path. Microbial. Scand. 64: 151, 1965.

Ericsson, J.L.E., Glinsmann, W.H. Observations on the subcellar organization of hepatic parenchymal cells I. golgi apparatus, cytosomes, and cytosegresomes in normal cells. Lab. Invest. 15: 750, 1966.

Glinsmann, W.H., Ericsson, J.L.E. Observations on the subcellular organization of hepatic parenchymal cells II. Evolution of reversible alterations induced by hypoxia. Lab. invest. 15: 762, 1966.

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Glinsmann, W.H., Mertz, W. Effect of trivalent chromium on glucose tolerance. Metabolism 15: 510, 1966.

Glinsmann, W.H., Feldman, F.J., Mertz, W. Plasma chromium during glucose loading. Science 152: 1243, 1966.
Mortimore, G., Mondon, C.E., King, E., Glinsmann, W.H. Effect of insulin on alterations in liver glycogen. Am. J. Physiol. 212: 179, 1967.

Glinsmann, W.H., Mertz, W. Studies on the relationship between chromium and glucose tolerance in man. Proc. VIIth Internat. Cong. Nutrition, Vol. 5, p. 714, 1967.

Glinsmann, W.H., Mortimore, G.E. Influence of glucagon and 3', 5'-AMP on insulin responsiveness of the perfused rat liver. Am. J. Physiol. 216: 698, 1969

Glinsmann, W.H., Hern, E.P., Linarelli, L.G., Farese, R.V. Similarities between effects of adenosine 3', 5'-monophosphate and guanosine 3', 5'-monophosphate on liver and adrenal metabolism. Endocrinology 85: 711, 1969.

Farese, R.V., Linarelli, L.G., Glinsmann, W.H., Ditzion, B.R., Paul, M.I., Pauk, G.L. Persistence of the steroidogenic effect of adenosine-3', 5'-monophosphate in vitro: Evidence for a third factor during the steroidogenic effect of ACTH. Endocrinology 85: 867, 1969.

Linarelli, L.G., Weller, J.L., Glinsmann, W.H. Stimulation of fetal rat liver tyrosine aminotransferase activity in utero by 3', 5'-cyclic nucleotides. Life Sciences 9: 535, 1970.

Klein, D.C., Berg, G.R., Weller, J., Glinsmann, W.H. Pineal gland: dibutyryl cyclic adenosine monophosphate stimulation of labelled melatonin production. Science 167: 1738, 1970.

Glinsmann, W.H., Pauk, G., Hern E. Control of rat liver glycogen synthetase and phosphorylase activities by glucose. Biochem. Biophys. Res. Comm. 39: 774, 1970.

Berg, G., Glinsmann, W.H. Cyclic AMP in depression and mania. Lancet 1: 834, 1971.

Sherline, P., Lynch, A., Glinsmann, W.H. Cyclic AMP and adrenergic receptor control of rat liver glycogen metabolism. Endocrinology 91: 680, 1972.

Eisen, H.J., Glinsmann, W.H., Sherline, P. Effect of insulin on glycogen synthesis in fetal rat liver in organ culture. Endocrinology 92: 584, 1973.

Zieve, F.J., Glinsmann, W.H. Activation of glycogen synthetase and inactivation of phosphorylase kinase by a single phosphoprotein phosphatase. Biochem. Biophys. Res. Comm. 50: 872, 1973.

Eisen, H.J., Goldfine, I.E., Glinsmann, W.H. Regulation of hepatic glycogen synthesis during fetal development: roles for hydrocortisone, insulin receptors. Proc. Nat. Acad. Sci. (U.S.A.) 70: 759, 1973.

Sherline, P., Eisen, H., Glinsmann, W.H. Acute hormonal regulation of cyclic AMP content and glycogen phosphorylase activity in fetal liver in organ culture. Endocrinology 94: 935, 1974.

Glinsmann, W.H., Eisen, H.J., Lynch, A., Chez, R.A. Glucose regulation by isolated near-term fetal monkey liver. Pediat. Res. 9: 600, 1975.

Eisen, H.J., Glinsmann, W.H. Partial purification of glucocorticoid receptor from rat liver using

DNA-cellulose. J. Steroid Biochem. 6: 1171, 1975.

Huang, K. P., Huang, F.F., Glinsmann, W.H., Robinson, J.C. Regulation of glycogen synthetase activity by two kinases. Biochem. Biophys. Res. comm. 65: 1163, 1975.

Huang, F.L., Glinsmann, W.H. Inactivation of rabbit muscle phosphorylase phosphatase by cyclic AMP-dependent kinase. Proc. Nat. Acad. Sci. (U.S.A.) 72: 3004, 1975.

Sparks, J.W., Lynch A., Glinsmann, W.H. Regulation of rat liver glycogen synthesis and activities of glycogen cycle enzymes by glucose and galactose. Metabolism 25: 47, 1976.

Sparks, J.W., Lynch A., Chez, R.A., Glinsmann, W.H. Glycogen regulation in isolated perfused near-term monkey liver. Pediat. Res. 10: 51, 1976.

Huang, F.L., Glinsmann, W.H. A second heat-stable protein inhibitor of phosphorylase phosphatase from rabbit muscle. FEBS Lett. 62: 326, 1976.

Eisen, H.J., Glinsmann, W.H. Partial purification of the glucocorticoid receptor from rat liver: a rapid two-step procedure using DNA-cellulose. Biochem, Biophys, Res. Comm. 70: 367, 1976.

Huang, K. P., Huang, F.L., Glinsmann, W.H., Robinson, J.C. Effect of limited proteolysis on activity and phosphorylation of rabbit muscle glycogen synthetase. Arch. Biochem. Biophys. 173: 6, 1976.

Huang, F.L., Glinsmann, W.H. Separation and characterization of two phosphorylase phosphatase inhibitors from rabbit skeletal muscle. European J. Biochem. 70: 419, 1976.

Nakai, C., Glinsmann, W.H. Effects of polyamines on nucleosidediphosphate kinase activity. Biochem. Biosphys. Res. Comm. 74: 1419, 1977.

Nakai, C., Glinsmann, W.H. Inhibition of rabbit skeletal muscle phosphorylase phosphatase by spermine. Molec. Cellular Biochem. 15: 141, 1977.

Nakai, C., Glinsmann, W.H. Protein inhibitors of phosphorylase phosphatase and cyclic AMP-dependent protein kinase from rabbit muscle. Molec. Cellular Biochem. 15: 133, 1977.

Glinsmann, W.H., Huang, F.L., Tao, S., Nakai, C. Control of rabbit muscle phosphorylase phosphatase activity. Proc. FEBS Congress, Copenhagen. Elsevier Press, 1977.

Huang, F., Tao, S., Glinsmann, W.H. Multiple forms of protein phosphatase inhibitors in mammalian tissues. Biochem. Biophys. Res. Comm. 78: 615, 1977.

Eisen, H.J., Glinsmann, W.H. Maximizing purification of the activated glucocorticoid receptor by DNA-cellulose chromatography. The Biochem. J., Molecular Aspects, 17: 1977.

Nakai, C., Glinsmann, W.H. Interaction between polyamines and nucleotides. Biochemistry 16: 5636, 1977.

Buffone, G.J., Sparks, J.W., Johnson, J., Iosefsdin, M., Lewis, S.A., Glinsmann, W.H. Evaluation of an immobilized enzyme electrode system for the monitoring of therapeutic galactose concentrations in neonates. Clin. Chem. 23: 1166, 1977.

Tao, S.H., Huang, F.L., Lynch, A., Glinsmann, W.H. Control of rat skeletal muscle phosphorylase activity by adrenalin. Biochem. J. 176: 347, 1978.

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Simpkins, R.A., Eisen, H.J., Sparks, J.W., Glinsmann, W.H. Development of gluconeogenesis from galactose by fetal liver explants in organ culture. Devel. Biol. 66: 353, 1978.

Simpkins, R.A., Eisen, H.J., Glinsmann, W.H. Functional integrity of fetal rat liver explants cultured in a chemically defined medium. Devel. Biol. 66: 344, 1978.

Sparks, J.W., Avery, G.B., Fletcher, A.B., Simmons, M.A., Glinsmann, W.H. Parenteral galactose therapy in the glucose-intolerant premature infant. The J. of Pediatrics 100: 255, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Urinary chromium excretion of human subjects; effects of chromium supplementation and glucose loading. Amer. J. Clin. Nutr. 36: 1184, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Mertz, W., and Glinsmann, W.H. Chromium supplementation of human subjects: effects on glucose, insulin, and lipid variables. Metabolism 32: 894, 1983.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters. J. Nutr. 113: 276, 1983.

Yetley, E.A., Glinsmann, W.H. Regulatory issues regarding iron bioavailability. Food Technol. 37: 121, 1983.

Archer, D.L., Glinsmann, W.H. Hypothesis: Intestinal infection and malnutrition initiate acquired immune deficiency syndrome (AIDS). Nutrition Research 5: 9, 1985.

Archer, D.L., Glinsmann, W.H. Enteric infections and other co-factors in AIDS: Possible intervention points from a historical perspective. Immunology Today 6: 292, 1985.

Glinsmann, W.H., Irausquin, H., Park, Y.K. Evaluation of health aspects of sugars contained in carbohydrate sweeteners; report of task force 1986. J. Nutr. 116 - supplement 11: S1-216, 1986.

Glinsmann, W.H., Tollefson, L.K., Hattan, D.G. Evaluation of adverse reactions reported to be associated with the use of aspartame-containing products. *Proc. International Aspartame Workshop*, Ed. P.B. Dews. Publ. Int'l Life Sci. Inst. - Nutr. Found., Washington, D.C., 1987.

Tollefson, L.K., Barnard, R.J., Glinsmann, W.H. Monitoring of adverse reactions to aspartame. Proc. *First International Meeting on Dietary Phenylalanine and Brain Function*. Ed. R.J. Wurtman and E. Ritter-Walker, p. 347-72, Publ. Ctr. for Brain Sciences and Metabolism Charitable Trust, Cambridge, Massachusetts, 1987.

Glinsmann, W.H., L.K. Tollefson, Park, Y.K. Regulatory status and health aspects of sweeteners. In *Sweeteners: Health Effects*, Ed. G.M. Williams, p. 263-74, Princeton Sci. Publ. Inc., Princeton, New Jersey, 1988.

Glinsmann, W.H., Dennis, D.A. Regulation of nonnutritive sweeteners and other sugar substitutes. In *Sweeteners*, Eds. N. Kretchmer and C. Hollenbeck, p. 257-85, CRC Press, Boca Raton, Florida, 1991.

Glinsmann, W.H. Usefulness of clinical studies in establishing safety of food products. In *ACS*

Symposium Series, No 484, Food Safety Assessment, Eds. J.W. Finley, S.F. Robinson, and D.J. Armstrong, p. 105-13, Amer. Chem. Society, 1992.

Vanderveen, J.E., Glinsmann, W.H. Fat substitutes: a regulatory perspective. In Ann. Rev. Nutr., Vol. 12, Eds. R.E. Olsen, D.M. Bier, and D.B. McCormick, p. 473-87, Annual Reviews Inc., Palo Alto, California, 1992.

Workshop on Dietary Fatty Acids and Thrombosis, March 1991, Proceedings Eds. J.C. Hoak, W.H. Glinsmann, J.T. Judd. Amer. J. Clin. Nutr. 56 - supplement 4: 7835-8265, 1992.

Hyman, F.N., Sempos, E., Saltsman, J., Glinsmann, W.H. Evidence for success of caloric restriction in weight loss and control: summary of data from industry. *NIH Technology Assessment Conference on Methods for Voluntary Weight Loss and Control.* Ann. Int. Med. 119: 681-87, 1993.

Glinsmann, W.H., Bowman, B. Public health significance of dietary fructose. In *Health Effects of Dietary Fructose*, Eds. A.L. Forbes and B.A. Bowman. Amer. J. Clin. Nutr. 58 - Supplement 5:820-23, 1993.

Glinsmann, W.H., Park, Y.K. Perspective on the 1986 FDA assessment of the safety of carbohydrate sweeteners; uniform definitions and recommendations for future assessments. Amer. J. Clin. Nutr. 62 (suppl): 161S-9S, 1995.

Shank, F.R., Carson, K., Glinsmann, W.H. Putting things in perspective: building on our experience. (1995 Ceres Forum: *Fortifying Policy with Science - The Case for Folate*) J. Nutrition 126 (suppl): 781-87S, 1996.

Glinsmann, W. Focus on substitutes that alter gastrointestinal physiology. (*Proceedings of the Workshop on Safety and Regulatory Aspects of Macronutrient Substitutes,* Nov. 1994, Washington, D.C.) Regulatory Toxicol. and Phamacol. 23(suppl): S27-30, 1996.
Glinsmann, W. H., Bartholmay, S.J., Coletta, F. Dietary guidelines for infants: a timely reminder. Nutrition Reviews 54:50-57, 1996.

Glinsmann, W.H. Functional foods in North America. In *Proceedings of First International Conference on Functional Foods*, Singapore, September 1995. Eds. F.M. Clydesdale and S.H. Chan. Nutrition Reviews, Vol. 54, No. 11, Part II, S33-37, 1996.

Glinsmann, W.H. Perspective on functional food development and commercialization. J. Nutraceuticals, Functional & Medical Foods, 1:89-93, 1997.

Glinsmann, W.H. Functional foods: an overview of regulatory status. Nutrition Today, 34:1-4, 1999.

Glinsmann, W. Functional Foods: Special Considerations in the Pediatric Diet. Pediatric Basics, 92:2-15, 2000.

Flamm, G., Glinsmann, W., Kritchevsky, D., Prosky, L., Roberfroid, M. Inulin and oligofructose as dietary fiber: A review of the evidence. Critical Reviews in Food Science Nutrition, 41:353-62, 2001.

Campbel, E., Rheinhardt, W., Glinsmann, W.H. Claims regarding the health Benefits of foods. Nutrition and the M.D., in press

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CURRICULUM VITAE

NORMAN I. KRINSKY, Ph.D.

Professor Emeritus, Department of Biochemistry

Scientist,
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

Born:
Married:
Children:

EDUCATION

1948 B.S.	University of Southern California, Los Angeles, CA
1950 M.S.	University of Southern California, Los Angeles, CA (Biochemistry and Nutrition)
1953 Ph.D.	University of Southern California, Los Angeles, CA (Biochemistry, with Harry J. Deuel, Jr.)

PROFESSIONAL EXPERIENCE

1953-55	U.S. Public Health Service Post-doctoral Fellow; Harvard University (with George Wald)
1955-56	National Council to Combat Blindness Post-doc. Fellow; Harvard University (with George Wald)
1956-60	Instructor, Lecturer, Department of Biology, Harvard University
1960-64	Assistant Professor, Department of Pharmacology, Tufts University School of Medicine (TUSM)
1964-67	Associate Professor, Department of Pharmacology, TUSM
1967-69	Associate Professor, Department of Biochemistry, TUSM
1969-70	Professor, Department of Biochemistry, TUSM
1970-87	Professor, Department of Biochemistry and Pharmacology, TUSM
1973	Visiting Professor, Department of Physiology/Anatomy, University of California, Berkeley, CA
1981-82	Research Associate, Boston Veterans Administration Medical Center
1987-2000	Professor, Department of Biochemistry, Tufts University School of Medicine
1993-present	**Scientist, USDA Human Nutrition Research Center on Aging, Tufts University**
2000-present	**Professor Emeritus, Department of Biochemistry, Tufts Univ. School of Medicine**

RESEARCH INTERESTS

Function and metabolism of carotenoids, including antioxidant and anticarcinogenic actions and metabolism to retinoic acid and apocarotenoids. Role of carotenoids in primate macula. Analysis of tissue carotenoids. Biological oxidant damage, and mechanisms of lipophilic and hydrophilic protection.

EDITORIAL BOARDS

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1984-1986	Journal of Free Radicals in Biology and Medicine

1984-1986	Advances in Free Radical Biology and Medicine
1987-1994	Free Radical Biology and Medicine
1993-2003	Archives of Biochemistry and Biophysics
1994-2002	Free Radical Research
1997-present	Environmental & Nutritional Interactions
2002-present	Nutrition Reviews

PUBLICATIONS (see attached listing)

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PROFESSIONAL SOCIETIES

1948	American Association for the Advancement of Science (Fellow, 1966)
1949	Society of the Sigma Xi
1951	American Chemical Society
1951	New York Academy of Sciences
1959	American Society for Biochemistry and Molecular Biology
1972	American Society for Photobiology
1982	Society for Free Radical Research
1988	The Oxygen Society (2003: Society for Free Radical Biology and Medicine)
1988	International Society for Nutrition and Cancer
1993	European Retinoid Research Group
1994	International Carotenoid Society
1998	American College of Nutrition (Fellow, 1998)
1999	International Society for Coenzyme Q Research

PROFESSIONAL ACTIVITIES/HONORS

1950	Phi Sigma Award in the Biological Sciences, University of Southern California
1952	Phi Lambda Upsilon
1966	Fellow, American Association for the Advancement of Science
1967-1968	President, Tufts University Chapter, Society of the Sigma Xi
1975-1981	Secretary-Treasurer, American Society for Photobiology
1978	Organizing Committee, Fifth International Symp. on Carotenoids and Vitamin A, Madison, WI
1980	Co-Chairman, Workshop on Biological Chemiluminescence, American Society for Photobiology, Colorado Springs, CO
1981	Chairman, 1st Gordon Research Conference on "Oxygen Radicals in Biology and Medicine" Ventura, CA
1981-1984	Teaching Award, Tufts University School of Medicine
1982-1983	President, American Society for Photobiology
1984	Treasurer, Ninth International Congress on Photobiology, Philadelphia, PA
1987	Organizing Committee, Fourth International Congress on Oxygen Radicals, La Jolla, CA
1987	Chairman, Eighth International Symposium on Carotenoids, Boston, MA
1988-1991	Council, The Oxygen Society
1989-2000	Executive Committee, International Society for Nutrition and Cancer
1990	Lottie Arnrich Lecturer, Dept of Food & Nutrition, Iowa State University, Ames, IA May 1. 1990
1992	Chairman, 1st Gordon Research Conf. on "Chemistry and Biology of Carotenoids", Oxnard, CA
1993	Co-Chair, New York Academy of Sciences Conference on "Carotenoids in Human Health ", San Diego, CA
1993	Honorary Member, The Vitamin Society of Japan
1993	Distinguished Faculty Award, Tufts University School of Medicine
1994	Fellow, The Oxygen Society
1994	Co-Chair, Second International Conference on "Antioxidant Vitamins and ß-Carotene in Disease Prevention", October 10-12, Berlin, Germany
1994-1999	President, New England Free Radical/Oxygen Society
1995	Co-Chair, FASEB Summer Research Conference on "Antioxidant Nutrients in the Cellular Biology of Health and Disease", Saxtons River, VT
1995-1996	Secretary-General, The Oxygen Society
1996-1998	Advisory Committee, International Antioxidant Research Centre, King's College, London.
1997	Mordechai Avron Memorial Lecturer, Nikken Sohonsha Corp., Gifu and Tokyo, Japan, 2/21/97

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1997	Award Lecturer, American College of Nutrition, New York, NY September 27, 1997
1997-1999	Chair, Panel on Antioxidants and Related Nutrients, Food & Nutrition Board, Inst. of Med./NAS
1998	Fellow, American College of Nutrition
1998	Dozor Visiting Professor, Ben-Gurion University of the Negev, Beer-Sheva, Israel
1999	Visiting Scholar, Linus Pauling Institute, Oregon State University, Corvallis, OR
1999	Honorary Member, Oxygen Club of California
1999	Lars Ernster Lecture, Oxygen Club of California 1999 World Congress, Santa Barbara, CA
2000	Robert S. Harris Lecture, Massachusetts Institute of Technology, Cambridge, MA
2001	National Associate, National Academy of Science/National Research Council
2002	Chair, Committee on the Examination of the Evolving Science for Dietary Supplements, Food & Nutrition Board, IOM/NAS
2003-2007	Member, Food Advisory Committee, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety, FDA
2003-2007	Chair, Nutrition Subcommittee, Food Advisory Committee, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety, FDA

RESEARCH TRAINEES: PRE-DOCTORAL PRESENT POSITION

RESEARCH TRAINEES: POST-DOCTORAL PRESENT POSITION

RESEARCH TRAINEES - UNDERGRADUATES/MEDICAL STUDENTS

Research Trainees redacted under the Privacy Act of 1974.

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FACULTY ACTIVITIES

TUFTS UNIVERSITY SCHOOL OF MEDICINE

1963-1966	Pre-Clinical Curriculum Study (Director)
1963-1967	Curriculum Committee
1967-1969	Faculty Medical Education Group
1968-1971	Committee on Extended Educational Opportunity (Chairman)
1968-1969	Health Information Sciences Committee
1969-1970	Advisory Committee on Medical Education
1970-1972	Committee on Faculty Affairs
1973-1978	Committee on Educational Affairs
1974-1975	Fringe Benefits Subcommittee, Faculty Affairs Committee
1974-1975	Admissions Committee
1977	Medical Bylaws Committee
1978-1979	Faculty Affairs Committee (Chairman)
1979-1981	Budgetary Advisory Subcommittee, Faculty Affairs Committee
1979-1981	Boston Tuition Scholarship Benefits Committee
1980-1983	Curriculum Coordinator, Year I
1980-1983	Student Promotions Committee
1981-1982	Ad Hoc Committee on Student Performance Evaluation
1981	Special Program Development Committee
1981-1983	Library and Educational Spaces Planning Subcommittee
1981-1986	Curriculum Committee
1982-1983	Committee on the Teaching of Nutrition at TUSM (Co-Chairman)
1982-1985	Ad Hoc Grievance Committee
1982-1983	Basic Science Appointment, Promotion and Tenure Committee
1983-1985	Task Force on Curriculum Planning
1983-1985	Faculty Advisor
1984-1987	Course Director, Biochemistry
1984-1987	Faculty Affairs Committee
1985-1987	Curriculum Committee Sub-Committee on Curriculum Planning and Implementation
1985-1990	Problem-Based Learning Committee
1988-1989	Curriculum Committee
1989-1992	Faculty Affairs Committee (Chairman, 1990-1992)
1991-1992	Self-Study Sub-Committee on Governance and Administration, LCME, (Chairman)
1992-1993	Steering Committee, RWJ Foundation Generalist Physician Initiative Program
1993-1994	Member, Faculty Senate
1994-1995	Member, Core Curriculum Collaborators Group
1994-1996	Member, Faculty Prizes/Awards Committee
1996-1998	Self-Study Sub-Committee on Governance and Administration, LCME

TUFTS-NEW ENGLAND MEDICAL CENTER

1963	Committee on the Role of the Basic Scientist in the Medical Center, (Chairman)
1968-1969	Audio-visual Task Force
1970-1971	Advisory Committee on Minority Opportunity and Planning
1982-1984	Board of Directors, Women's Resource Center

TUFTS UNIVERSITY

1966-1968	Policy and Program Committee, Graduate School of Arts and Sciences

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1967-1973	Molecular Basis of Biological Phenomena Program (Chairman)
1968-1971	Committee on Equal Educational Opportunity, Faculty of Arts and Sciences
1968-1970	Faculty Representative, Trustees Committee on Honorary Degrees
1970-1971	University-wide Committee on Equal Employment Advancement
1970-1971	Committee on Educational Planning
1978-1979	Advisory Committee on University Investments
1986-1987	Faculty Representative, Trustees Academic Affairs Committee
1993-1999	University-wide Benefits Advisory Committee

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SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

1983-1984 Faculty Secretary
1983-1987 Nominating Committee (Chairman)

TUFTS UNIVERSITY SCHOOL OF DENTAL MEDICINE

1964-1965 Curriculum Committee

JEAN MAYER HUMAN NUTRITION RESEARCH CENTER ON AGING AT TUFTS UNIVERSITY

1995-2000 Promotions Committee

TEACHING EXPERIENCE

HARVARD UNIVERSITY

1956-1960 Biology 191 (Experimental Biochemistry)
1956-1960 Undergraduate Advisor, Department of Biology
1958 Biology 190 (General Biochemistry, with George Wald)

TUFTS UNIVERSITY SCHOOL OF MEDICINE

1960-1967 Pharmacology
1967-1999 Biochemistry (Course Director; 1984-1987, 1994)
1968-1986 Neuropharmacology
1974-1979 Biochemistry of Disease
1980-1985 Principles of Pharmacology
1985-1991 Problem-Based Learning Facilitator
1990 Nutrition and Medicine Facilitator

TUFTS UNIVERSITY SCHOOL OF DENTAL MEDICINE

1960-1966 Pharmacology
1966-1968 Basic Health Sciences
1968-1988 Pharmacology
1984-1993 Biochemistry

TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE

1979-1985 Biochemistry
1980-1985 Neuropharmacology
1980-1985 Pharmacology

TUFTS UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

1960-1967 Graduate Pharmacology
1970 Mitochondrial Membranes and Bacterial Envelopes (BCM 294)
1972 Energy Flow in Biological Systems (BCM 214)
1974, 1978 Metabolic Pathways (BCM 213)
1978, 1982 Membranes (BCM 211)
1981-1982 Advanced Biochemistry (BCM 223)

TUFTS UNIVERSITY SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

1984 Membranes (BCM 221)

1984-1999	Graduate Biochemistry (BCM 223)
1985	Recent Advances in Neurochem. and Neuropharm. (BCM 220)
1995	Free Radicals in Biology & Medicine (BCM 293)

TUFTS UNIVERSITY SCHOOL OF NUTRITION

1991, '93, '99 Dietary Antioxidants and Degenerative Diseases (Nutrition 291-DA)

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SCIENTIFIC CONFERENCES AND MEETINGS: INVITED PARTICIPATION

1. Invited Speaker: The Lipoprotein Nature of Rhodopsin. Symposium on "Visual Mechanisms" (Sponsored by National Institutes of Health) Bethesda, Maryland, September 11-12, 1957.

2. Invited Speaker: The Role of Carotenoid Pigments as Protective Agents against Photosensitized Oxidations in Chloroplasts. Symposium on "Biochemistry of Chloroplasts" NATO Advanced Study Institute, Aberystwyth, Wales, U.K., August 5-9, 1965.

3. Invited Speaker: A Biochemical Basis for Carotenoid Function in Green Plants and Algae. Joint Japan-U.S. Seminar on "Carotenoid Biosynthesis and Related Topics" National Science Foundation/Japan Society for the Promotion of Science, Kyoto, Japan, November 29 - December 1, 1965.

4. Invited Speaker: Carotenoid De-epoxidation Reactions. Conference on "Photosynthetic Pigments" in honor of Harold H. Strain, Argonne National Laboratory, Argonne, Illinois, November 7-8,1968.

5. Invited Speaker: Minority Programs at Tufts University School of Medicine. Conference on "Minority Groups in Professional Schools" American Personnel and Guidance Association, Las Vegas, Nevada, March 30 - April 2, 1969.

6. Invited Participant: Minority Enrollment at Tufts University School of Medicine. Conference on "The Impact of Cultural and Economic Background on Programs to Recruit Negroes for Medicine" Macy Foundation, Princeton, NJ, April 13-16, 1969.

7. Invited Speaker: Evolution of Photosensitive Pigments in Microbes. Colloquium on "Photosynthetic Organisms: Origin and Evolution on Early Earth" 123rd meeting of the American Association for the Advancement of Science, Boston, MA, December 26, 1969.

8. Invited Speaker: The Protective Function of Carotenoid Pigments against Aerobic Photosensitivity. Colloquium on "Molecular Mechanisms of Photodynamic Action with and without Molecular Oxygen" VIth International Congress on Photobiology, Bochum, W. Germany, Aug. 21-25, 1972.

9. Sigma Xi Lecturer: Function of Carotenoids. University of Rhode Island, Kingston, RI, October 10, 1973.

10. Invited Speaker: Photosensitization and Protection of Biomembranes and Model Systems. Colloquium on "Photochemistry of Biomembranes" at the 2nd Meeting of the American Society for Photobiology, Vancouver, British Columbia, Canada, July 24, 1974.

11. Theme Speaker: Light and Life: Biochemical Responses to Light. New England Association of Chemistry Teachers 36th Summer Conference, St. Anselem's College, Manchester, New Hampshire, Aug. 20-24, 1974.

12. Invited Speaker: Singlet Oxygen Production in Biological Systems. Workshop on "The Role of Oxygen in the Production of Excited States in Biological Systems" Photobiology Group, Biophysical Society, Philadelphia, PA, February 18, 1975.

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13. Invited Speaker: Damage and Protection against Singlet Oxygen. Workshop on "Free Radical Damage and Protection" Bioenergetics Group, Biophysical Society Seattle, WA, February 24, 1976.

14. Invited Speaker: Cellular Damage Initiated by Visible Light. Symposium on "The Survival of Vegetative Microbes" Society for General Microbiology, Cambridge, England, April 5-8, 1976.

15. Invited Speaker: Non-Photosynthetic Functions of Carotenoids. Discussion. Meeting on "The Biochemical Functions of Terpenoids in Plants" The Royal Society, London, England, January 26-27, 1978.

16. Invited Speaker: Carotenoid Protection against Oxidation. Fifth International Symposium on "Carotene and Vitamin A" Madison, WI, July 24-28, 1978.

17. Invited Participant: Joint Seminar on "Chemi- and Bio-energized Processes" Universidade de Sáo Paulo, Sáo Paulo, Brazil, August 5-7, 1978.

18. Invited Speaker: Cholesterol Oxidation by Either Polymorphonuclear Leukocyte or by Isolated Myeloperoxidase. International Conference on "Chemi- and Bio-energized Processes" Guaruja, Estado de Sáo Paulo, Brazil, August 8-10, 1978.

19. Invited Speaker: Carotenoid Pigments: Multiple Mechanisms for Coping with the Stress of Photosensitized Oxidations. Conference on "Strategies of Microbial Life in Extreme Environments" Dahlem Konferenzen, Berlin, Fed. Rep. Germany, November 20-24, 1978.

20. Invited Speaker: Is Singlet Oxygen Involved in Biological Chemiluminescence? Symposium on "Biological Basis of Chemiluminescence" American Society for Photobiology, Colorado Springs, CO, February 21, 1980.

21. Invited Speaker: Photosensitized Damage. Round Table on "Sensitized Photooxidation of Biomolecules" International Conference in Oxygen and Oxy-Radicals in Chemistry and Biology, Austin, TX, May 25-29, 1980.

22. Invited Speaker: Molecular Bases for Cellular Damage Initiated by Photosensitized Oxidations. Round Table on "Endogenous and Exogenous Inhibitors and Sensitizers. Fundamental Aspects" 8th International Congress on Photobiology, Strasbourg, France, July 20-25, 1980.

23. Invited Speaker: Interaction of Oxygen and Oxyradicals with Carotenoids Symposium on "Photochemical Toxicity" Food and Drug Administration, Bethesda, MD, March 16-17, 1981.

24. Invited Speaker: Possible Participation of Singlet Oxygen in Biological Systems. Symposium on "Radicals and Excited States in Biological Systems" Seventh International Biophysics Congress and Third Pan-American Biochemistry Congress, Mexico City, Mexico, August 24-28, 1981.

25. Invited Speaker: In vivo Analysis of UV-B Formation of 5.6-a-Epoxy- cholesterol. 2nd NCI/EPA/NIOSH Collaborative Workshop on "Progress on Joint Environmental and Occupational Cancer Studies" Rockville, MD, September 9-11, 1981.

26. Invited Speaker: The Biological Implications of Singlet Oxygen Production. Table Ronde Roussel Uclaf on "New Concepts of Free Radicals in Chemistry and Biology" Paris, France, October 22-23, 1981

27. Invited Speaker: Photosensitization. Singlet Oxygen Damage and Cancer. "International Workshop on Photobiology" Cheju, Korea, May 25-June 1, 1982.

28. Invited Speaker: Introduction to Photobiology and Photosensitization. Symposium on "Photobiology" Chosun University, Gwang Ju, Korea, June 2, 1982.

29. Invited Speaker: Free Radicals as Possible Mutagens and Carcinogens. Symposium on "Free Radicals and Cancer" Council for Tobacco Research, New York, NY, June 21, 1982.

30. Invited Speaker: Mutagenic and Carcinogenic Effects of Oxygen Radicals Symposium on "Possible Roles of Free Radicals in Aging" Gerontological Society of America, Boston, MA, Nov. 21, 1982.

31. Invited Speaker: Biology and Photobiology of Singlet Oxygen 3rd International Conference on Oxygen Radicals, Munich, FRG, July 10-15, 1983.

32. Invited Speaker: Comparison of the Oxidant Mechanisms of Myeloperoxidase and UV-B Irradiation EMBO Workshop on "Oxidative Enzymes-Damage and Consequences" Grottoferrata, Italy, October 2-7, 1983.

33. Public Lecture: New Findings on the Role of Provitamin A in Health and Disease. Institute for Research on Aging, University of California, San Diego, CA, September 13, 1984.

34. Invited Speaker: The Action of Carotenoids In vitro as Compared to their Function In vivo. Symposium on "Nutrition and Disease: Cancer" Helicon Foundation, San Diego, CA, September 15, 1984.

35. Invited Speaker: Detection and Biological Function of Active Oxygen Species School Lecture, American Society for Photobiology, New Orleans, and LA, June 27, 1985.

36. Invited Speaker: The Unique Singlet Oxygen Quenching Properties of Carotenoids. FASEB Summer Research Conference on "Micronutrients Retinoids" Saxtons River, VT, June 22-27, 1986.

37. Invited Speaker: Mechanisms of Inactivation of Oxygen Species by Carotenoids. 2nd International Conference on Anticarcinogenesis and Radiation Protection, National Bureau of Standards, Gaithersburg, MD, March 9-12, 1987.

38 Invited Speaker: Beta-carotene and Cancer: Overview and Rationale. VNIS Health Communications Conference: Beta-Carotene, Boca Raton, FL, April 11-12, 1987.

39. Invited Speaker: Overview of Carotenoids in Medicine. Eighth International Symposium on Carotenoids, Boston, MA, July 26-31, 1987.

40. Invited Speaker: Enzymic and Pigment Protection from Photodynamic Damage. FEMS/Society for Applied Bacteriology Symposium on "Homeostatic Mechanisms in Micro-organisms." Warwick University, Coventry, UK, September 14-18, 1987.

41. Invited Speaker: The Evidence for the Role of Carotenes in Preventive Health Symposium on "Carotenes in Food and Health" Department of Food Science and Office of Continuing Professional Education, Rutgers, The State University of New Jersey, Iselin, NJ, December 3, 1987.

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42. Invited Speaker: Carotenoids as Chemopreventive Agents. Third International Conference on "The Prevention of Human Cancer: Chemoprevention" Arizona Cancer Center, Tucson, AZ, January 12-15,

1988.

43. Invited Speaker: Theoretic and Experimental Basis for Anti-carcinogenic Effects of Retinoids. Workshop on "Emerging Role of Retinoids in the Treatment of Aging and Skin Cancer" Miami, FL, March 11-13, 1988.

44. Invited Speaker: Experimental Studies on Carotenoids and Cancer in Animal Models. Symposium on "The Biological Actions of Carotenoids" American Institute of Nutrition, Las Vegas, NV, May 1-6, 1988.

45. Invited Speaker: Biological Functions of Carotenoids and Retinoids. Symposium on "Biology of Human Skin Aging" American Academy of Dermatology, Philadelphia, PA, May 18-20, 1988.

46. Invited Speaker: Membrane Antioxidants. Conference on Biological Membranes in Cancer Cells, New York Academy of Sciences, Torgiano, Italy, June 13-18, 1988.

47. Invited Speaker: Pigment and Enzymic Protection Against Photodynamic Damage. Tenth International Congress of Photobiology. Jerusalem, Israel, October 31 1988.

48. Invited Speaker: Cancer Prevention: Animal and In vitro Studies. International Conference on "Anti-Oxidant Vitamins and Beta-Carotene in Disease Prevention" British Nutrition Foundation, London, U.K. October 2-4, 1989.

49. Invited Speaker: Carotenoid Metabolism. Workshop on "Carotenoids" FASEB Annual Meeting, Washington, DC, April 1, 1990.

50. Invited Speaker: Carotenoids and Cancer. Symposium on "Nutrition Related Cancer Research: An Interdisciplinary Update" Nutrition Council at Tufts, Boston, MA, April 25, 1990.

51. Invited Speaker: Carotenoid Function. Workshop on "Carotenoids" FASEB Annual Meeting, Atlanta GA, April 20, 1991.

52. Invited Speaker: Role of Carotenoids. Seminar on "Recipe for Cancer Prevention: Food Issues for the 1990s" American Cancer Society and Nestlé Beverage Company, New York, NY, June 12, 1991.

53. Invited Speaker: Mechanisms of Action of Antioxidants. Conference on Molecular and Comparative Nutrition, US-Japan Malnutrition Panel, Bethesda, MD, July 22-24, 1991.

54. Invited Participant: National Heart, Lung and Blood Institute Workshop on "Antioxidants in the Prevention of Human Atherosclerosis" Bethesda, MD, September 5-6, 1991.

55. Invited Speaker: Carotenoids in Cellular and Animal Systems: Effects on Mutagenesis, Carcinogenesis and Age-related Diseases. Symposium on "Free Radicals and Aging" Society for Free Radical Research (Europe), Paris, France, September 26-28, 1991.

56. Invited Speaker: Conversion of Carotenoids to Retinoids. Symposium on "Retinoids: New Trends in Research and Clinical Applications" Palermo, Italy, October 21-24, 1991.

57. Invited Speaker: Beta-Carotene - Animal Data. Symposium on "Vitamins and Cancer Prevention" Pennington Biomedical Research Center, Baton Rouge, LA, October 30 - November 1, 1991.

58. Invited Speaker: Carotenoids as Biological Antioxidants. Symposium on "Active Oxygens, Lipid Peroxides and Antioxidants" 5th International Congress on Oxygen Radicals, Kyoto, Japan, November 17-21, 1991.

59. Invited Speaker: Excentric Cleavage Mechanism(s) for Carotenoid Metabolism. Gordon Research Conference on "Chemistry and Biology of Carotenoids" Oxnard, CA, March 9-13, 1992

60. Invited Speaker: Nutritional Factors an Their Influence on Mutagenicity and Malignant Transformation. Tobacco and Health Research Institute, University of Kentucky Symposium on "Tobacco Smoking and Nutrition: Influence of Nutrition on Tobacco Associated Health Risks" Lexington, KY, September 14-16, 1992

61. Invited Speaker: Excentric Cleavage of Carotenoids. New York Academy of Sciences Conference on "Carotenoids in Human Health" San Diego, CA, February 6-9, 1993.

62. Invited Speaker: Antioxidant Effects of Carotenoids. International Conference on "Critical Aspects of Free Radicals in Chemistry, Biochemistry and Medicine" Vienna, Austria, February 14-17, 1993.

63. Invited Speaker: Antioxidant Properties of Carotenoids. The Kurashiki Symposium for Medical Science, Kurashiki, Japan, May 21-22, 1993.

64. Invited Speaker: ß-Carotene: Disease Prevention and Its Health Impact. Japan Vitamin Society, Gifu City, Japan, May 25-27, 1993.

65. Invited Speaker: Function, Actions, and Associations of Carotenoids. Tenth International Symposium on Carotenoids, Trondheim, Norway, June 20-25, 1993.

66. Invited Speaker: Antioxidants: Classification and Mode of Action. Symposium on "Antioxidants and Disease Prevention: Biochemical, Nutritional, and Pharmacological Aspects" Stockholm, Sweden, June 30-July 3, 1993.

67. Invited Speaker: Carotenoid Metabolism. Symposium on "Retinoids: New Trends in Research and Clinical Applications" Genoa, Italy, October 4-7, 1993.

68. Invited Speaker: The Effects of Carotenoids on Cells. Workshop on "Cell Proliferation and Differentiation: Modulation by Free" Rome, Italy, October 8, 1993.

69. Invited Discussant: Antioxidant Nutrients. Symposium on "Nutritional Assessment of Elderly Population Measure and Function" Boston, MA, October 11-13, 1993.

70. Invited Speaker: Clinical and Experimental Studies of ß-Carotene and Cancer. FDA Public Conference on Antioxidant Nutrients and Cancer and Cardiovascular Disease. Washington, DC, November 1-3, 1993.

71. Invited Speaker: Recent Research Findings on Beta-Carotene. Henkel Symposium on Vitamin E Palm Beach, FL, June 7-8, 1994.

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72. Invited Speaker: Comments on Antioxidant Vitamins and ß-Carotene. "Second International Conference on Antioxidant Vitamins and Beta Carotene in Disease Prevention" Berlin, Germany, October 10-12, 1994.

73. Invited Speaker: Plant Carotenoids and Related Molecules - Important Dietary Antioxidants. Symposium on "Free Radicals and Oxidative Stress - Environment, Drugs and Food Additives" Biochemical Society, Brighton, U.K., December 14-16, 1994

74. Invited Speaker: Antioxidants and Their Role in Human Health. 22nd Annual Texas Human Nutrition Conference, "Health Claims for Foods and Nutrients" Texas A & M Univ., Tyler, TX, February 3, 1995.

75. Plenary Lecture: An Overview of the Functions and Actions of Carotenoids: A Personal Perspective. 2nd Gordon Research Conference on Carotenoids, Ventura, CA February 5-9, 1995.

76. Invited Speaker: Carotenoids as Biological Antioxidants. 2nd Symposium on Vitamins and Biofactors, San Diego, CA February 15-19, 1995.

77. Invited Speaker: Overview of Carotenoids. USAID Workshop on the Bioavailability and Bioconversion of Carotenoids. Washington, DC April 4-5, 1995

78. Invited Speaker: Functions of Carotenoids. FASEB Summer Conference on Antioxidant Nutrients in the Cellular Biology of Health and Disease, Saxtons River, VT August 17-21, 1995

79. Invited Speaker: Biological Effects of Radicals on Carotenoids, 6th European Society for Photobiology, Cambridge, UK September 2-9, 1995.

80. Invited Speaker: Low Molecular Weight Antioxidants; You are What You Eat, Oxygen '95 Free Radical School, Annual Meeting of the Oxygen Society, Pasadena, CA November 17, 1995

81. Invited Speaker Carotenoids: Structure and Function, Workshop on "Potential Effects of Reducing Carotenoid Levels on Human Health" Department of Nutrition, Harvard School of Public Health, Boston, MA January 17th, 1996

82. Invited Speaker Metabolism and Mechanism of Action of Antioxidants, The Toxicology Forum, Givens Institute, Aspen, CO, July 9, 1996.

83. Invited Speaker Are the Oxidative Breakdown Products of Carotenoids Evidence of Antioxidant Action or the Generation of Biologically Active Molecules? VIII Biennial Meeting, International Society for Free Radical Research, Barcelona, Spain October 4, 1996

84. Invited Speaker ß-Carotene and Disease: A Causal Relationship? Oxygen '96, Annual Meeting of the Oxygen Society, Miami Beach. FL November 22, 1996

85. Invited Lecturer: Natural and Synthetic Carotenoids: Their Actions in Biology. 5th Mordechai Avron Memorial Lecture, Gifu and Tokyo, Japan, Nikken Sohonsha Corp., February 21 and 23, 1997

86. Invited Speaker: Overview of Lycopene, Carotenoids and Disease Prevention, International Symposium on the Role of Lycopene and Tomato Products in Disease Prevention, American Health Foundation/Tomato Research Council, New York, NY, March 3, 1997

87. Invited Speaker: Hypothetical Health Benefits Of ß-Carotene And Other Carotenoids, Society of Toxicology, Cincinnati, OH, March 11, 1997

88. Invited Lecturer: The Properties of Carotenoids that Define Their Actions (June 1) and The Actions of Carotenoids in Biology and Medicine (June 3), NATO Advanced Study Institute on Free Radicals, Oxidative Stress and Antioxidants: Pathological and Physiological Significance, Antalya, Turkey, May 24-June 4, 1997

89. Invited Speaker: Carotenoids and Chronic Degenerative Diseases, International Conference on Nutrition and Cancer, Irvine, CA July 16-July 19, 1997

90. Invited Speaker: The Antioxidant and Biological Properties of the Carotenoids, 7th Congress of the International Association of Biomedical Gerontology, Adelaide, Australia, August 15-August 18, 1997

91. Invited Speaker: Biochemistry of Carotenoids: Actions and Functions. American College of Nutrition Award Lecture, American College of Nutrition Annual Meeting, New York, NY, September 26-28, 1997

92. Invited Speaker: Measurement of Carotenoids, WORKSHOP on Quantitative Methods for Determination of Hydroxyl Radicals, Oxidation of Biological Molecules and Antioxidants, The Oxygen Society, San Francisco, CA, November 20-24, 1997.

93. Invited Speaker: Actions of Carotenoids, Oxygen Club of California, Santa Barbara, CA, February 7, 1998

94. Plenary Lecture: Carotenoids in Health and Disease, Gordon Research Conference on Oxygen Radicals in Biology, Ventura, CA, February 12, 1998

95. Invited Speaker: Role of Carotenoids in Health and Disease, The First Regional Meeting on Medical Sciences: "The Roles of Free Radicals in Health and Disease" Jerusalem and Amman, March 22-27, 1998

96. Invited Speaker: Activity of ß-Carotene Oxidation Products, European Conference on Biomedical Research and Peace, Paralimni, Cyprus, October 17-21, 1999

97. Invited Speaker: What is the Scientific Evidence for Establishing Carotenoids as Recommended Nutrients? Symposium on Dietary Antioxidants: the New Dietary Reference Indices, The Oxygen Society, New Orleans, LA, November 21, 1999

99. Invited Speaker: The Relationship Between Antioxidant and Chronic Disease, Symposium on Dietary Reference Intakes, Experimental Biology '00, San Diego, CA April 17, 2000

100. Invited Speaker: Carotenoids, Smoking and Cancer, 3rd International Conference on Antioxidants and Free Radicals in Health and Disease, Vancouver, BC, Canada July 23, 2000

101. Invited Speaker: Antioxidants and Chronic Diseases: How Much Science is Enough? Symposium on Dietary Reference Intakes, American Dietetic Association, Denver, CO October 18, 2000

102. Invited Speaker: Antioxidants and Chronic Diseases, Symposium on Dietary Reference Intakes, American Public Health Association, Boston, MA Nov. 13, 2000

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103. Invited Speaker: Carotenoids in Health and Disease, Robert S. Harris Lecture, Massachusetts Institute of Technology, Cambridge, MA March 15, 2001

104. Invited Speaker Possible Biologic Mechanism for the Protective Role of Xanthophylls, Symposium on Lutein and Macular Degeneration, FASEB Meeting, Orlando, FL, April 1, 2001

105. Invited Speaker: Carotenoid Research in the Past and Present Millennia, CARIG Lecturer, EB'01 Conference, Orlando, FL, April 2, 2001

106. Invited Speaker: Possible Biologic Mechanism for the Protective Role of Xanthophylls in Age-Related Macular Degeneration, American Society of Nutritional Sciences (EB'01), Orlando, FL, April 1, 2001

107. Invited Speaker: Dietary Carotenoids: What do They Do? PAX Mechanisms Conference, Cambridge, MA, September 30, 2001

108. Invited Plenary Lecturer Historical Critical Evaluaiton of free Radical and Antioxidant Research Oxygen Club of California, Santa Barbara, CA, March 8, 2002

109. Invited Speaker: Health Benefits of Carotenoids, Helmut Sies Festschrift, L'Abbaye de Royamount, Royamount, France, July 15, 2002

110. Invited Speaker: Dietary Carotenoids Modify Human Plasma Lipid Oxidizability, International Society for Free Radical Research Meeting, Paris France, July 16-20, 2002

111. Invited Plenary Lecturer Human Requirements for Fat-Soluble Vitamins, XIIth European Meeting on Fat-Soluble Vitamins, Rieti, Italy March 13-15, 2003

112. Invited Speaker: Overview of Lutein and Zeaxanthin, Advisory Committee, National Eye Institute, May 17, 2004

NORMAN I. KRINSKY, Ph. D. PUBLICATIONS

A. Peer Reviewed Journal Articles (99)

1. Ganguly, J, Krinsky, NI, Mehl, JW and Deuel, HJ Jr, Studies of the Distribution of Vitamin A as Ester and Alcohol and of Carotenoids in Plasma Proteins of Several Species. Arch. Biochem. Biophys. 38:275-282 (1952).

2. Krinsky, NI and Ganguly, J, Intracellular Distribution of Vitamin A Ester and Vitamin A Alcohol in Rat Liver. J. Biol. Chem. 202:227-232 (1953).

3. Ganguly, J and Krinsky, NI, Absence of Relationship between Vitamin A Alcohol Levels in Plasma and Liver of Rats. Biochem. J. 54:177-181 (1953).

4. Ganguly, J, Krinsky, NI, Pinckard, JH and Deuel, HJ, Jr., Untersuchungen über den Carotinoid-Stoffwechsel, XIV. Biologische Wirksamkeit von Echinenon. Z. Physiol. Chem. 295:61-66 (1953).

5. Ganguly, J, Krinsky, NI and Pinckard, JH, Isolation and Nature of Echinenone, a Provitamin A. Arch. Biochem. Biophys. 60:345-351 (1956).

6. Stefanini, M, Krinsky, NI and Magalini, SI, Studies on Platelets, XIX. Carotenoid Pigments in Human Platelets. J. Lab. Clin. Med. 50:225-228 (1957).

7. Krinsky, NI, Cornwell, DG and Oncley, JL, The Transport of Vitamin A and Carotenoids in Human Plasma. Arch. Biochem. Biophys. 73:233-246 (1958).

8. Krinsky, NI, Enzymatic Esterification of Vitamin A. J. Biol. Chem. 232:881-894 (1958).

9. Krinsky, NI, The Lipoprotein Nature of Rhodopsin. Arch. Ophthal. 60:688-694 (1958).

10. Goldsmith, TH and Krinsky, NI, The Epoxide Nature of the Carotenoid Neoxanthin. Nature (London) 188:491-493 (1960).

11. Krinsky, NI and Goldsmith, TH, The Carotenoids of the Flagellated Alga, Euglena gracilis. Arch. Biochem. Biophys. 91:271-279 (1960).

12. Krinsky, NI, A Relationship between Partition Coefficients of Carotenoids and their Functional Groups. Anal. Biochem. 6:293-302 (1963).

13. Krinsky, NI, Gordon, A and Stern, AI, The Appearance of Neoxanthin During the Re-greening of Dark-grown Euglena. Plant Physiol. 39:441-445 (1964).

14. Krinsky, NI and Levine, RP, Carotenoids of Wild Type and Mutant Strains of the Green Alga, Chlamydomonas reinhardi. Plant Physiol. 39:680-687 (1964).

15. Krinsky, NI, Carotenoid De-epoxidations in Algae. I. Photochemical Transformation of Antheraxanthin to Zeaxanthin. Biochim. Biophys. Acta 88:487-491 (1964).

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16. Bamji, MS and Krinsky, NI, Carotenoid De-epoxidations in Algae. II. Enzymatic Conversion of Antheraxanthin to Zeaxanthin. J. Biol. Chem. 240:467-470 (1965).

17. Mathews, MM and Krinsky, NI, The Relationship between Carotenoid Pigments and Resistance to Radiation in Non-photosynthetic Bacteria. Photochem. Photobiol. 4:813-817 (1965).

18. Krinsky, NI, The Carotenoids of the Brine Shrimp, Artemia salina. Comp. Biochem. Physiol. 16:181-187 (1965).

19. Krinsky, NI and Lenhoff, HM, Some Carotenoids in Hydra. Comp. Biochem. Physiol. 16:189-198 (1965).

20. Bamji, MS and Krinsky, NI, The Carotenoid Pigments of a Radiation-resistant Micrococcus sp. Biochim. Biophys. Acta 115:276-284 (1966).

21. Schimmer, BP and Krinsky, NI, The Structure of Neoxanthin and the Trollein-like Carotenoid from Euglena gracilis. Biochemistry 5:1814-1820 (1966).

22. Schimmer, BP and Krinsky, NI, Reduction of Carotenoid Epoxides with Lithium Aluminum Hydride. Biochemistry 5:3649-3657 (1966).

25. Mathews-Roth, MM and Krinsky, NI, Carotenoid Pigments and the Stability of the Cell Membrane of Sarcina lutea. Biochim. Biophys. Acta 203:357-359 (1970).

26. Mathews-Roth, MM and Krinsky, NI, Studies on the Protective Function of the Carotenoid Pigments of *Sarcina lutea*. Photochem. Photobiol. 11:419-428 (1970).

27. Mathews-Roth, MM and Krinsky, NI, Failure of Conjugated Octaene Carotenoids to Protect a Mutant of Sarcina lutea Against Lethal Photosensitization. Photochem. Photobiol. 11:555-557 (1970).

28. Cooney, JJ and Krinsky, NI, Photodynamic Killing of Acholeplasma laidlawii. Photochem. Photobiol. 16:523-526 (1972).

29. Kornhauser, A, Krinsky, NI, Huang, P-KC and Clagett, DC, A Comparative Study of Photodynamic Oxidation and Radiofrequency Discharge Generated $^1O_2$ Oxidation of Guanosine. Photochem. Photobiol. 18:63-69 (1973).

30. Anderson, SM and Krinsky, NI, Protective Action of Carotenoid Pigments against Photodynamic Damage to Liposomes. Photochem. Photobiol. 18:403-408 (1973).

31. Krinsky, NI, Bymun, EN and Packer, L, Retention of K^+ Gradients in Imidoester Cross-Linked Erythrocyte Membranes. Arch. Biochem. Biophys. 160:350-352 (1974).

32. Mathews-Roth, MM, Wilson, T, Fujimori, E and Krinsky, NI, Carotenoid Chromophore Length and Protection against Photosensitization. Photochem. Photobiol. 19:217-222 (1974).

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33. Anderson, SM, Krinsky, NI, Stone, MJ and Clagett, DC, Effect of Singlet Oxygen Quenchers on Oxidative Damage to Liposomes Initiated by Photosensitization or by Radiofrequency Discharge. Photochem. Photobiol. 20:65-69 (1974).

34. Krinsky, NI, Singlet Excited Oxygen as a Mediator of the Antibacterial Action of Leukocytes. Science 186:363-365 (1974).

35. Levine, PH, Weinger, RS, Simon, J, Scoon, KL and Krinsky, NI, Leukocyte-Platelet Interaction: Release of Hydrogen Peroxide by Granulocytes as a Modulator of Platelet Reactions. J. Clin. Investigation 57:955-963 (1976).

36. Deneke, CF and Krinsky, NI, Enhanced Dimol Emission of Singlet Oxygen by Cyclic Tertiary Amines. J. Am. Chem. Soc. 98:3041-3042 (1976).

37. Deneke, CF and Krinsky, NI, Inhibition and Enhancement of Singlet Oxygen ($^1\Delta_g$) Dimol Chemiluminescence. Photochem. Photobiol. 25:299-304 (1977).

38. Deneke, CF and Krinsky, NI, A Cheap and Durable Cuvet Washer. J. Chem. Educ. 54:257 (1977).

39. Krinsky, NI, Scoon, KL, Hardin, JC and Levine, PH, The Source of Hydrogen Peroxide and of Chemiluminescence Observed in Activated Human Platelet Preparations. Blood 50:597-602 (1977).

40. Lederman, DM, Cumming, RD, Petschek, HE, Levine, PH and Krinsky, NI, The Effect of Temperature on the Interaction of Platelets and Leukocytes with Materials Exposed to Flowing Blood. Trans. Am. Soc. Artif. Intern. Organs. 24:557-560 (1978).

41. Levine, PH, Hardin, JC, Scoon, KL and Krinsky, NI, Effect of Corticosteroids on the Production of Superoxide and Hydrogen Peroxide and the Appearance of Chemiluminescence by Phagocytosing Polymorphonuclear Leukocytes. Inflammation 5:19-27 (1981).

42. Andrews, PC and Krinsky, NI, The Reductive Cleavage of Myeloperoxidase in Half, Producing Enzymically Active Hemi-Myeloperoxidase. J. Biol. Chem. 256:4211-4218 (1981).

43. Krinsky, NI, Sladdin, DG, Levine, PH, Taub, IA and Simic, MG, Modification of Platelet Function by Radical Species Produced During Irradiation of Oxygenated Water. Thromb. Haemostasis 45:116-120 (1981).

44. Levine, PH, Sladdin, DG and Krinsky, NI, Superoxide, Xanthine Oxidase and Platelet Reactions. Further Studies on Mechanisms by which Oxidants Influence Platelets. Thromb. Haemostasis 45:290-293 (1981).

45. Krinsky, NI and Deneke, SM, The Interaction of Oxygen and Oxy-Radicals with Carotenoids. JNCI 69:205-210 (1982).

46. Andrews, PC and Krinsky, NI, A Kinetic Analysis of the Interaction of Human Myeloperoxidase with Hydrogen Peroxide, Chloride Ions and Protons. J. Biol. Chem. 257:13240-13245 (1982).

000088

47. Andrews, PC and Krinsky, NI, Quantitative Determination of Myeloperoxidase Using Tetramethylbenzidine as Substrate. Anal. Biochem. 127:346-350 (1982).

48. Andrews, PC, Parnes, C and Krinsky, NI, Comparison of Myeloperoxidase and Hemi-Myeloperoxidase with Respect to Catalysis, Regulation and Bactericidal Activity. Arch. Biochem. Biophys. 228:439-442 (1984).

49. Peak, MJ, Foote, CS, Krinsky, NI and Peak, JG, Oxygen-Independent Direct DNA Backbone Breakage Caused by Rose Bengal and Visible Light. J. Photochem. 25:309-315 (1984).

50. Mathews-Roth, MM and Krinsky, NI, Effect of Dietary Fat Level on UV-B Induced Skin Tumors, and Anti-Tumor Action of Beta-Carotene. Photochem. Photobiol. 40:671-673 (1984).

51. Mathews-Roth, MM and Krinsky, NI, Carotenoid Dose Level and Protection Against UV-B Induced Skin Tumors. Photochem. Photobiol. 42:35-38 (1985).

52. Cunningham, ML, Krinsky, NI, Gioranazzi, SM and Peak, MJ, Superoxide Anion is Generated from Cellular Metabolites by Solar Radiation and its Components. J. Free Radic. Biol. Med. 1:381-385 (1985).

53. Ito, A, Krinsky, NI, Cunningham, ML and Peak, MJ, Comparison of the Inactivation of *Bacillus subtilis* Transforming DNA by the Potassium Superoxide and Xanthine-Xanthine Oxidase Systems for Generating Superoxide. Free Radical Biol. Med. 3:111-118 (1987).

54. Mathews-Roth, MM and Krinsky, NI, Carotenoids Affect Development of UV-B Induced Skin Cancer. Photochem. Photobiol. 46:507-509 (1987).

55. Krinsky, NI, Mathews-Roth, MM, Welankiwar, S, Sehgal, PK, Lausen, NCG and Russett, M, The Metabolism of [14C]-ß-Carotene and the Presence of Other Carotenoids in Rats and Monkeys. J. Nutr. 120:81-87 (1990).

56. Mathews-Roth, MM, Welankiwar, S, Sehgal, PK, Lausen, NCG, Russett, M and Krinsky, NI, Distribution of [^{14}C]Canthaxanthin and [^{14}C]Lycopene in Rats and Monkeys. J. Nutr. 120:1205-1213 (1990).

57. Krinsky, NI, Russett, MD, Handelman, GJ and Snodderly, DM, Structural and Geometrical Isomers of Carotenoids in Human Plasma. J. Nutr. 120:1654-1661 (1990).

58. Snodderly, DM, Russett, MD, Land, RI and Krinsky, NI, Plasma Carotenoids of Monkeys (*Macaca Fascicularis and Saimiri Sciureus*) Fed a Nonpurified Diet. J. Nutr. 120:1663-1671 (1990).

59. Handelman, GJ, Snodderly, DM, Krinsky, NI, Russett, MD and Adler, AJ, Biological Control of Primate Macular Pigment. Biochemical and Densitometric Studies. Invest. Ophthalmol. Vis. Sci 32:257-267 (1991).

60. Wang, X-D, Tang, G-W, Fox, JG, Krinsky, NI and Russell, RM, Enzymatic Conversion of ß-Carotene into ß-Apo-Carotenals and Retinoids by Human, Monkey, Ferret, and Rat Tissues. Arch. Biochem. Biophys. 285:8-16 (1991).

61. Mathews-Roth, MM, Lausen, N, Drouin, G, Richter, A and Krinsky, NI, Effects of Carotenoid Administration on Bladder Cancer Prevention. Oncology 48:177-179 (1991).

62. Handelman, GJ, van Kuijk, FJGM, Chatterjee, A and Krinsky, NI, Characterization of Products Formed During the Autoxidation of ß-Carotene. Free Radical Biol. Med. 10:427-437 (1991).

63. Palozza, P and Krinsky, NI, The Inhibition of Radical-Initiated Peroxidation of Microsomal Lipids by both α-Tocopherol and ß-Carotene. Free Radical Biol. Med. 11:407-414 (1991).

64. Tang, G, Wang, X-D, Russell, RM and Krinsky, NI, Characterization of ß-Apo-13-Carotenone and ß-apo-14'-Carotenal as Enzymatic Products of the Excentric Cleavage of ß-Carotene. Biochemistry 30:9829-9834 (1991).

65. Wang, X-D, Krinsky, NI, Tang, G and Russell, RM, Retinoic Acid can be Produced from Excentric Cleavage of ß-Carotene in Human Intestinal Mucosa. Arch. Biochem. Biophys. 293:293-304 (1992).

66. Palozza, P and Krinsky, NI, ß-Carotene and α-Tocopherol are Synergistic Antioxidants. Arch. Biochem. Biophys. 297:184-187 (1992).

67. Palozza, P, Moualla, S and Krinsky, NI, Effects of ß-Carotene and α-Tocopherol on Radical-Initiated Peroxidation of Microsomes. Free Radical Biol. Med. 13:127-136 (1992).

68. Palozza, P and Krinsky, NI, Astaxanthin and Canthaxanthin are Potent Antioxidants in a Membrane Model. Arch. Biochem. Biophys. 297:291-295 (1992).

69. Wang, XD, Krinsky, NI, Marini, R, Tang, G, Yu, J, Fox, JG and Russell, RM, Intestinal Uptake and Lymphatic Absorption of ß-Carotene in Ferrets: A Model for Human ß-Carotene Metabolism. Am. J. Physiol. 263:G480-G486 (1992).

70. Wang, X-D, Russell, RM, Marini, R, Tang, G, Dolnikowski, G, Fox, JG and Krinsky, NI, Intestinal Perfusion of ß-Carotene in the Ferret Raises Retinoic Acid Levels in Portal Blood. Biochim. Biophys. Acta 1167:159-164 (1993).

71. Wang, X-D, Krinsky, NI and Russell, RM, Retinoic Acid Regulates Retinol Metabolism via Feedback Inhibition of Retinol Oxidation and Stimulation of Retinol Esterification in Ferret Liver. J. Nutr. 123:1277-1286 (1993).

72. Palozza, P and Krinsky, NI, Antioxidant Effects of Carotenoids on Biological Membranes. Acta Medica Romano 31:131-140 (1993).

73. Wang, X-D, Krinsky, NI, Benotti, PN and Russell, RM, Biosynthesis of 9-*cis*-retinoic acid from 9-*cis*-ß-carotene in human intestinal mucosa in vitro. Arch. Biochem. Biophys. 313:150-155 (1994).

74. Kennedy, AR and Krinsky, NI, Effects of retinoids, ß-carotene and canthaxanthin on UV and X-ray-induced transformation of C3H10T1/2 cells *in vitro*. Nutr. Cancer 22:219-232 (1994).

000090

75. Gaziano, JM, Hatta, A, Flynn, M, Johnson, EJ, Krinsky, NI, Ridker, PR, Hennekens, CH and Frei, B, Supplementation with ß-carotene in vivo and in vitro does not inhibit low density lipoprotein (LDL) oxidation. Atherosclerosis 112:187-195 (1995).

76. Wang, X-D, Marini, RP, Hebuterne, X, Fox, JG, Krinsky, NI and Russell, RM, Vitamin E enhances the lymphatic transport of ß-carotene and is conversion into vitamin A in the ferret. Gastroent. 108:719-726 (1995).

77. Gaziano, JM, Johnson, EJ, Russell, RM, Frei, B, Manson, JE, Stampfer, M, Ridker, PR, Hennekens, CH and Krinsky, NI, Discrimination in absorption or transport of ß-carotene isomers following oral supplementation with either all-*trans*- or 9-*cis*-ß-carotene. Am. J. Clin. Nutr. 61:1248-1252 (1995).

78. Hébuterne, X, Wang, X-D, Johnson, EJ, Krinsky, NI and Russell, RM, Intestinal absorption and metabolism of 9-*cis*-ß-carotene *in vivo*: biosynthesis of 9-*cis*-retinoic acid. J. Lip. Res. 36: 1264-1273 (1995).

79. Yeum, K-J, Lee-Kim, YC, Yoon, S, Lee, KY, Park, IS, Lee, KS, Kim, BS, Tang, G, Russell, RM and Krinsky, NI, Similar metabolites formed from ß-carotene by either human gastric mucosal homogenates, lipoxygenase or linoleic acid hydroperoxide. Arch. Biochem. Biophys. 321: 167-174 (1995).

80. Hammond, BR, Jr., Curran-Celentano, J, Judd, S, Fuld, K, Krinsky, NI, Wooten, BR and Snodderly, DM, Sex Differences in Macular Pigment Density: Relation to Plasma Carotenoid Concentrations and Dietary Patterns. Vision Research 36: 2001-2012 (1995).

81. Yeum, K-J, Booth, S, Sadowski, J, Lin, C, Tang, G, Krinsky, NI and Russell, RM Human Plasma Carotenoid Response to the Ingestion of Controlled Diets High in Fruits and Vegetables Am. J. Clin. Nutr., 64: 594-602 (1996)

82. Wang, X-D, Russell, RM, Stickel, F, Smith, D and Krinsky, NI ß-Oxidation in Rabbit Liver *in vitro* and in the Perfused Ferret Liver Contributes to Retinoic Acid Biosynthesis from ß-Apo-Carotenoic Acids. J. Biol. Chem., 271: 26490-26498 (1996)

83. Snodderly, DM, Shen, B, Land, RI, and Krinsky, NI, Dietary Manipulation of Plasma Carotenoid Concentrations of Squirrel Monkeys (*Saimiri sciureus)* J. Nutr. 127: 122-129 (1997)

84. Johnson, EJ, Krinsky, NI and Russell, RM, Bioavailability of all-*trans* and 9-*cis* isomers of ß-carotene in humans. J. Am. Coll. Nutr. 15: 620-624 (1997).

85. Hammond, BR, Jr., Johnson, EJ, Russell, RM, Krinsky, NI, Yeum, K-J, Edwards, R B and Snodderly, DM, Dietary Modification of Human Macular Pigment Density Invest. Ophthalmol. Vis. Sci. 38: 1795-1801 (1997)

86. Johnson, EJ, Qin, J, Krinsky, NI and Russell, RM, Ingestion by Men of a Combined Dose of ß-Carotene and Lycopene does not effect the Absorption of ß-Carotene but improves that of Lycopene. J. Nutr. 127: 1833-1837 (1997).

000091

87. Johnson, EJ, Qin, J, Krinsky, NI and Russell, RM, ß-Carotene Isomers in Human Serum, Breast Milk and Buccal after Continuous Oral Doses of all-*trans* and 9-*cis* ß-Carotene. J. Nutr. 127: 1993-1999 (1997).

88. Yeum, K-J, Ahn, S-H, de Paiva, SAR, Lee-Kim, YC, Krinsky, NI and Russell, RM, Correlations between Carotenoid Concentrations in Serum and Breast Adipose Tissue of Women with Benign Breast Tumor or Breast Cancer. J. Nutrition, 128: 1920-1926 (1998)

89. Wang, X-D, Liu, C, Bronson, RT, Smith, DE, Krinsky, NI and Russell, RM Altered Retinoid Signaling and AP-1 Expression by ß-Carotene and Smoking Leads to Lung Metaplasia. J. Natl. Cancer Inst., 91: 60-66 (1999)

90. Ferreira, A.L.A., Yeum, K.-Y., Liu, C., Smith, D., Krinsky, N.I., Wang, X.-D. and Russell, R.M. Tissue distribution of lycopene in ferrets and rats after lycopene supplementation J. Nutr., 130:1256-1260 (2000)

91. Yeum, K.-Y., Ferreira, A.L.A., Smith, D., Krinsky, N.I. and Russell, R.M. The Effect of α-Tocopherol on The Mechanisms of ß-Carotene Cleavage. Free Radic. Biol. Med. 29:105-114 (2000)

92. Liu, C., Wang, X.-D., Bronson, R.T., Smith, D.E., Krinsky, N.I. and Russell, R.M. Effects of Physiological versus Pharmacological ß-Carotene Supplementation on Cell Proliferation and Histopathological Changes in the Lungs of Cigarette Smoke-exposed Ferrets. Carcinogenesis 21:101-110 (2000)

93. Prakash, P., Russell, R.M. and Krinsky, N.I. *In vitro* Inhibition of Proliferation of Estrogen-dependent and Estrogen-independent Human Breast Cancer Cells Treated with Carotenoids or Retinoids. J. Nutr. 131:1574-1580 (2001)

94. Aldini, G, Yeum, K-J, Russell, RM and Krinsky, NI, A selective Method to Measure the Oxidizability of the Aqueous and Lipid Compartments of Plasma. Free Radic. Biol. Med. 31:1043-1050 (2001)

95. Krinsky, NI, Possible Biological Mechanisms for a Protective role of Xanthophylls. J. Nutrition 132:540S-542S (2002)

96. Tibaduiza, EC, Fleet, JC, Russell, RM and Krinsky, NI, Excentric Cleavage Products of ß-Carotene Inhibit Estrogen Receptor Positive and Negative Breast Tumor Cell Growth in Vitro and Inhibit Activator Protein-1-Mediated Transcriptional Activation. J. Nutrition 132:1368-1375 (2002)

97. Aldini, G., Yeum KJ., Carini M., Krinsky, N.I. and Russell, RM, (-)-Epigallocatechin-(3)-gallate Spares Carotenoids, Recycles α-Tocopherol and Prevents Oxidative Damage in Both the Aqueous and Lipid Compartments of Human Plasma. Biochem Biophys Res Commun 302:413-418 (2003)

98. Yeum, K.-J., Aldini, G., Chung H.-Y., Krinsky N.I. and Russell, R.M., J Nutrition 133:2688-2691 (2003) The Activities of Antioxidant Nutrients Human Plasma Depend on the Localization of Attacking Radical Species

000092

99. Ferreira, A.L.A., Yeum, K.-Y., Russell, R.M., Krinsky, N.I. and Tang, G., J. Nutr. Biochem. 14:531-540 (2003) Enzymatic and Oxidative Metabolites of Lycopene

100. Prakash, P., Liu, C., Hu, K.-Q., Krinsky, N.I., Russell, R.M. and Wang, X.-D. Effects of ß-Carotene, ß-Apo-14'-carotenoic Acid and Benzo[a]pyrene on Retinoic Acid Receptor ß Expression and Growth of Normal Human Bronchial Epithelial Cells. J. Nutr. 134:667-673 (2004)

101. Yeum, K.-Y., Russell, R.M., Krinsky, N.I. and Aldini, G. Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma. Arch. Biochem. Biophys. in press (2004)

C. Book Chapters and Invited Reviews (66)

1. Krinsky, NI, The Role of Carotenoid Pigments as Protective Agents against Photosensitized Oxidations in Chloroplasts **in:** Biochemistry of Chloroplasts (Goodwin, TW, Eds.) pp. 423-430, Academic Press, New York (1966), vol. 1,

2. Krinsky, NI, The Protective Function of Carotenoid Pigments **in:** Photophysiology (Giese, AC, Eds.) pp. 123-195, Academic Press, New York (1968), vol. 2,

3. Krinsky, NI, Function of Carotenoids **in:** Carotenoids (Isler, O, Eds.) pp. 669-716, Birkhäuser, Basel/Stuttgart (1971)

4. Krinsky, NI, Cellular Damage Initiated by Visible Light **in:** The Survival of Vegetative Organisms (Gray, TGR and Postgate, JR, Eds.) pp. 209-239, Cambridge Univ. Press, Cambridge (1976), vol. 26,

5. Krinsky, NI, Singlet Oxygen in Biological Systems. Trends in Biochemical Science 2:35-38 (1977).

6. Krinsky, NI, Non-photosynthetic Functions of Carotenoids. Phil. Trans. Roy. Soc. London B. 284:581-590 (1978).

7. Krinsky, NI, Carotenoid Protection against Oxidation. Pure & Appl. Chem. 51:649-660 (1979).

8. Krinsky, NI, Biological Roles of Singlet Oxygen **in:** Singlet Oxygen (Wasserman, HH and Murray, RW, Eds.) pp. 597-641, Academic Press, New York (1979)

9. Kuenen, JG, Hassan, HM, Krinsky, NI, Morris, JG, Pfenning, N, Schlegel, H, Shilo, M, Vogels, GS, Weser, U and Wolfe, R, Oxygen Toxicity: Group Report. **in:** Strategies of Microbial Life in Extreme Environments (Shilo, M, Eds.) pp. 223-241, Dahlem Konferenzen, Berlin (1979)

10. Krinsky, NI, The Biological Implications of Singlet Oxygen Production **in:** New Concepts of Free Radicals in Chemistry and Biology, pp. 30-31, Table Ronde Roussel UCLAF, France (1981), vol. 41,

11. Krinsky, NI, Sladdin, DG and Levine, PH, Effects of Oxygen Radicals on Platelet Functions **in:** Oxygen and Oxy-Radicals in Chemistry and Biology (Rodgers, MAJ and Powers, EL, Eds.) pp. 153-160, Academic Press, New York (1981)

12. Krinsky, NI, Photobiology of Carotenoid Protection **in:** The Science of Photomedicine (Regan, JD and Parrish, JA, Eds.) pp. 397-403, Plenum Press, New York (1982)

13. Krinsky, NI, Photosensitization and Singlet Oxygen Damage **in:** Topics In Photobiology (Kim, H-O and Song, PS, Eds.) pp. 67-71, Jeju National University, Jeju, Korea (1983)

14. Krinsky, NI and Welankiwar, S, Assay of Carotenoids. Meth. Enzymol. 105:155-162 (1984).

15. Krinsky, NI, Biology and Photobiology of Singlet Oxygen **in:** Oxygen Radicals In Chemistry And Biology (Bors, W, Saran, M and Tait, D, Eds.) pp. 453-464, Walter de Gruyter & Co., Berlin (1984)

16. Andrews, PC and Krinsky, NI, Myeloperoxidase Activity **in:** Handbook of Methods for Oxygen Radical Research (Greenwald, RA, Eds.) pp. 297-302, CRC Press, Boca Raton, FL (1985)

17. Andrews, PC and Krinsky, NI, Human Myeloperoxidase and Hemi-myeloperoxidase **in:** Immunochemical Techniques, Part J. Phagocytosis and Cell-Mediated Cytotoxicity. (Di Sabato, G and Everse, J, Eds.) pp. 369-378, Academic Press, New York (1986), vol. 132,

18. Krinsky, NI, Mechanisms of Inactivation of Oxygen Species by Carotenoids **in:** Anticarcinogenesis and Radiation Protection (Cerutti, PA, Nygaard, O and Simic, MG, Eds.) pp. 41-46, Plenum Press, New York (1987)

19. Krinsky, NI, The Evidence for the Role of Carotenes in Preventive Health. Clin. Nutr. 7:107-114 (1988).

20. Krinsky, NI, Theoretical Basis for Anticarcinogenic Effects of Retinoids. J. Cutan. Aging Cosm. Derm. 1:53-58 (1988).

21. Krinsky, NI, Membrane Antioxidants. Ann. N.Y. Acad. Sci. 551:17-33 (1988).

22. Krinsky, NI, Carotenoids and Cancer in Animal Models. J. Nutr. 119:123-126 (1989).

23. Krinsky, NI, Beta-Carotene: Functions **in:** New Protective Roles for Selected Nutrients (Spiller, GA and Scala, J, Eds.) pp. 1-15, Alan R. Liss, New York (1989)

24. Krinsky, NI, Carotenoids as Chemopreventive Agents. Prev. Medicine 18:592-602 (1989).

25. Krinsky, NI, Antioxidant Functions of Carotenoids. Free Radical Biol. Med. 7:617-635 (1989).

26. Krinsky, NI, Carotenoids in Medicine **in:** Carotenoids: Chemistry and Biology (Krinsky, NI, Mathews-Roth, MM and Taylor, RF, Eds.) pp. 279-292, Plenum Press, New York and London (1989)

27. Krinsky, NI, Effects of Carotenoids in Cellular and Animal Systems. Am. J. Clin. Nutr. 53:238S-246S (1991).

28. Krinsky, NI, Photooxidative Stress and Photodynamic Therapy: An Overview **in:** Oxidative Damage & Repair: Chemical, Biological and Medical Aspects (Davies, KJA, Eds.) pp. 298-299, Pergamon Press, Oxford (1991)

000094

29. Krinsky, NI, Mechanism of Action of Biological Antioxidants. Proc. Soc. Exp. Biol. Med. 200:248-254 (1992).

30. Steinberg, D, et al., Antioxidants in the Prevention of Human Atherosclerosis. Circulation 85:2337-2344 (1992).

31. Krinsky, NI, Anticarcinogenic Activities of Carotenoids in Animals and Cellular Systems **in:** Free Radicals and Aging (Emerit, I and Chance, B, Eds.) pp. 227-234, Birkhäuser, Basel (1992)

32. Mathews-Roth, MM and Krinsky, NI, Mammalian Metabolism of Carotenoids Other than Vitamin A. Meth. Enzymol. 213:265-272 (1992).

33. Handelman, GJ, Shen, B and Krinsky, NI, High-Resolution HPLC Analysis of Carotenoids in Human Plasma. Meth. Enzymol. 213:336-346 (1992).

34. Palozza, P and Krinsky, NI, Antioxidant Effects of Carotenoids *in Vitro* and *in Vivo*: An Overview. Meth. Enzymol. 213:403-420 (1992).

35. Krinsky, NI, Actions of Carotenoids in Cells and Animals **in:** Vitamins and Cancer Prevention (Bray, GA and Ryan, DH, Eds.) pp. 260-270, Louisiana State Univ. Press, Baton Rouge (1993)

36. Krinsky, NI, Wang, X-D, Tang, G and Russell, RM, Conversion of Carotenoids to Retinoids **in:** Retinoids: Progress in Research and Clinical Applications (Livrea, MA and Packer, L, Eds.) pp. 1-16, Marcel Dekker, New York (1993)

37. Tang, G and Krinsky, NI, Differentiation between Central and Excentric Cleavage of ß-Carotene. Meth. Enzymol. 214:69-74 (1993).

38. Krinsky, NI, Micronutrients and Their Influence on Mutagenicity and Malignant Transformation. Ann. N. Y. Acad. Sci. 686:229-242 (1993).

39. Krinsky, NI, Actions of Carotenoids in Biological Systems. Annu. Rev. Nutr. 13:561-587 (1993).

40. Krinsky, NI, Effects of Carotenoids on Cells. Mol. Aspects Med. 14:241-246 (1993).

41. Krinsky, NI, Wang, X-D, Tang, G and Russell, RM, Mechanism of Carotenoid Cleavage to Retinoids **in:** Carotenoids in Human Health (Canfield, LM, Krinsky, NI and Olson, JA, Eds.) pp. 156-166, New York Acad. Sci., New York (1993), vol. 691,

42. Krinsky, NI, The biological properties of carotenoids. Pure & Appl. Chem. 66:1003-1010 (1994).

43. Krinsky, NI, Wang, X-D, Tang, G and Russell, RM, Cleavage of ß-carotene to retinoids **in:** Retinoids: From Basic Science to Clinical Applications (Livrea, MA and Vidali, G, Eds.) pp. 21-28, Birkhaüser, Basel (1994)

44. Palozza, P and Krinsky, NI, Antioxidant properties of carotenoids **in:** Retinoids: From Basic Science to Clinical Applications (Livrea, MA and Vidali, G, Eds.) pp. 35-41, Birkhaüser, Basel (1994)

45. Krinsky, NI, Carotenoids and Cancer: Basic Research Studies **in:** Natural Antioxidants in Human Health and Disease (Frei, B, ed.) pp. 239-261, Academic Press, San Diego (1994)

000095

46. Krinsky, NI, Selected actions of micronutrient antioxidants **in**: Nutritional Assessment of Elderly Populations: Measure and Function (Rosenberg, IH, ed.) pp. 205-211, Raven Press, New York (1994)

47. Krinsky, NI, Plant Carotenoids and Related Molecules: Important Dietary Antioxidants **in**: Free Radicals and Oxidative Stress: Environment, Drugs and Food Additives (Rice-Evans, C., Halliwell, B. and Lunt, G.G., Eds.) Biochem. Soc. Symp. 61: 117-126, Portland Press, London (1995).

48. Krinsky, NI and Sies, H, The present status of antioxidant vitamins and beta-carotene. Am. J. Clin. Nutr. 62 (Suppl): 1299S-1300S (1995).

49. Olson, J.A. and Krinsky, N.I., The Colorful Fascinating World of the Carotenoids. FASEB J., 9: 1547-1550 (1995)

50. Krinsky, NI, Cellular aspects of carotenoids **in**: Handbook of Antioxidants (Cadenas, E and Packer, L, Eds.) pp. 315-336, Marcel Dekker, New York (1996).

51. Wang, X-D and Krinsky, NI, Identification and Quantification of Retinoic Acid and other Metabolites from ß-Carotene Excentric Cleavage in Human Intestine *in vitro* and Ferret Intestine *in vivo*. **in** METHODS IN ENZYMOLOGY (Suttie, JM and McCormack, D, eds.) 282: 117-130 (1997)

52. Omaye, ST, Krinsky, NI, Kagan, VE, Mayne, ST, Liebler, DC and Bidlack, WR, ß-Carotene: Friend or Foe? Fundam. Appl. Toxicol. 40: 163-174 (1997)

53. Krinsky, NI, Carotenoid Properties Define Primary Biological Actions And Metabolism Defines Secondary Biological Actions, **in** FREE RADICALS, OXIDATIVE STRESS, AND ANTIOXIDANTS: PATHOLOGICAL AND PHYSIOLOGICAL SIGNIFICANCE (Özben, T, ed.) pp. 323-332, NATO Advanced Study Institute (1998).

54. Wang, X-D and Krinsky, NI, The Bioconversion of ß-Carotene into Retinoids **in** SUBCELLULAR BIOCHEMISTRY, VOL. 30: FAT-SOLUBLE VITAMINS (Quinn, PJ and Kagan, V, eds.) pp. 159-180, Plenum/London (1998)

55. Krinsky, NI, Overview of Lycopene, Carotenoids, and Disease Prevention. Proc. Soc. Exp. Biol. Med. 218: 95-97 (1998)

56. Krinsky, NI, The Antioxidant and Biological Properties of the Carotenoids. Annals, New York Academy of Sciences 854: 443-447 (1998)

57. Krinsky, NI and Rock, C.L, Carotenoids (a) Chemistry, sources and physiology **in** ENCYCLOPEDIA OF HUMAN NUTRITION (Sadler, M, Strain, S and Caballero, B eds.) pp. 304-314, Academic Press, London (1998)

58. Krinsky, NI and Mayne, ST, Current Views on Carotenoids: Biology, Epidemiology and Trials **in** VITAMIN A AND RETINOIDS: AN UPDATE OF BIOLOGICAL ASPECTS AND CLINICAL APPLICATIONS, (Livrea, MA, ed.) pp. 45-57, Birkhäuser, Basel (2000)

000096

59. Prakash, P, Krinsky, NI. and Russell, RM, Retinoids, Carotenoids, and Human Breast Cancer Cultures: A Review of Differential Effects. Nutrition Reviews 58:170-176 (2000)

60. Krinsky, NI, Carotenoids as Antioxidants. Nutrition 17:815-817 (2001)

61. Krinsky, NI, Carotenoids and Oxidative Stress **in** CRITICAL REVIEWS OF OXIDATIVE STRESS AND AGING: ADVANCES IN BASIC SCIENCE, DIAGNOSTICS AND INTERVENTION, (Cutler, RG and Rodriguez, H, eds.) 598-611, World Scientific Publishing Co., New York (2003)

62. Krinsky, NI, Landrum, JT and Bone, RA, Biologic Mechanism of the Protective Role of Lutein and Zeaxanthin in the Eye, Annual Review of Nutrition 23:000-000 (2003)

63. Krinsky, NI and Yeum, K-J., Biochem Biophys Res Commun 305:754-60 (2003) Carotenoid-Radical Interactions

64. Aldini, G., Yeum KJ., Russell, R.M. and Krinsky, N.I., Nutritional Sciences 6:12-19 (2003) A Selective Assay to Measure Antioxidant Capacity in both the Aqueous and Lipid Compartments of Plasma

65. Krinsky, NI., Molecular Aspects of Medicine 24:317-324 (2003) Human Requirements for Fat-soluble Vitamins, and Other Things Concerning These Nutrients

66. Krinsky, N.I., Mayne, S.T. and Sies, H. in CAROTENOIDS IN HEALTH AND DISEASE (Krinsky, N.I., Mayne, S.T. and Sies, H., eds.) in press Marcel Dekker, New York (2004) Carotenoids: Looking Forward

D. Books and Proceedings

1. Krinsky, NI, Mathews-Roth, MM and Taylor, RF, Eds., Carotenoids*: Chemistry and Biology* (Plenum Press, New York and London, 1989).

2. Canfield, LM, Krinsky, NI and Olson, JA, Eds., *Carotenoids in Human Health*, vol. 691 (New York Acad. Sci., New York, 1993).

3. Krinsky, NI and Sies, H, Eds., *Antioxidant Vitamins and Beta-Carotene in Disease Prevention*, Am J. Clin. Nutr. 62 (Suppl): 1299S-1540S (1995)

4. Olson, JA and Krinsky, NI, Eds., *Carotenoids*, FASEB J. 9: 1547-1558 (1995).

5. Krinsky, N.I., Guest Editor, Proceedings of Symposium to Honor the Memory of James Allen Olson: Functions and Actions of Retinoids and Carotenoids: Building on the Vision of James Allen Olson J. Nutr. 134 (Suppl 1S) 218S-293S (2004)

6. Krinsky, N.I., Mayne, S.T. and Sies, H. (eds.) CAROTENOIDS IN HEALTH AND DISEASE in press Marcel Dekker, New York (2004)

000097

E. Letters

1. Krinsky, NI and Leff, J, Visible Light: Mutagen or Killer? Science 160:1255-1256 (1968).

2. Krinsky, N.I., Peacocke, M. and Russell, R.M. Antioxidant Vitamins, Cancer and Cardiovascular Disease. New Engl. J. Med. 335: 1066-1067 (1996).

3. Krinsky, NI and Russell, RM, Regarding the Conversion of ß-Carotene to Vitamin A. Nutr. Rev. 59: 309 (2001).

SUBMISSION END

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September 29, 2004

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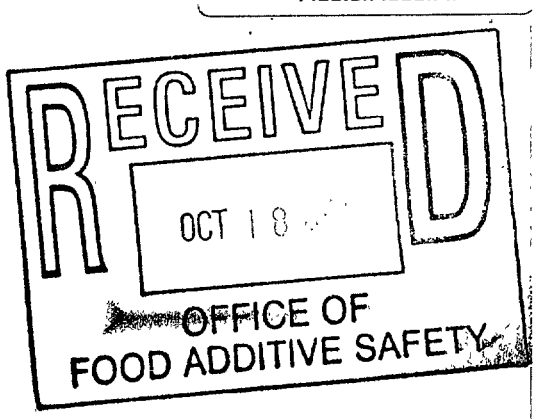

Laura Tarantino, Ph.D.
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Dr. Tarantino:

In accordance with proposed 21 CFR § 170.36 (a notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18937-18964), I am submitting in triplicate, as the representative of the notifier, LycoRed Natural Products Industries, Ltd, P.O. Box 320, Hebron Road, Industrial Zone, Beer-Shiva 84102, Israel, a GRAS notification of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract for use as a dietary addition of lycopene, at levels up to 14.3 mg/kg Lyc-O-Mato® 70% Concentrate (containing 10 mg/kg lycopene) and up to 668 mg/kg Lyc-O-Mato® 1.5% Extract (containing 10 mg/kg lycopene). These compounds will be used in baked goods, breakfast cereals, cheeses, condiments and relishes, confections, dairy product analogs, frozen dairy desserts, gelatins, puddings and fillings, grain products, gravies and sauces, jams and jellies, meat products, milk products, processed vegetables and vegetable juices, snack foods, soft candies and soups and soup mixes. A GRAS panel report, setting forth the basis for the GRAS determination, as well as CVs of the members of the GRAS panel for review by the Agency, are also enclosed.

Best regards,

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition

000204.001

1. GRAS Exemption Claim

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36 (c) (1)

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract have been determined to be generally recognized as safe (GRAS) and, therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

Date 30 Sept 04

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
Burdock Group
888 Seventeenth Street, NW, Suite 810
Washington, DC 20006

(i) Name and Address of the Notifier

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
Burdock Group
888 Seventeenth Street, NW, Suite 810
Washington, DC 20006

Telephone: 202-785-8200
Facsimile: 202-785-8666
Email: gburdock@burdockgroup.com

(ii) Common Name of the Notified Substance

The common name of Lyc-O-Mato® 70% Concentrate has been defined as:

Tomato extract containing lycopene (70%)

The common name of Lyc-O-Mato® 1.5% Extract has been defined as:

Tomato extract containing lycopene (1.5%)

(iii) Conditions of Use

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are intended to be used as ingredients to provide consumers with a supplementary source of lycopene in their diets. Lyc-O-Mato® 70% Concentrate will be used up to 14.3 mg/kg and, Lyc-O-Mato® 1.5% Extract will be used at levels up to 668 mg/kg, as a nutrient supplement, to give a maximum of 10 mg/kg lycopene to the following food products: baked goods, breakfast cereals, cheeses, condiments and relishes, confections, dairy product analogs, frozen dairy desserts, gelatins, puddings and fillings, grain products, gravies and sauces, jams and jellies, meat products, milk products, processed vegetables and vegetable juices, snack foods, soft candies and soups and soup mixes.

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract would not be used for production of the same food products, as their properties and characteristics are different. The estimated mean and 90th percentile intake of lycopene (the main functional ingredient of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract) by the total population from all proposed uses, at the maximum use levels in the United States, was determined to be 53.9 and 100.2 mg *per* person *per* day, respectively, for consumption of either Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract.

(iv) Basis of GRAS Determination

Pursuant to 21 CFR § 170.3, Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract have been determined GRAS by scientific procedures for their intended conditions of use. The safety of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract is supported by use of their constituents in tomato-based foodstuffs for millennia, as well as animal and clinical studies. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of substances used as ingredients in food.

(v) Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at a reasonable time at the office of:

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
Burdock Group
780 US Highway 1, Suite 300
Vero Beach, FL 32962

Telephone: 772-562-3900
Facsimile: 772-562-3908
E-mail: gburdock@burdockgroup.com

Alternatively, copies of data and information can be provided to FDA upon request, by contacting Dr. Burdock.

2. Detailed Information About the Identity of the Notified Substance

A. Identity

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are prepared from Lyc-O-Mato® Oleoresin 6%, which involves a solvent extraction from naturally-selected, non-genetically modified, hybrid, high lycopene content (150-250 ppm) varieties of tomato (*Lycopersicon esculentum* (L.) Karst Ex. Farwell; trade names include: Lycogold™ or LRT 90™ and Lycorich™ or LRT 89™), by an ethyl acetate extraction process. The product contains only the fat-soluble solids from the fruit.

Common or Usual Name:

The common name of Lyc-O-Mato® 70% Concentrate has been defined as:

Tomato extract containing lycopene (70%)

The common name of Lyc-O-Mato® 1.5% Extract has been defined as:

Tomato extract containing lycopene (1.5%)

Table 1. General description and analytical information of Lyc-O-Mato® 70% Concentrate

Botanical Source	*Lycopersicon esculentum* (L.) Karst Ex. Farwell.
Physical description	Dark red, free flowing powder.
Packaging	Packaged under nitrogen in laminate bags.
Storage	Store frozen.
Labeling	Tomato extract containing lycopene (70%).
Functional Use in Food	Source of supplemental lycopene.

Table 2. General description and analytical information of Lyc-O-Mato® 1.5% Extract

Botanical Source	*Lycopersicon esculentum* (L.) Karst Ex. Farwell.
Physical description	Viscous, dark red liquid.
Packaging	Packaged in metal drums with high-density polyethylene liners.
Storage	Store at room temperature.
Labeling	Tomato extract containing lycopene (1.5%).
Functional Use in Food	Source of supplemental lycopene.

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B. Composition

Chemical composition of the tomato extract containing lycopene (70%) is summarized in Table 3. Lyc-O-Mato® 70% Concentrate is an extract from tomatoes that contains a high lycopene content, with lower levels of other carotenoids, phytosterols and tocopherols.

Table 3. Chemical analysis of Lyc-O-Mato® 70% Concentrate*.

Chemical Analysis	Value
Water soluble matter	4.3 ± 1.5%
Total lycopene	70.2 ± 5.8%
Total tocopherols	Trace
Phytosterols	0.29 ± 0.14%
Total fatty acids	7.5 ± 1.7%
Phospholipids	7.3 ± 3.3%

*Additional information is given in Table 5.

Chemical composition of the tomato extract containing lycopene (1.5%) is summarized in Table 4. Lyc-O-Mato® 1.5% Extract is an extract from tomatoes that contains lycopene in a high fatty acid base content, with lower levels of other carotenoids and phytosterols.

Table 4. Chemical analysis of Lyc-O-Mato® 1.5% Extract*.

Chemical Analysis	Value
Water soluble matter	< 0.5%
Total lycopene	1.7 ± 0.35%
Total tocopherols	1.8 ± 0.44%
Total fatty acids	75 - 80%
Total carotenoids	3.1 ± 0.35%
Phytoene:	0.5 to 0.95%
Phytofluene:	0.4 to 0.75%
ß-carotene	0.05 to 0.5%

*Additional information is given in Table 6.

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Method of Manufacture of Lyc-O-Mato® 6%

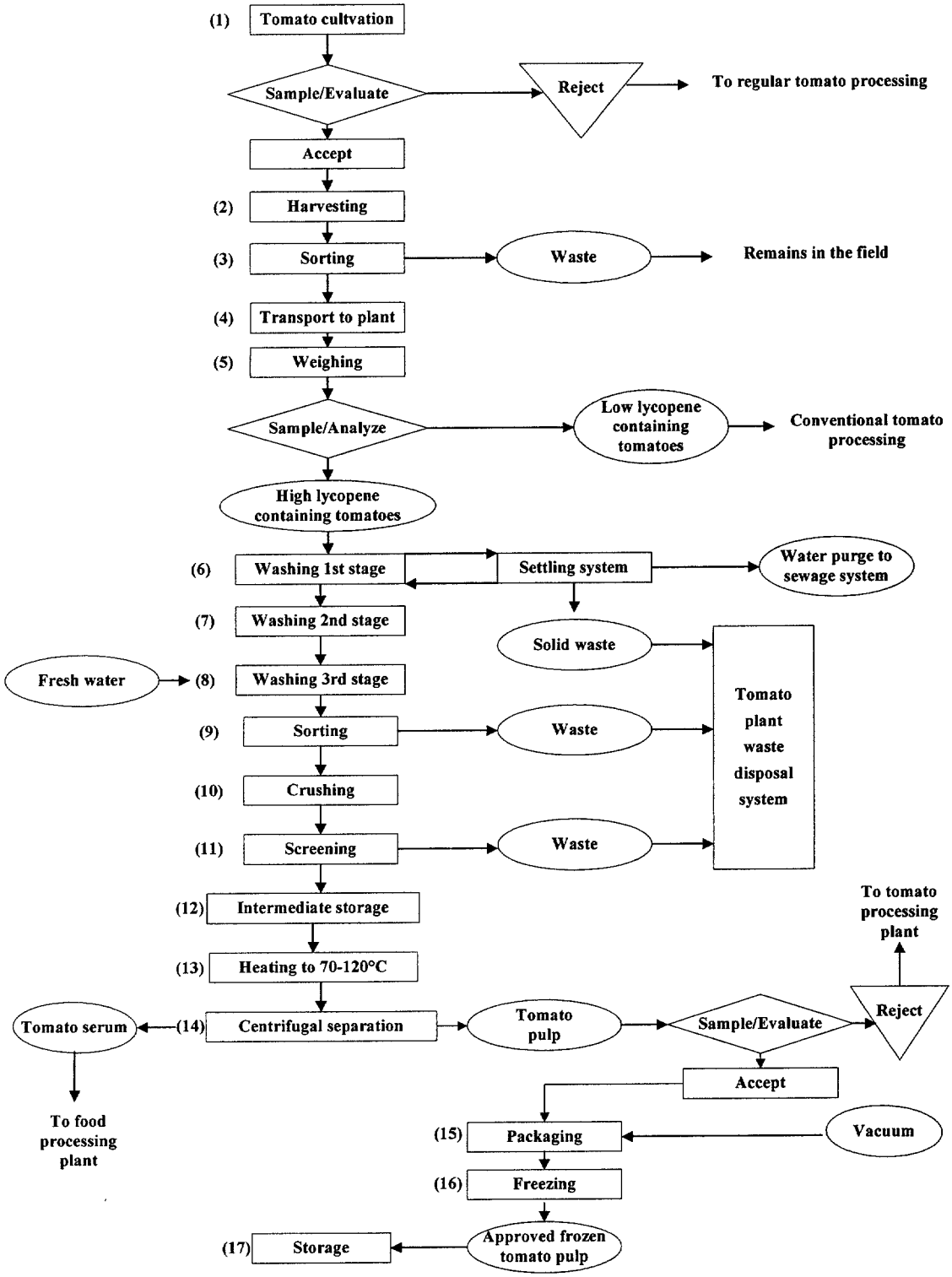


Figure 1. Lyc-O-Mato® Oleoresin 6% production scheme.

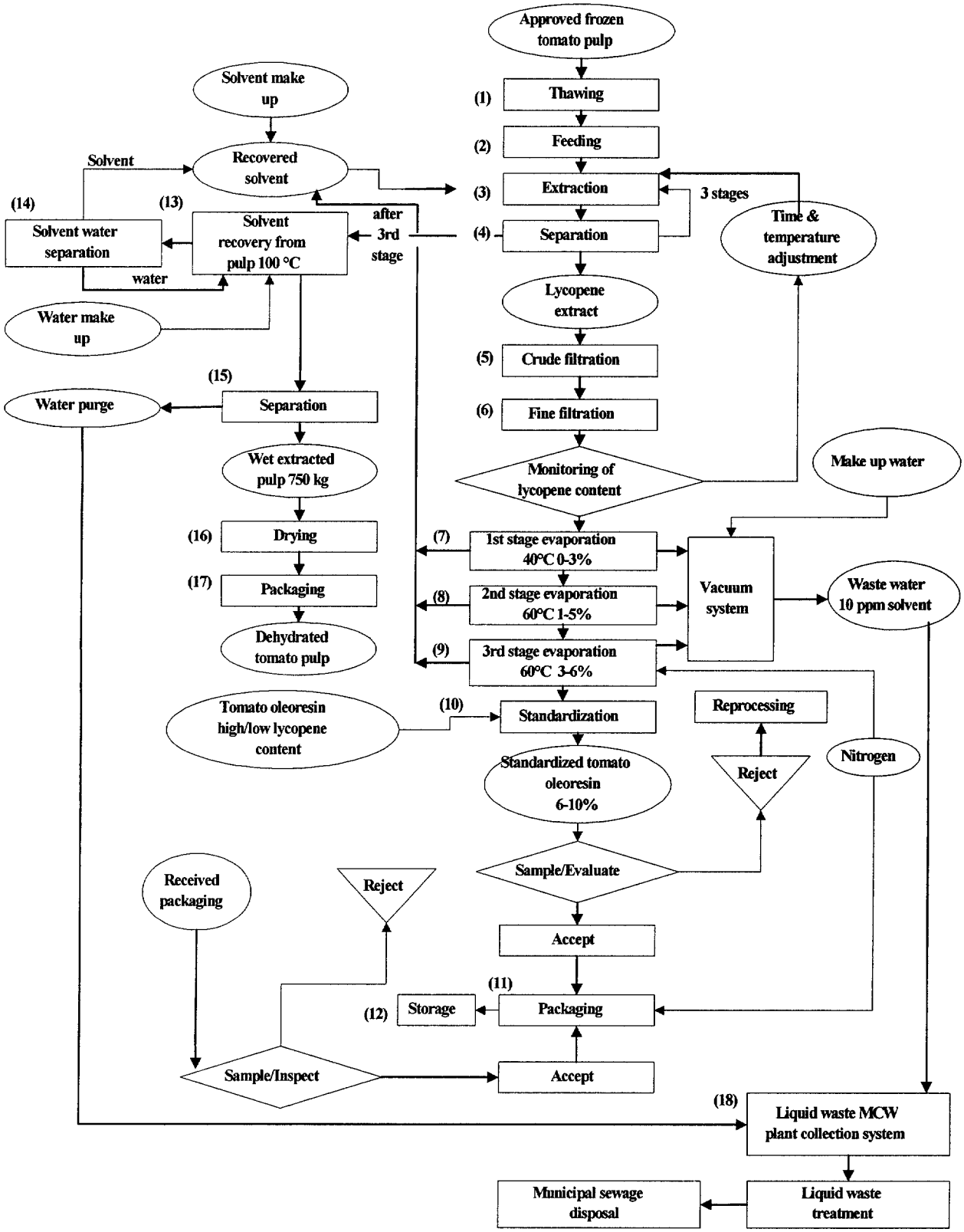
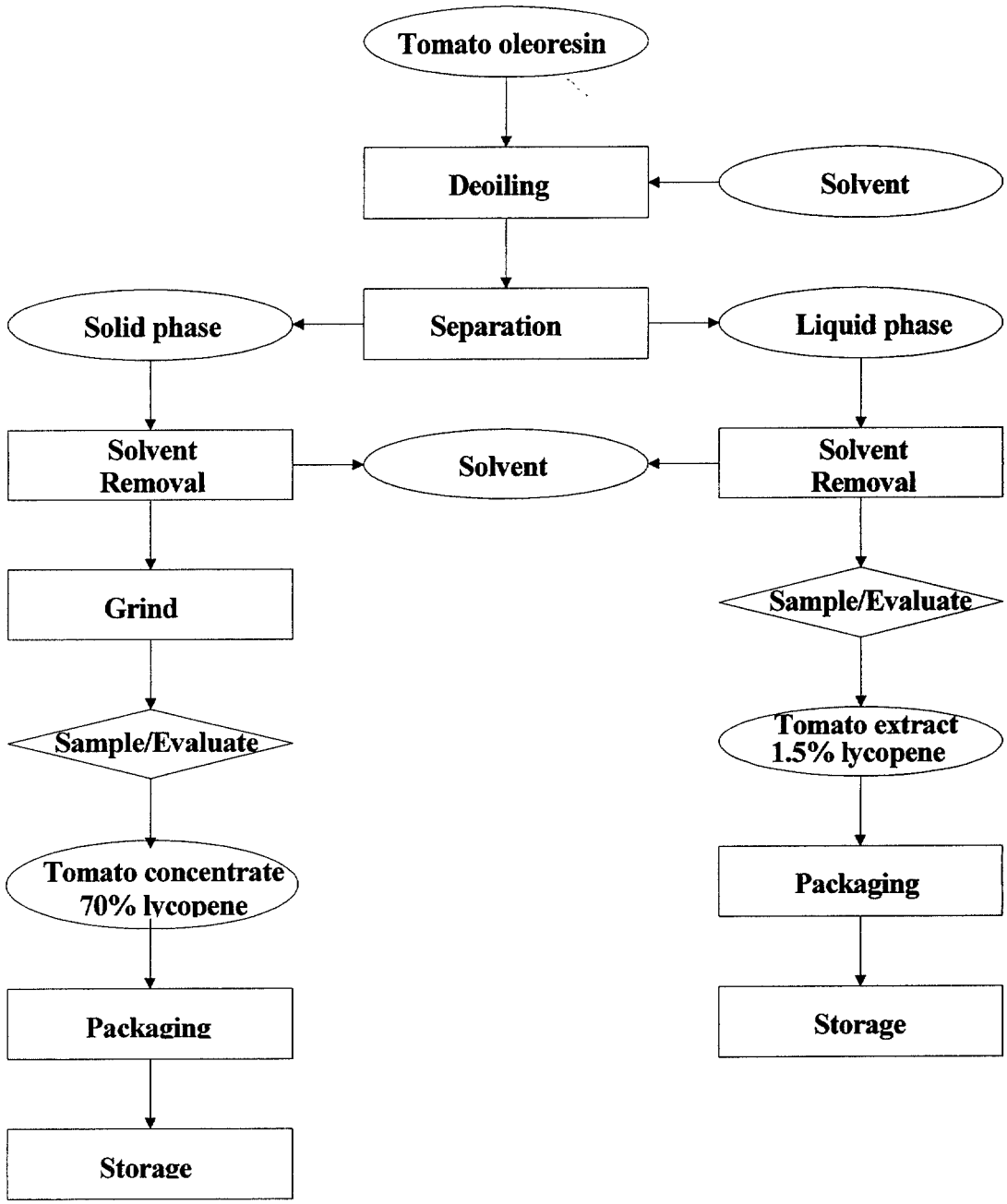


Figure 2. Lyc-O-Mato® Oleoresin 6% production scheme, continued.

Figure 3. Production of Lyc-O-Mato® 70% Concentrate and 1.5% Extract from Lyc-O-Mato® Oleoresin 6%.



C. Specifications for Food Grade Material

Table 5. Specifications of Lyc-O-Mato® 70% Concentrate.

Analysis	Specifications and Analytical Methods Specification	Method
Appearance	Dark red, free flowing powder	Visual inspection
Lycopene identity	Three peaks ~ 502, 472 and 444 nm	LAB/106/01[a]
Total lycopene[b]	60-80%	LAB/106/01[a]
% *trans*-Lycopene	90% minimum	LAB/119/01[a]
Total carotenoids[c]	60-80%	LAB/102/02[a]
Other carotenoids	Trace (below limit of detection)	LAB/118/03[a]
Total tocopherols	Trace (below limit of detection)	LycoRed[a]
Phospholipids	2.5-11%	LAB/98/021[a]
Waxes	0.2-1.0%	LAB/98/021[a]
Water soluble matter	3-7%	LAB/98/021[a]
Total fatty acids	5-12%	LycoRed[a]
Phytosterols	0.1-0.5%	Study 98/021
Lycopene crystal particle size	< 200 μ	Microscopic
Loss on drying	2.5% maximum	20 min., 110°C (halogen dryer)
Sulphated ash	1.5% maximum	AOAC® 34.104[d]
Residual solvent (ethyl acetate)	0.3% maximum	LAB/114/01[a]
Pesticides	Meets USP 24 NF 19/561	DFG-S19[e]
Heavy metals	Pb: < 1ppm; Cd, Hg: <1ppm	I.C.P.[e]
Arsenic	As: < 1ppm	I.C.P.[e]
Microbiology	Total count: < 2000/g; Mold, Yeast: < 100/g each; *Escherichia coli*: 0/g; *Salmonella* sp.: 0/20g; *Pseudomonas aeruginosa:* <10/g; *Staphylococcus aureus:* < 50/g	USP 24 NF 19/<61>

[a]LycoRed method, SOP available on request; [b]Combined *cis*- and *trans*-lycopenes; [c]Analysis method SOP available on request; [d]Official Methods of Analysis of the AOAC® International; NF = National Formulary; nm = nanometer; ppm = parts *per* million; USP = United States Pharmacopoeia

D. Specifications for Food Grade Material.

Table 6. Specifications of Lyc-O-Mato 1.5% Extract.

Analysis	Specification	Method
Appearance	Viscous, dark red liquid	Visual inspection
Lycopene identity	Three peaks at approx. 502, 472 and 444nm	LAB/109/01[a]
Total lycopene[b]	1-2%	LAB/109/01[a]
% *trans*-Lycopene	80% minimum	LAB/109/01[a]
Total carotenoids	2-4%	LAB/102/02[a]
Other carotenoids	Phytoene: 0.5 to 0.95% Phytofluene: 0.4 to 0.75% ß-carotene: 0.05 to 0.5%	LAB/118/01[a]
Total tocopherols	1-3%	LAB/118/01
Unsaponifiable matter	12-13%	Study 98/021[a]
Total fatty acids	75-80%	Study 98/021
Clearness	Clear solution	Study 98/021
Lycopene crystal particle size	90% < 5 μ 1% > 10 μ	Microscopic evaluation
Water	< 0.5%	Karl Fisher
Sulphated ash	1.5% maximum	AOAC® 34.104[d]
Residual solvent (ethyl acetate)	50 ppm maximum	LAB/114/01[a]
Pesticides	Meets USP 24 NF 19/561	DFG-S19[c]
Heavy metals	Pb: < 1ppm Cd, Hg: <1ppm	I.C.P.[c]
Arsenic	As: < 1ppm	I.C.P.[c]
Microbiology	Total count: < 1000/g Mold, Yeast: < 100/g each *Escherichia coli*: 0/10g *Salmonella* sp.: 0/10g *Pseudomonas aeruginosa:* 0/10g *Staphylococcus aureus:* 0/10g	USP 24 NF 19/<61>

[a]LycoRed method, SOP available on request; [b]Combined *cis*- and *trans*-lycopenes; [c]Analysis method SOP available on request; [d]Official Methods of Analysis of the AOAC® International; NF = National Formulary; nm = nanometer; ppm = parts *per* million; USP = United States Pharmacopoeia

III. Self Limiting Levels of Use

At high levels (exceeding the concentrations proposed), certain food items may acquire an undesirable red color.

IV. Basis of GRAS Determination

The determination that Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are GRAS is on the basis of scientific procedures. See attached- DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® 70% CONCENTRATE AND LYC-O-MATO® 1.5% EXTRACT AS FOOD INGREDIENTS

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® 70% CONCENTRATE AND LYC-O-MATO® 1.5% EXTRACT AS FOOD INGREDIENTS

June 7, 2004

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® 70% CONCENTRATE AND LYC-O-MATO® 1.5% EXTRACT AS FOOD INGREDIENTS

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1. SUMMARY

The undersigned, an independent panel of recognized experts (hereinafter referred to as the Expert Panel)[1], qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, was requested by LycoRed Natural Product Industries Ltd. (hereafter referred to as LycoRed) to determine the Generally Recognized As Safe (GRAS) status, based on scientific procedures, of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract. Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are to be used as ingredients to provide consumers with a supplementary source of lycopene in their diets, so that total daily consumption of lycopene from all sources does not exceed 120 mg *per* day of lycopene. In particular, the Expert Panel has evaluated the proposed use of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract at specified levels in the foods listed in Table 4 of this document. A comprehensive search of the scientific literature was conducted for safety and toxicity information on lycopene and related compounds and, along with supporting documentation, was made available to the Expert Panel. In addition, the Expert Panel independently evaluated materials submitted by LycoRed and other materials deemed appropriate and necessary. Following an independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein.

2. INTRODUCTION

Lyc-O-Mato® 70% Concentrate is concentrated natural lycopene (70% w/w average) extracted from tomatoes that contain a high lycopene content. Lyc-O-Mato® 1.5% Extract is composed of natural tomato lycopene (1.5% w/w average) and other natural tomato components. Lycopene (ψ,ψ-carotene), the predominant colorant in tomatoes, is an acyclic carotenoid with 11 linear conjugated double bonds (Figure 1). Lycopene is increasingly the subject of intense study because of its potential ability to help maintain the healthy structure and function of the body. Humans do not synthesize lycopene and depend entirely on dietary sources of lycopene such as red and pink colored vegetables and fruits. Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% are a good source of lycopene that can be used as an ingredient to provide consumers with a supplementary source of lycopene in their diets. This dossier is a summary of the scientific evidence that supports the general recognition that Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% as safe for human consumption as food ingredients.

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[1] Modeled after that described in Section 201(s) of the Federal Food, Drug, and Cosmetic Act, as amended. See also attachments (*curriculum vitae*) documenting the expertise of the Panel members.

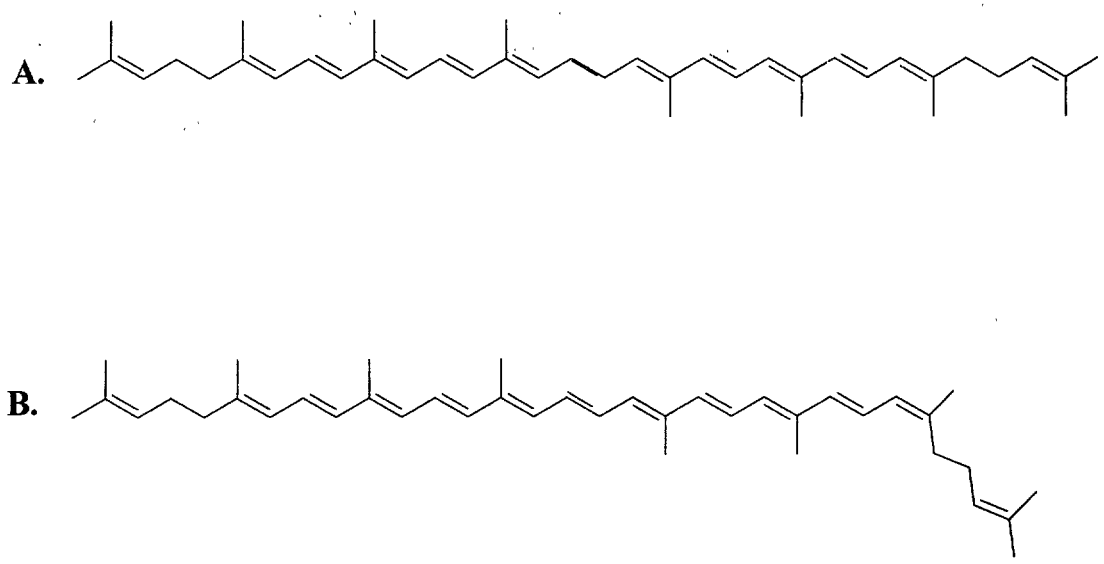

Figure 1 Structures of all-*trans*-Lycopene (A) and 5-*cis*-Lycopene (B)

2.1. Mechanism of Action: Antioxidant

Similar to other carotenoids, lycopene acts as an anti-oxidant, giving rise to the hypothesis that it protects cells against the damaging effects of free radicals. The anti-oxidant properties of lycopene rely on the conjugated double bond system (Figure 1). This system allows the establishment of a resonance condition and stabilizes carbon-centered radicals (Burton and Ingold, 1984). *In vitro*, carotenoids quench singlet oxygen-induced lipid peroxidation and intercept the propagation step of lipid peroxidation (Burton and Ingold, 1984; Rice-Evans *et al.*, 1997). Some *in vitro* studies have reported that the antioxidant activity of β-carotene and possibly other carotenoids, may have shifted into pro-oxidant activity, however, the conditions used to demonstrate this pro-oxidant activity appear non-physiological and required artificially high oxygen concentrations (Burton and Ingold, 1984; Palozza *et al.*, 1997). Thus, it is unlikely that carotenoids are pro-oxidants *in vivo* under normal physiological conditions. An important distinction between lycopene and other carotenoids, such as β-carotene, is that lycopene is not a Vitamin A precursor. This and other differences between lycopene and β-carotene are discussed in greater detail below (see β-carotene human intervention trials).

2.2. Regulatory Status

The European Union's Scientific Committee on Food has ruled that the use of lycopene (Natural Yellow 27) prepared from natural foods (such as tomatoes) by physical processes (*i.e.*, solvent extraction) and containing not less than 5% lycopene is acceptable for use as a colorant in foods including tomato products, confectionery products, and beverages (EU, 1995; EUSCF, 1975). The Committee did not establish an Acceptable Daily Intake (ADI) for lycopene in humans. Lycopene extracted from tomato is also an allowed food colorant in Japan, where it is used in processed vegetable products, soft drinks and confectionery products at levels from 50 to 200 parts per million (ppm). The FDA has recently been notified of a GRAS self-affirmation determination for synthetic lycopene as a food ingredient (BASF, 2002).

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% are produced from Lyc-O-Mato® Oleoresin 6%, which is currently under final review by the FDA's Division of Petition Review, Office of Food Additive Safety as a food color additive (Color Additive Petition #1C0273) submitted 4 September 2001. The proposed use of tomato lycopene at concentrations up to 50 ppm in foods has received preliminary approval and a regulation concerning its use is currently in preparation. It will be released for public comment in the near future.

Table 1. Physical and chemical properties of *all-trans*-lycopene (Budavari *et al.*, 1996).

Characteristic	Value
CAS No.	all-trans: 502-65-8 all-*cis* : 4418-71-7 15-*cis* : 59092-07-8 13-*cis* : 13018-46-7 9-*cis* : 64727-64-6
Mol. Wt.	536.85
Chemical formula	$C_{40}H_{56}$
Percent Composition	C = 89.5%, H = 10.5%
Melting Point	172-173°C; mp approximately 105°C then solidifies again
Appearance	Long, deep red needles from carbon disulfide + ethanol, from methylene chloride + methanol
Physical form	Solid
Assay	Absorption max, *trans*-form (petroleum ether): 446, 472, 505 nm ($E_{1cm}^{1\%}$ 2250, 3450, 3150). 15,15'-*cis*-Form: mp approximately 105°C then solidifies again; absorption max (petroleum ether): 361, 444, 470, 502 nm ($E_{1cm}^{1\%}$ 1110, 1280, 1660, 1280).
Solubility	One gram dissolves in 50 ml carbon disulfide, in 3 ltr boiling ether, in 12 ltr boiling petr ether, in 14 ltr hexane at 0°C. Sol in chloroform, benzene. Almost insol in methanol, ethanol.

3. MANUFACTURING PROCESS, DESCRIPTION AND SPECIFICATIONS

3.1. Description

The large family of carotenoids is based upon the same C_{40} isoprenoid skeleton. The vast arrays of different structures are brought about through cyclization, addition, elimination, rearrangement and substitution of the isoprenoid skeleton (Rice-Evans *et al.*, 1997). The carotenoids are classified into two major categories: the oxygen-containing xanthophylls (*e.g.* lutein, zeaxanthin, β-cryptoxanthin) and the non-oxygen containing carotenoid hydrocarbons (*e.g.* β-carotene, lycopene). The subject substance(s) of this GRAS monograph are Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract which consist of lycopene, the predominant colorant and antioxidant in the tomato oleoresin, and natural tomato lipid. Lycopene is a hydrocarbon carotenoid composed solely of carbon and hydrogen. Lycopene has 11 conjugated double bonds, which account for its spectral absorbance maximum of approximately 472 nm and its intensely red-orange to red color in concentrated forms (Figure 1). The physical and chemical properties of lycopene and specifications for Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are provided in Table 1, Table 2 and Table 3, respectively.

3.2. Manufacturing Process and Specifications

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are manufactured from Lyc-O-Mato® Oleoresin 6%. Lyc-O-Mato® Oleoresin 6% is manufactured by a patented process (United States Patent, #5,837,311) involving solvent extraction of naturally-selected, non-genetically modified, hybrid, high lycopene content (150-250 ppm) variety of tomato (*Lycopersicon esculentum* (L.) Karst. Ex. Farwell; tradenames Lycogold™, or LRT 90™; and Lycorich™ or LRT 89™). The extract (oleoresin) contains 6% lycopene on average, with the balance made up of other tomato lipids and carotenoids (**Table 2**).

Production of the tomato lycopene oleoresin is done in two steps. In the first step, high lycopene content tomatoes are used to prepare tomato pulp (Figure 2). After sorting and washing, the tomatoes are crushed and screened. The resulting tomato juice is passed through a heat exchanger at 80 to 90°C and centrifuged to produce the tomato pulp. Pulp with a satisfactory lycopene content (>1200 ppm lycopene) is cooled, packed into laminate bags under nitrogen, then into drums, and stored at -18°C until extracted. The production process introduces no exogenous substances to the tomato pulp.

In the second step, lycopene is extracted from the tomato pulp (Figure 3). The tomato pulp is crushed and extracted with ethyl acetate in a three-stage extraction process. After each stage, the pulp is separated from the lycopene extract and the extract filtered twice to remove all traces of pulp from the extract. The ethyl acetate in the extract is then removed under vacuum at 40 to 60°C in a three stage stripping process. The resulting oleoresin, Lyc-O-Mato® Oleoresin 6%, containing an average of 6% lycopene, is then further processed (Figure 2) to make Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract.

The oleoresin is deoiled to separate the Lyc-O-Mato® Oleoresin 6% into two fractions. One with an average of 70% lycopene (Lyc-O-Mato® 70% Concentrate; **Table 2**) and the second containing an average of 1.5% lycopene with the balance composed mainly of tomato lipids (Lyc-O-Mato® 1.5% Extract; Table 3). De-oiling is done by decantation of the oleoresin, or alternatively, by mixing it with food grade ethyl acetate that dissolves most of the tomato lipids, but only minute quantities of lycopene. The lycopene crystals are separated from the lipids dissolved in ethyl acetate, by filtration, decantation or centrifugation. Ethyl acetate is removed from both fractions producing: (1) a solid crystalline lycopene-rich (70% w/w) powder (Lyc-O-Mato® 70% Concentrate) and; (2) Lyc-O-Mato® 1.5% Extract, an oleoresin containing all the other tomato lipids and relatively small amounts of lycopene (1.5% w/w).

Lyc-O-Mato® 70% Concentrate is ground into a powder and packed under nitrogen in laminate bags and placed in frozen storage. Lyc-O-Mato® 1.5% Extract is packed in metal drums with high-density polyethylene liners and stored at room temperature.

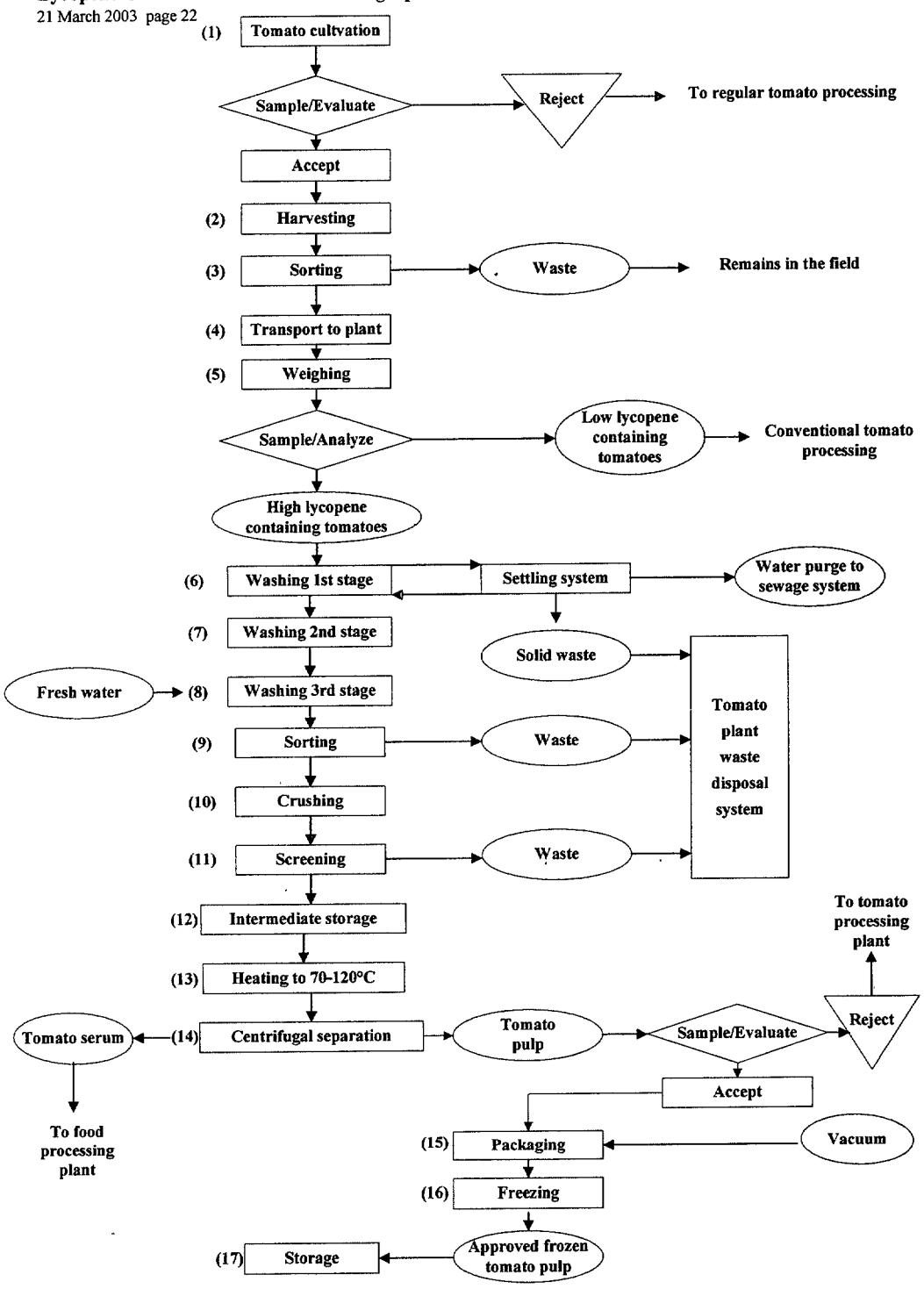

FIGURE 2: Pulp Production Scheme

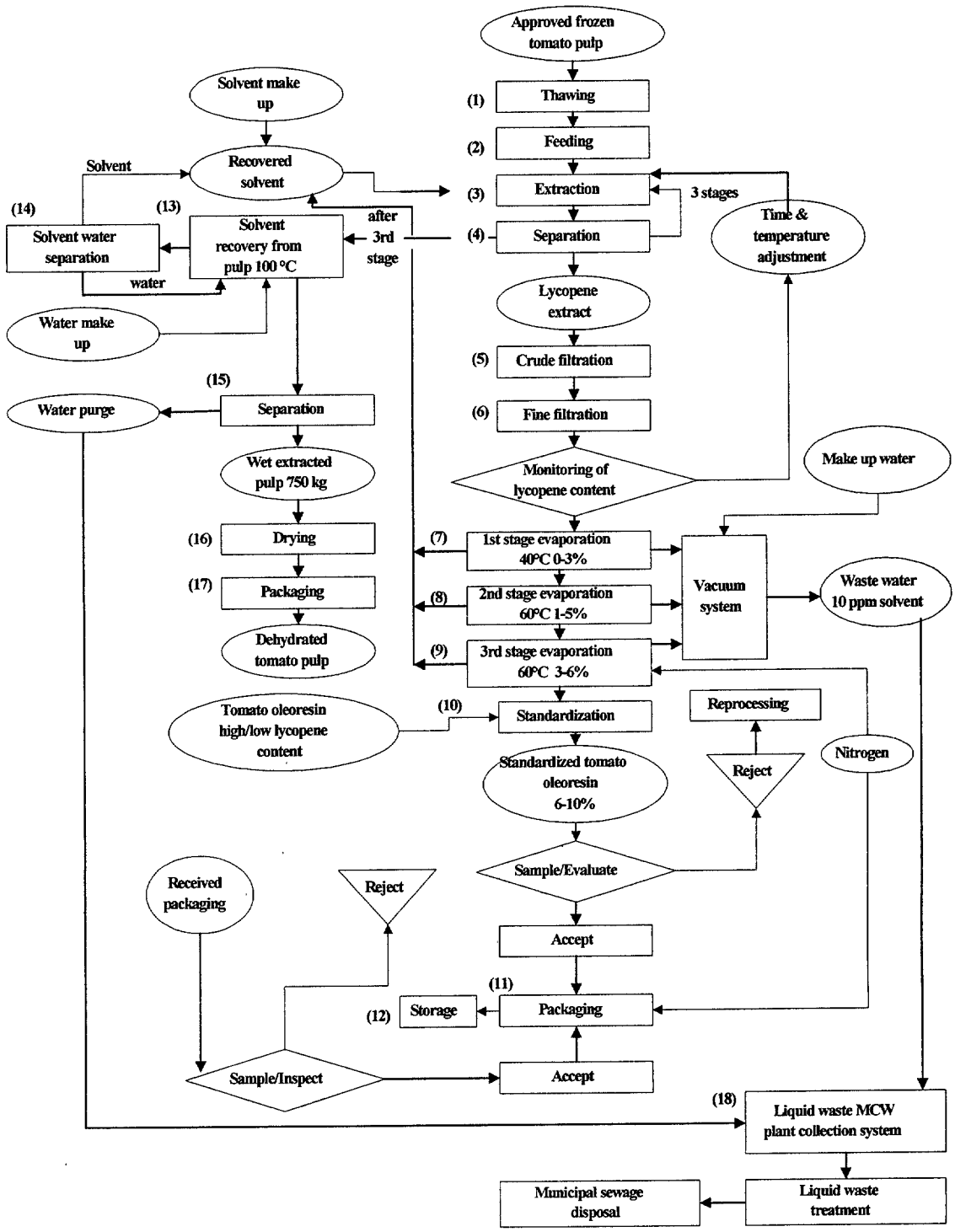

Figure 3. Lyc-O-Mato® Oleoresin 6% production scheme

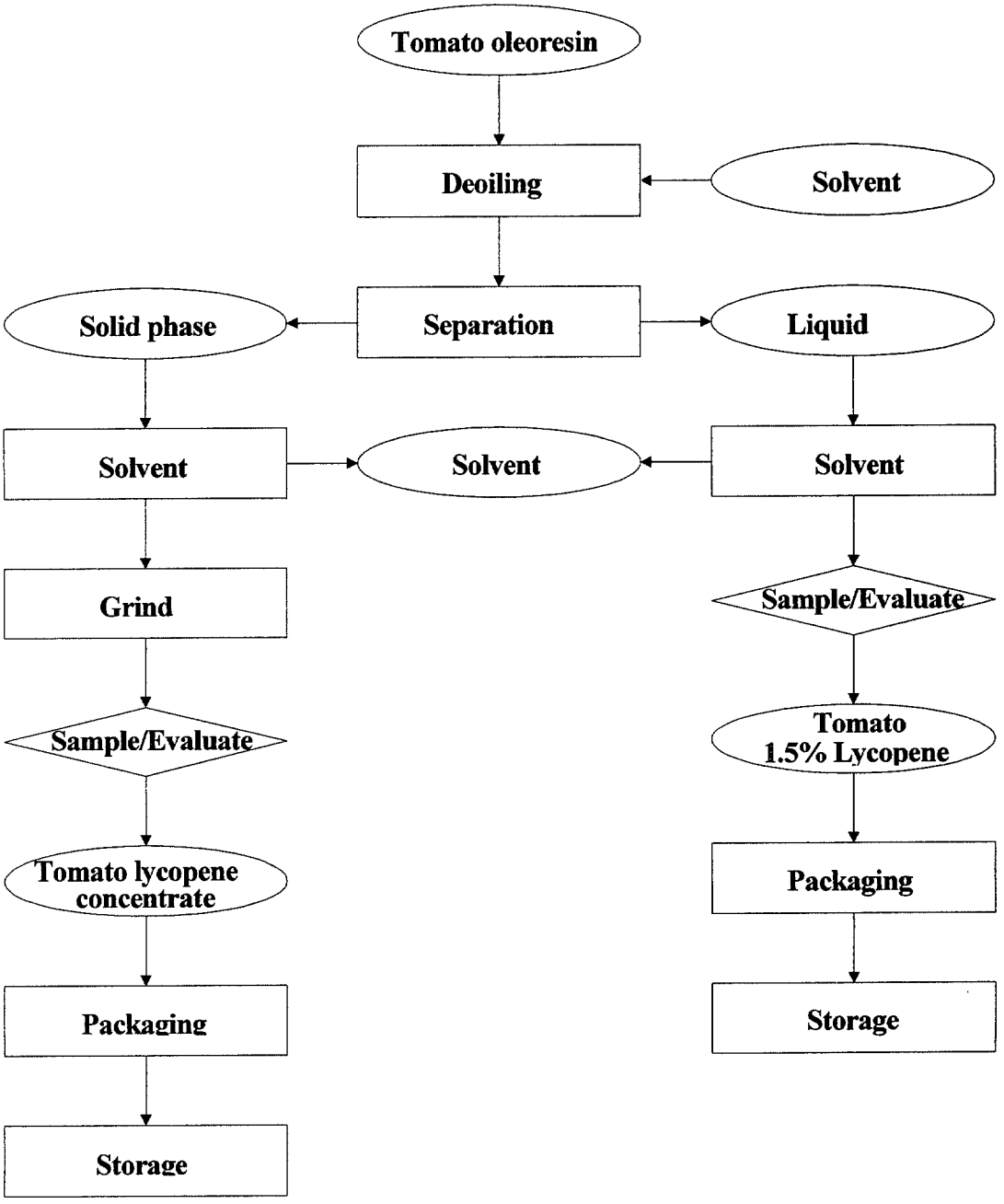

Figure 2. Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract production schemes

Table 2. Specifications of Lyc-O-Mato® 70% Concentrate

Analysis	Method	Specification	Batch Analysis Results	
			Range	Average and/or N
Appearance	Visual inspection	Dark red, free flowing powder	Meets limits	N=15
Lycopene identity	LAB/106/01[a]	Three peaks ~ 502, 472 and 444 nm	Meets limits	N=15
Total lycopene[b]	LAB/106/01[a]	60-80%	61.3 to 78.9%	70.2 ± 5.81% (N=15)
% *trans*-Lycopene	LAB/119/01[a]	90% minimum	91.6 to 92.5%	92.2 ± 0.4% (N=6)
Total carotenoids[c]	LAB/102/02[a]	60-80%	61.3 to 78.9%	70.2 ± 5.81% (N=15)
Other carotenoids	LAB/118/03[a]	Trace (below limit of detection)	Meets limits	N=15
Total tocopherols	LycoRed[a]	Trace (below limit of detection)	Meets limits	N=15
Phospholipids	LAB/98/021[a]	2.5-11%	4.9-11%	7.3 ± 3.3 (N=3)
Waxes	LAB/98/021[a]	0.2-1.0%	0.2-0.8%	0.5 ± 0.3% (N=3)
Water soluble matter	LAB/98/021[a]	3-7%	3.2-6.0%	4.3 ± 1.5% (N=3)
Total fatty acids[d]	LycoRed[a]	5-12%	5.4 to 10.5%	7.5 ± 1.7% (N=9)
Phytosterols	Study 98/021	0.1-0.5%	0.13 to 0.40%	0.29 ± 0.14% (N=3)
Lycopene crystal particle size	Microscopic	< 200 μ	99% < 200 μ	N=15
Loss on drying	20 min., 110°C (halogen dryer)	2.5% maximum	1.2 to 1.8%	1.5 ± 0.2% (N=15)
Sulphated ash	AOAC 34.104	1.5% maximum	0.7 to 1.5%	1.1 ± 0.3% (N=6)
Residual solvent (ethyl acetate)	LAB/114/01[a]	0.3% maximum	0.1 to 0.3%	0.23 ± 0.07% (N=15)
Pesticides	DFG-S19[e]	Meets USP 24 NF 19/561	Meets limits	Total < 3 ppm (N=10)
Heavy metals	I.C.P.[e]	Pb < 1ppm; Cd, Hg <1ppm	Meets limits	Each < 1 ppm (N=10)
Arsenic	I.C.P.[e]	As < 1ppm	Meets limits	< 0.03 ppm (N=10)
Microbiology	USP 24 NF 19/<61>	Total count < 2000/g; Mold, Yeast < 100/g each; *Escherichia coli*: 0/1g; *Salmonella* sp.: 0/20g *Pseudomonas aeruginosa* < 10/1g *Staphylococcus aureus* < 50/1g	Meets limits	N=15

[a]LycoRed Method, SOP available on request
[b]Combined *cis*- and *trans*-lycopenes
[c]Calculated as lycopene
[d]Free fatty acids (myristic acid (14:0); palmitic acid (16:0); stearic acid (18:0); oleic acid (18:1); linoleic acid (18:2); linolenic acid (18:3); arachidic acid (20:0); behenic acid (22:0)); mono-, di- and tri-glycerides
[e]Analysis method SOP available on request

Table 3. Specifications of Lyc-O-Mato® 1.5% Extract

Analysis	Method	Specification	Batch Analysis Results	
			Range	Average and/or N
Appearance	Visual inspection	Viscous, dark red liquid	Meets limits	N=15
Lycopene identity	LAB/109/01[a]	Three peaks at approx. 502, 472 and 444 nm	Meets limits	N=15
Total lycopene[b]	LAB/109/01[a]	1-2%	1.2 to 2.4%	1.7 ± 0.35 (N=9)
% *trans*-Lycopene	LAB/109/01[a]	80% minimum	80 to 90%	85 ± 5% (N=6)
Total carotenoids[c]	LAB/102/02[a]	2-4%	2.5 to 3.6%	3.1 ± 0.35% (N=12)
Other carotenoids	LAB/118/01[a]	Phytoene: 0.5 to 0.95% Phytofluene: 0.4 to 0.75% ß-carotene: 0.05 to 0.5%	0.6 to 0.9% 0.5 to 0.6% 0.1 to 0.4%	0.65 ± 0.1% (N=12) 0.51 ± 0.03% (N=12) 0.22 ± 0.08% (N=12)
Total tocopherols	LAB/118/01	1-3%	1.5 to 2.9%	1.8 ± 0.44% (N=12)
Unsaponifiable matter	Study 98/021[a]	12-13%	12 to 13%	N=2
Total fatty acids[d]	Study 98/021	75-80%	75 to 80%	N=2
Clearness	Study 98/021	Clear solution	Meets limits	N=15
Lycopene crystal particle size	Microscopic evaluation	90% < 5 μ 1% > 10 μ	Meets limits	N=15
Water	Karl Fisher	< 0.5%	Meets limits	N=15
Sulphated ash	AOAC 34.104	1.5% maximum	Meets limits	N=6
Residual solvent (ethyl acetate)	LAB/114/01[a]	50 ppm maximum	20 to 50 ppm	27 ± 12 ppm (N=15)
Pesticides	DFG-S19[e]	Meets USP 24 NF 19/561	Meets limits	N=10
Heavy metals	I.C.P.[e]	Pb < 1ppm Cd, Hg all <1ppm	Meets limits	N=10
Arsenic	I.C.P.[e]	As < 1ppm	Meets limits	N=10
Microbiology	USP 24 NF 19/<61>	Total count < 1000/g Mold, Yeast < 100/g each *Escherichia coli*: 0/10g *Salmonella* sp.: 0/10g *Pseudomonas aeruginosa* 0/10g *Staphylococcus aureus* 0/10g	Meets limits	N=15

[a]LycoRed Method, SOP available on request; [b]Combined *cis*- and *trans*-lycopenes; [c]Calculated as lycopene; [d]Free fatty acids (myristic acid (14:0); palmitic acid (16:0); stearic acid (18:0); oleic acid (18:1); linoleic acid (18:2); linolenic acid (18:3); arachidic acid (20:0); behenic acid (22:0)); mono-, di- and tri-glycerides; [e]Analysis method SOP available on request

3.3. Stability

Lyc-O-Mato® 70% Concentrate was very stable (measured by lycopene integrity) for at least six months when packed in an aluminum bag under air, under nitrogen or in a vacuum and stored at 37°C (LycoRed, 2003a, b). Lyc-O-Mato® 70% Concentrate was stable as a food ingredient in yogurt (30 days), Soya sausages (6 months), ice cream (6 months), pink grapefruit soft drink (12 months) and toffee (6 months) with greater than ninety percent of the added lycopene recovered following the processing of these different foods (LycoRed, 2003c).

There was no loss of lycopene in Lyc-O-Mato® 1.5% Extract that was stored at 4-6°C for up to 39 months (LycoRed, 2003d). Similarly, no loss of lycopene was observed over six months in margarine made with Lyc-O-Mato® 1.5% Extract (LycoRed, 2003e).

Thus, the chemical stability of lycopene under storage and a variety of food processing conditions demonstrates that Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are stable food ingredients.

4. ESTIMATED DAILY INTAKE

The intake profile (amount and frequency) by individuals in USDA's Continuing Survey of Food Intakes by Individuals 1994-96, 98 (CSFII 1994-96, 2000) was used to calculate the estimated daily intake (EDI) of Lyc-O-Mato® 70% Concentrate, Lyc-O-Mato® 1.5% Extract and lycopene for individuals consuming the food groups selected for the addition of Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract *per* this GRAS evaluation. The reference to lycopene in this GRAS review is due to its biological significance. The food groups as defined by the FDA (21 CFR 170.3(n)) are listed in Table 4.

The mean and 90th percentile EDIs were calculated for: (1) current lycopene intake from natural sources (current); (2) lycopene intake following addition of Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract to the selected food groups (added) and; (3) total estimated EDI from natural sources combined with levels from addition to the foods (total).

Foods in which lycopene is a known constituent were identified using the USDA-NCC[2] carotenoid database as reported by Holden *et al.* (1999). The USDA-NCC database also provided the concentration of lycopene in these foods. A total of 26 foods and food products were selected that included fruits, vegetable products, meat products, as well as tomato and tomato products. Food and lycopene consumption were estimated by (1) weighting of the data for estimation of consumption by individuals in the entire United States population and (2) multiplying the estimated food consumption (grams food/day) with the lycopene concentration (mg lycopene/g food). The current consumption analysis done presently for all individuals that consume lycopene-containing food indicates that the mean daily intake for lycopene is estimated to be 8.2 mg/day, with a 90th percentile intake of 15.7 mg/day (Table 5, Line A).

If Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract is added to the selected foods at the levels specified in Table 4, the added mean and 90th percentile lycopene consumption will be 10.4 mg/day and 15.3 mg/day, respectively (Table 5, Line B).

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[2] United States Department of Agriculture-Nutrition Coordinating Center

Table 4. Food groups selected for Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract supplementation*

Food Category	Intended use level (ppm)		
	Lyc-O-Mato® 70% Concentrate	Lyc-O-Mato® 1.5% Extract	Lycopene
Baked goods and baking mixes, including all ready-to-eat and ready-to-bake products, flours, and mixes requiring preparation before serving (1)	14.3	668	10
Breakfast cereals, including ready-to-eat and instant and regular hot cereals (4)	14.3	668	10
Cheeses, including curd and whey cheeses, cream, natural, grating, processed, spread, dip, and miscellaneous cheeses (5)	14.3	668	10
Condiments and relishes, including plain seasoning sauces and spreads, olives, pickles, and relishes, but not spices or herbs (8)	14.3	668	10
Confections and frostings, including candy and flavored frostings (9)	14.3	668	10
Dairy product analog, including nondairy milk, frozen or liquid creamers, coffee whiteners, toppings, and other nondairy products (10)	14.3	668	10
Frozen dairy desserts and mixes, including ice cream, ice milks, sherbets, and other frozen dairy desserts and specialties (20)	14.3	668	10
Gelatins, puddings, and fillings, including flavored gelatin desserts, puddings and custards, parfaits, pie fillings, and gelatin base salads (22)	14.3	668	10
Grain products and pastas, including macaroni and noodle products, rice dishes, and frozen multicourse meals, without meat or vegetables (23)	14.3	668	10
Gravies and sauces, including all meat sauces and gravies, and tomato, milk, buttery, and specially sauces (24)	14.3	668	10
Jams and jellies, commercial, including only commercially processed jams, jellies, fruit butters, preserves, and sweet spreads (28)	14.3	668	10
Meat products, including all meats and meat containing dishes, salads, appetizers, frozen multicourse meat meals, and sandwich ingredients prepared by commercial processing or using commercially processed meats with home preparation (29)	14.3	668	10
Milk products, including toppings, snacks dips, spreads, weight control milk beverages, and other milk origin products (31)	14.3	668	10
Processed vegetables and vegetable juices, including all commercially processed vegetable, vegetable dishes, frozen multicourse vegetable meals, and vegetable juices and blends (36)	14.3	668	10
Snack foods, including chips, pretzels, and other novelty snacks (37)	14.3	668	10
Soft candy, including candy bars (38)	14.3	668	10
Soups and soup mixes, including commercially prepared meat, fish, poultry, vegetable, and combination soups and soup mixes (40)	14.3	668	10

*The food categories correspond to those listed in 21 CFR 170.3(n). The number in parenthesis following each food category is the paragraph listing in 21 CFR 170.3(n) for that food category.
ppm=parts *per* million

000204.025

A Color Additive Petition for Lyc-O-Mato® Oleoresin 6% was recently submitted with the FDA (Orstan, 2002). This may add to the consumption of lycopene and Lyc-O-Mato® Oleoresin 6% in the diet. The stated use level of Lyc-O-Mato® Oleoresin 6% as a color additive is not to

exceed 50 ppm, which would equate to a mean of 5.3 mg/day and a 90th percentile of 9.2 mg/day intake of lycopene, in the foods found in Table 4 (Table 5, Line C).

Combining the current and added intake levels, as well as the amount of lycopene potentially consumed as a color additive gives the total lycopene consumption level. The estimated total mean and 90th percentile consumption of lycopene, if Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract were added to the selected foods at the levels specified in Table 4, as well as the amount of lycopene added as a Color Additive, would be 23.9 mg/day and 40.2 mg/day, respectively (Table 5, Line D).

Another possible source of lycopene in the diet is from consumption of dietary supplements. Lycopene consumption from dietary supplements is difficult to determine. The 1987 National Health Interview Survey identified that 51.1% of the adults aged 19-99 years in the US consumed a vitamin/mineral supplement in the past year, but that only 23.1% did so daily (Subar and Block, 1990). Multivitamins were the most commonly consumed supplement at that time. Lyc-O-Mato® Oleoresin 6% is available as a dietary supplement (Lyc-O-Mato® Lycopene Softgels™, Healthy Origins, Pittsburgh, PA), with the recommended dosage of two capsules providing 500 mg Lyc-O-Mato® Oleoresin 6% (30 mg lycopene)[3]. Since there are no available statistical data on consumption of dietary supplements that are a source of lycopene, we have used the levels reported in labeling as a basis for estimating consumption ranges (Healthy Origins, 2003). Thus, the potential theoretical lycopene consumption from dietary supplements may equal 30 mg (Table 5, Line E). These estimates need to be added to those in Table 4 to arrive at the total theoretical background consumption of lycopene from both conventional foods and dietary supplements (Table 5, Line F).

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000204.026

[3] The website recommends two 15 mg capsules *per* day.

Table 5. Current lycopene intake, predicted lycopene intake following supplementation of selected foods at the indicated levels (Table 4) and total lycopene intake (predicted + current) for individuals consuming selected supplemented foods

	Per User (mg/day)	
Lycopene intake from:	**Mean**	**90th Percentile**
A. Current consumption from food	8.2[a]	15.7
B. Possible maximum consumption with Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract as an added ingredient to food [b]	10.4	15.3
C. Consumption as a color additive	5.3	9.2
D. Total consumption from conventional food (current + added)	23.9	40.2
E. Potential consumption from dietary supplement use	30.0	60.0
F. Total consumption from all sources (food + dietary supplements)	53.9	100.2

[a]Levels calculated using consumption values from CSFII 1994-1996, 1998 (CSFII 1994-96, 2000) and food lycopene concentrations from Holden *et al.*, 1999.
[b]Levels calculated using consumption values from CSFII 1994-1996, 1998 (CSFII 1994-96, 2000) and lycopene levels from Table 4 (See text for details).

It should be noted, however, that the Color Additive Petition for a tomato lycopene extract to the addition to foods is set at a maximum addition of 50 ppm of liquid, solid or semisolid food. Assuming a tomato lycopene extract was added to all foods eaten (3000 grams/person/day, liquid and solids) at 50 ppm, the total amount of lycopene that could be consumed as a color additive would be 150 mg/day[4]. In reality, the addition of lycopene as a color additive at this maximal level of 150 mg/day would be very difficult to achieve.

[4] This is an extremely conservative assumption as (1) the 3000 gms/day includes foods which would not be colored (*e.g.,* water; fresh vegetables, meat, poultry and dairy products and; other products whose standard of identity would preclude addition of a color additive); (2) there are certain technical limitations of a tomato lycopene extract as a food color (*e.g.,* it is not compatible with aqueous systems and the development of a strong tomato flavor at higher use levels) and; (3) all foods consumed (solid and liquid) would be colored red; in reality, few foods are colored red (for example, exposure to citrus red color was 0.00008474 mg/kg; carmine color was 0.03686 mg/kg; FD&C Red No. 40 was 1.0 mg/kg; FD&C Red No. 40 aluminum lake was 0.179 mg/kg; FD&C Red No. 3 was 0.036 mg/kg; grape skin extract was 0.06398 mg/kg, canthaxanthin was 0.001483 mg/kg, cochineal was 0.002683 mg/kg); as compared to foods colored brown, *e.g.,* caramel color, which is consumed at a level of 132 mg/kg (~8000 mg/day) (Clydesdale, 1997d; 1997c; 1997h; 1997i; 1997g; 1997f; 1997a; 1997e; 1997b). However, because addition of lycopene as a color additive to all foods is technically impossible, if it is assumed that half of the liquid consumed (1500/2 = 750 grams) and half of the solid/semi-solid food consumed (1500/2 = 750 grams) is either fresh or standardized, precluding the addition of color and, of the remaining 1500 grams, one half is technically incompatible with the addition of lycopene, the remaining 750 grams is colored with lycopene (to the exclusion of all ~125 color additives/adjuncts), at 50 ppm, approximately 38 mg could be consumed. This remains a conservative estimate as it assumes lycopene would have 100% market penetration, in a very competitive market, filled with less expensive synthetic colors.

5. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION (ADME)

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are food ingredient sources of lycopene. There were numerous studies identified in the public literature that reported on the ADME of lycopene from various sources.

Carotenoids, which are fat-soluble compounds, are absorbed in parallel with fat digestion and absorption. Chylomicrons are the main intestinal lipoprotein particles responsible for the transport of carotenoids, retinyl esters and other fat-soluble vitamins in the lymphatic system. Thus, the carotenoid pattern in chylomicrons is an early indicator for carotenoid composition of these compounds after absorption from the gut, before liver-dependent modifications will occur. Lipoproteins are structured such that the more polar constituents are situated toward the outside of the lipoprotein, whereas the more non-polar compounds, such as lycopene, are located toward the inner core (Bierer *et al.*, 1995). In the systemic circulation, chylomicrons are processed to chylomicron remnants, which are taken up primarily by the liver (Wingerath *et al.*, 1995). Once in the liver, the internalized hydrocarbon carotenoids (*e.g.*. lycopene) are then assembled into very low-density lipoproteins (VLDL) and released into the blood circulation, or in the case of β-carotene, are also utilized to produce retinoids (Wingerath *et al.*, 1995).

Interactions between carotenoids exist that can affect the bioavailability of other carotenoids (reviewed in van den Berg, 1999). The best evidence of this occurring is between the hydrocarbon carotenoid, β-carotene and the oxycarotenoids, lutein and canthaxanthin. Evidence demonstrating interactions between lycopene and other carotenoids is equivocal with many discrepancies between studies. Thus, at this time it is unknown whether lycopene can affect the bioavailability or biological effects of other carotenoids.

The predominant form of lycopene in foods is all-*trans*-lycopene, including Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract, but the predominant forms of lycopene identified in human serum and tissues are the *cis*-isoforms. Some investigators have suggested that the *cis*-lycopene isomers that are in food are preferentially absorbed (Boileau *et al.*, 2002). While others have suggested -and provided evidence- that the *trans*-isomer is isomerized to the *cis*-isomers by the gastric milieu prior to absorption (Holloway *et al.*, 2000; Re *et al.*, 2001). The proportions of the *cis/trans* isomers in serum appear constant regardless of the isomer distribution in the supplement/diet, thus serum isomer distribution appears to be independent of that in the supplement/diet. The majority (>50%) of tissue and serum lycopene consists as the 9-*cis*-, 13-*cis*- and 15-*cis*-isomers, while the 5-*cis*- and 9-*cis* are the main *cis*-isomers in plasma.

Lycopene is found in high concentrations in the testes and adrenals with significant amounts found in the liver, adipose tissue, prostate, kidney and ovary. Elimination of lycopene is by first-order kinetics providing a plasma half-life of 2 to 33 days (Brown *et al.*, 1989; Burri *et al.*, 2001; Rock *et al.*, 1992; Stahl and Sies, 1992). Human studies on the absorption and bioavailability, distribution, metabolism and elimination of lycopene are summarized below.

5.1. Absorption and Bioavailability

In men and women on self-selected diets, 43% and 35% of the total carotenoids measured in plasma were lycopene, respectively (Micozzi *et al.*, 1992; Yong *et al.*, 1994).

Olmedilla *et al.* (2002) reported the results from a multicenter, placebo-controlled intervention study in healthy male and female volunteers (N=400) recruited from five European regions designed to study the serum response of carotenoids and tocopherols. Subjects given ~222 mg/day Lyc-O-Mato® Oleoresin 6% (containing 13.3 mg/day lycopene) for 20 weeks had a 2-fold increase in serum lycopene. In addition, the isomer distribution of lycopene in the serum remained constant, regardless of the lycopene isomer composition in various natural extracts in the capsules from the different treatment groups. In Spanish volunteers, additional data showed that the serum response to lycopene supplementation reached a plateau after 4 weeks.

In a crossover study, volunteers (N=15F/9M; 5F/3M/group), after a 2-week lycopene depletion period, were given 4-weeks of lycopene (5 mg/day) in the form of capsules containing processed tomato oleoresins or processed tomato oleoresin formulations or synthetic lycopene (Böhm, 2002). Plasma lycopene levels at the end of the study period relative to week 1 of supplementation were elevated in all groups. The greatest absorption of lycopene was observed in subjects consuming capsules containing tomato lipids combined with lycopene crystal sizes < 10 μm in diameter.

A double-blind, randomized, crossover study was conducted in healthy men (N=10) who received either all-*trans* β-carotene (0.11 mmol; 60 mg) or all-*trans* lycopene (0.11 mmol; 60 mg) or by a combined oral dose of 0.11 mmol each (Johnson *et al.*, 1997). Serum lycopene concentrations significantly increased from baseline at 5 hours after the lycopene dose and returned to baseline thereafter with significant increase in serum concentrations still observed at 24 hours. The 24-hour area under the curve (AUC) for lycopene was significantly greater when lycopene was ingested with β-carotene than when ingested alone. Thus, ingestion of a combined dose of β-carotene and lycopene possibly improved the absorption of lycopene in men.

Lycopene bioavailability from a single dose of fresh tomatoes or tomato paste (23 mg lycopene) was studied in healthy subjects (N=5) (Gartner *et al.*, 1997). The lycopene isomer pattern was the same in both fresh tomatoes and tomato paste. Compared to fresh tomatoes, ingestion of tomato paste was found to yield 2.5-fold higher total and all-*trans*-lycopene peak concentrations and 3.8-fold higher area under the curve (AUC) responses. Only the AUC response for the *cis*-isomers was significantly higher after ingestion of tomato paste compared to fresh tomatoes.

Stahl and Sies (1992) studied the absorption of lycopene from processed (boiled with 1% corn oil for 1 hour) and unprocessed tomato juice in humans. Serum lycopene concentrations increased only when processed tomato juice was consumed. Peak serum lycopene concentrations were reached between 24 and 48 hours. Absorption was dose-dependent, but not linear, as there was greater absorption at lower doses. Absorption of 9-*cis* and 13-*cis* isomers was somewhat better than the all-*trans* form.

Men (N=30) on a controlled diet were fed defined daily doses of carotenoids, including lycopene, from foods (broccoli, carrots, or tomato juice) for 6 weeks (Micozzi *et al.*, 1992). Compared with baseline, lycopene declined in all groups except the tomato-juice group.

In a randomized, crossover study design, the bioavailability of lycopene from tomato juice and 2 dietary supplements, each containing 70-75 mg lycopene, was studied in healthy volunteers (N=15) (Paetau *et al.*, 1998). Subjects ingested lycopene-rich tomato juice, Lyc-O-Mato® Oleoresin 5% (the same as Lyc-O-Mato® Oleoresin 6%, but with average lycopene concentration of 5%), lycopene beadlets, and a placebo for 4 weeks each while consuming self-selected diets. Compared

to the placebo group, plasma lycopene concentrations were significantly higher in subjects consuming all forms of lycopene sources with no differences in mean lycopene levels (~0.24 μmol/L) between the treatment groups. Subjects in the three treatment groups also had increased plasma concentrations of phytofluene and phytoene, which were present in small amounts in tomato juice, Lyc-O-Mato® Oleoresin 5% and lycopene beadlets. Beta-carotene, zeta-carotene, and 2,6-cyclolycopene-1,5-diol (a metabolite of lycopene), also present in tomato juice and supplements, were significantly increased with consumption of the tomato juice and lycopene beadlets, but not with Lyc-O-Mato® Oleoresin 5% consumption. Thus, lycopene appears to be equally bioavailable from tomato juice and the supplements used in this study.

Following seven days of a lycopene-free diet, plasma lycopene concentrations were measured in healthy female subjects (N=11) that consumed 25 g tomato puree daily (containing 7.0 mg lycopene) for 14 consecutive days (Pellegrini *et al.*, 2000). The mean plasma lycopene levels increased approximately 3-fold by day 14 (0.57 μmol/L) when compared with baseline plasma levels (0.13 μmol/L).

Plasma lycopene concentrations increased by 3-fold in adult women (N=9) that consumed 25 g tomato puree (containing 7 mg lycopene) for 14 consecutive days, after a 7-day washout period (Porrini and Riso, 2000). The mean plasma lycopene concentrations were 0.13 μmol/L and 0.55 μmol/L at day 0 and day 14, respectively.

Porrini *et al.* (1998) studied the relationship between duration of lycopene intake and food matrix on plasma lycopene concentrations in healthy female subjects. Following a one-week lycopene-free washout period, subjects were given 16.5 mg/day total lycopene in tomato purée or fresh raw tomato for a single day (N=9) or seven consecutive days (N=10). In subjects consuming tomato products for a single day, the plasma area under the curve (AUC) (calculated from time 0 to 104 hours after consumption) for total lycopene and all-*trans*-lycopene, but not *cis*-lycopene, was significantly increased in the tomato purée group compared with the raw tomato group. In subjects consuming tomato products for seven consecutive days, the AUC (calculated from day 0 to day 11 after first consumption) for total-, *trans*- and *cis*-lycopene was significantly higher in the tomato purée group compared with the raw tomato group. Thus, there is a significant effect of food matrix on lycopene bioavailability.

After a 3-week lycopene-restricted washout period, healthy subjects ingested 25 mg lycopene/day for 8 weeks from Lyc-O-Mato® Oleoresin 6% in whey protein (lactolycopene; N=4M/6F), tomato paste (positive control; N=5M/7F) or a placebo of whey proteins (N=4M/7F) while consuming their self-selected diets (Richelle *et al.*, 2002). Plasma lycopene concentrations reached a maximum after 2 weeks of supplementation in both lycopene-treated groups and then a plateau was maintained until the end of the treatment. The mean plasma lycopene at week 8 were significantly increased in the treatment groups compared with placebo controls, but they were not different from each other (lactolycopene group=0.58 μmol/L; tomato paste group=0.47 μmol/L). Although lycopene was present mainly as all-*trans* isomers (>90%) in lactolycopene and tomato paste, plasma lycopene enrichment consisted of 40% as all-*trans* and 60% as *cis*-isomers. These results indicate that the lactolycopene formulation and tomato paste exhibited similar lycopene bioavailability in plasma.

In a crossover study, renal transplant patients (N=15) were randomized to daily consumption (400 ml/day) of either tomato juice or synthetic orange drink for 4 weeks (Sutherland *et al.*, 1999).

At week 4, plasma lycopene levels were significantly higher in patients that consumed tomato juice (1.57 μmol/L) compared with baseline levels (0.86 μmol/L) and in patients that consumed orange drink (0.91 μmol/L).

In a crossover study designed to measure the interactions of carotenoids during absorption, a study group of males (N=20) on a carotenoid-restricted diet received a single oral dose of 15 mg lycopene (Lyc-O-Mato® Oleoresin 5%) plus 15 mg β-carotene (palm oil carotenoids) (van den Berg and van Vliet, 1998). The areas under the curve (AUCs) for the lycopene plus β-carotene group was similar to the AUC for the β-carotene only group. Therefore, ingestion of a combined dose of β-carotene and lycopene (from Lyc-O-Mato® Oleoresin 5%) did not interfere with each others absorption.

In a split plot design, men and women consumed whole tomatoes, mildly homogenized tomatoes or severely homogenized tomatoes that were either minimally heated or extensively heated (N=33/group) (van het Hof *et al.*, 2000). The tomato products were consumed daily (22 mg/day lycopene) for 4 days. Plasma lycopene levels were measured at day 0 and day 4. The greatest lycopene absorption was observed in extensively heated, severely homogenized tomatoes. Thus, the intactness of the cellular matrix of tomatoes determines the bioavailability of carotenoids and matrix disruption by mechanical homogenization and/or heat treatment enhances the bioavailability.

Following two weeks on a low-carotenoid diet, female adults (N=22) were randomized into three groups that received a 5 mg/day lycopene for 6-weeks provided through a daily portion of tomatoes (N=6), tomato juice or Lyc-O-Mato® Oleoresin 6% in soft gel capsules (Böhm and Bitsch, 1999). Plasma lycopene levels increased to a similar level in subjects consuming Lyc-O-Mato® Oleoresin 6% and tomato juice, but no increase in plasma lycopene was observed in those consuming raw tomatoes. Thus, lycopene from Lyc-O-Mato® Oleoresin 6% capsules and tomato juice (processed tomatoes) was better absorbed from the intestine than lycopene from raw tomatoes.

In a crossover study, Lee *et al.* (2000) compared the effect of consumption of tomato products with extra-virgin olive oil vs. tomato products plus sunflower oil on plasma lycopene levels. Subjects (N=3M/5F) consumed tomato products (canned tomatoes (230 g) and tomato soup (200 g); ~ 46 mg lycopene) prepared with the same oil daily for 7 days. Results showed that the oil composition does not affect the absorption of lycopene from tomato products because similar mean levels of plasma lycopene were obtained on feeding tomatoes with either olive oil (1.2 μmol/L) or sunflower oil (1.14 μmol/L).

Following a two week carotenoid-depletion period, healthy male volunteers (N=23) consumed successively for two weeks each, 330 mL tomato juice (40 mg lycopene), 330 mL carrot juice (15.7 mg α-carotene and 22.3 mg β-carotene) and 10 g spinach powder preparation (11.3 mg lutein and 3.1 mg β-carotene) served with main meals (Müller *et al.*, 1999). During the tomato juice intervention, plasma concentrations of *trans*- and *cis*-lycopene increased 3-fold compared to the depletion period with no differences between the levels of each isomer. Lycopene oxidation products could also be demonstrated in plasma and were significantly elevated compared to control.

After an overnight fast, subjects (N=3M/3F) received a single dose of lycopene (38 mg) with β-carotene (40 mg) in a standard meal containing 43 g of fat (O'Neill and Thurnham, 1998). The lycopene was isolated from tomatoes. Plasma carotenoid levels were tracked for 8 hours after

dosing. Approximately 1.0 mg of the 38 mg lycopene dose (~2.6%) was absorbed. A two- to three-fold inter-individual variation in lycopene was observed, but was not sex-dependent.

In a controlled intervention study, male and female subjects consumed 330 ml/day tomato juice (47.1 mg/day lycopene; N=29) or mineral water (N=21) for 8 weeks (Watzl *et al.*, 2000). Tomato juice consumption resulted in significantly increased plasma lycopene concentrations over time with no significant differences in the levels of the *trans*- and *cis*-isomers at week 8.

In a controlled 4-week study, female students (N=16-17/group) were given 1, 2 or 3 cans of tomato juice *per* day and a control group received apple juice (Sakamoto *et al.*, 1994). Compared with their baseline levels, serum lycopene levels were significantly elevated in the groups reviving 2 or 3 cans *per* day. All three tomato juice groups has significantly elevated serum lycopene levels compared with the apple juice group. A large amount of the serum lycopene was identified as the *cis*-isomer.

Tyssandier *et al.* (2002) studied the short-term (24 hours) and long-term (3-weeks) interactive effects of carotenoids, including lycopene, on absorption in women (N=20). The lycopene groups received: (a) 96 g tomato puree/day (14.98 mg lycopene + 1.50 mg β-carotene); (b) 1 Lyc-O-Mato® Oleoresin 6% pill/day (15 mg lycopene) + 92 g chopped spinach/day (11.93 mg lutein + 7.96 mg β-carotene), or; (c) 96 g tomato puree/day (14.98 mg lycopene + 1.50 mg β-carotene) + 2 lutein pills (12 mg lutein). Plasma carotenoid levels in chylomicrons were measured on the day before the supplementation period, the first day of each supplementation period and the day after the supplementation period ended. In the short-term (24 hours) consumption of β-carotene and/or lutein with lycopene decreased serum lycopene levels (AUC) relative to consumption of lycopene (tomato puree) alone. However, there were no interactive effects on lycopene levels (nmol/L) observed following 3-weeks combined consumption of the carotenoids.

5.2. Distribution

Healthy Japanese female subjects were randomized to one of three treatment groups that consumed a control drink (control group; 0 mg lycopene; N=10), 160 g of tomato juice (low dose group; 15 mg lycopene; N=11) or 480 g of tomato juice (high dose group; 45 mg lycopene; N=10) for one menstrual cycle (Maruyama *et al.*, 2001). Plasma lycopene increased in the low and high dose groups relative to the control group. Sixty-nine percent of lycopene in plasma was distributed in the low-density-lipoprotein (LDL) fraction and 24% in the high-density-lipoprotein (HDL) fraction. In the low dose group, the lycopene concentration increased 160% each in the very-low-density-lipoprotein (VLDL) + intermediate-density-lipoprotein (IDL), LDL and HDL fractions. In the high dose group, the lycopene concentration increased 270% each in the VLDL+IDL and LDL fractions, and 330% in the HDL fraction.

Concentrations of carotenoids, including lycopene were determined in liver, kidney and lung tissue from autopsies of subjects (N=20; 4 months to 86 years) (Schmitz *et al.*, 1991). Within the same patient, total mean carotenoid concentrations in liver (21.0 nmol/g tissue) were always greater than in kidney (3.1 nmol/g tissue) or lung (1.9 nmol/g tissue. Lycopene concentrations ranged from 0.2 to 20.7 nmol/g tissue in the liver, 0.1 to 2.4 nmol/g tissue in the kidney and less than 0.1 to 4.2 nmol/g tissue in the lung.

Kaplan *et al.* (1990) determined the carotenoid content, including lycopene, in 10 different human organs obtained at autopsy (N=16). The median levels of lycopene varied disproportionately between organs with the highest levels in the adrenal and testes. Much lower lycopene levels (1% of adrenal levels) were identified in subcutaneous fat, pancreas, kidneys, heart, thyroid, ovary and spleen.

The isomeric composition of lycopene was measured in serum and seven human tissues (Stahl *et al.*, 1992). all-*trans*-, 9-*cis*-, 13-*cis*- and 15-*cis*-Lycopene combined accounted for more than 50% of total lycopene identified. The highest levels of lycopene were observed in the adrenals and testes with levels 3.4 and 1.5 times higher than in the liver, respectively. Lycopene was also present in ovary, fat and kidneys.

Concentrations of lycopene were quantitated in serum and prostate tissue from men (N=25; ages 53 to 74 years) undergoing prostatectomy for localized prostate cancer (Clinton *et al.*, 1996). Lycopene concentrations ranged from 0 to 2.58 nmol/g prostate tissue with a mean of 0.80 nmol/g tissue. all-*trans* Lycopene accounted for 12 to 21% and *cis* isomers for 79 to 88% of total lycopene in prostate tissues. Lycopene concentrations in the serum ranged between 0.60 and 1.9 nmol/ml, with 27 to 42% all-*trans* lycopene and 58 to 73% *cis*-isomers.

Plasma concentrations of lycopene were measured in men (N=121) and women (N=186) participating in two prospective investigations of dietary etiologies of chronic diseases (Ascherio *et al.*, 1992). The bioavailability of lycopene from these varied diets was evidenced by the detectable serum lycopene levels. Mean lycopene concentrations were 0.82 μmole/L in men and 0.76 μmole/L in women.

Paetau *et al.* (1999) reported significantly increased lycopene concentrations in buccal mucosa cells (BMCs) in subjects (N=15) consuming Lyc-O-Mato® Oleoresin 5% (the same as Lyc-O-Mato® Oleoresin 6%, but with average lycopene concentration of 5%) or lycopene beadlets, but not lycopene-rich tomato juice. There was only a weak correlation between BMC lycopene levels and plasma lycopene levels. Alternatively, Richelle *et al.* (2002) reported a good correlation between increased plasma lycopene concentrations and increased lycopene concentrations in BMCs in subjects that consumed 25 mg lycopene/day for 8 weeks from Lyc-O-Mato® Oleoresin 6% in whey protein (lactolycopene) or tomato paste.

Lymphocyte lycopene concentrations increased by 80% in adult women (N=9) that consumed 25 g tomato puree (containing 7 mg lycopene) for 14 consecutive days, after a 7-day washout period (Porrini and Riso, 2000).

5.3. Metabolism

In human serum, a metabolite of lycopene was identified (5,6-dihydroxy-5,6-dihydrolycopene), which apparently resulted from oxidation of lycopene to a lycopene epoxide intermediate, which then underwent metabolic reduction (Khachik *et al.*, 1995). Lycopene epoxide was identified in the plasma of men that consumed lycopene (Müller *et al.*, 1999). In breast milk and serum of lactating mothers (N=3), an oxidative metabolite of lycopene was identified (epimeric 2,6-cyclolycopene-1,5-diol) that contained a novel five-membered-ring end group (Bertram *et al.*, 2000; Khachik *et al.*, 1997).

5.4. Elimination

In a study conducted to determine the effects of processing food on lycopene absorption in humans, the estimated serum half-life of lycopene was 2-3 days (Stahl and Sies, 1992).

In a controlled, crossover study, men (N=30) on a low carotenoid diet were fed single dose of carotenoids, including lycopene, from foods (broccoli (600 g), carrots (270 g), or tomato juice (180 g)) (Brown *et al.*, 1989). The estimated plasma half-life for lycopene was approximately 14 days.

To investigate the effect of a low carotenoid diet on plasma carotenoid levels, including lycopene, healthy male subjects (N=12) housed in a live-in metabolic unit were fed a low carotenoid diet for 13 weeks (Rock *et al.*, 1992). Blood samples were drawn on days 2-3, 14-15, 35-36 and 63-64. The estimated mean plasma half-life of lycopene was between 12 and 33 days.

As part of two carotenoid isotopic studies, Burri *et al.* (2001) measured serum concentrations of carotenoids, including lycopene, in healthy young adult women (N=19) that were fed controlled low carotenoid diets for approximately 10 weeks. Serum lycopene concentration decreased during depletion and followed first-order kinetics with a half-life of 26 days. Half-life was unrelated to physical or demographic characteristics such as body mass, body fat, racial background or age in the relatively homogeneous groups.

In a study designed to measure the lycopene absorbance of various tomato oleoresin preparations, plasma lycopene levels significantly decreased 21 to 52 % of the basal values after volunteers (N=24) consumed a diet low in lycopene for 2-weeks (Böhm, 2002).

6. SAFETY EVALUATION

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are fractions of Lyc-O-Mato® Oleoresin 6%. Thus, all of the constituents in Lyc-O-Mato® Oleoresin 6% are found either in Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract. Accordingly, the results from the safety studies on Lyc-O-Mato® Oleoresin 5% or Lyc-O-Mato® Oleoresin 6% described below are relevant to the safety assessment of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract.

6.1. Acute Studies

Acute lethality studies were conducted on two batches of Lyc-O-Mato® Oleoresin 5% (Dreher, 1994a, b). Sprague-Dawley rats (N=5/sex; 124 to 162 g) received a single 5000 mg/kg dose of undiluted Lyc-O-Mato® Oleoresin 6% by gavage and were observed for 14 days. No signs of systemic toxicity were noted for 14 days after administration of the oleoresin. The animals were sacrificed and necropsy showed no macroscopic abnormalities in the abdominal and thoracic cavities. One female died 4 hours after dosing; this rat demonstrated signs of distress 2 hours after dosing and at necropsy showed hemorrhagic lungs, dark liver and dark kidney. It was concluded that the death of this single animal was inconsistent with the lack of any symptoms in the other animals and may have been due to maldosing. These studies demonstrated that the LD_{50} for Lyc-O-Mato® Oleoresin 5% was greater than 5000 mg/kg bodyweight.

Lyc-O-Mato® Oleoresin 5% was applied with semi-occlusion for 24 hours at 2000 mg/kg to a shaved area of intact skin on Sprague-Dawley rats (N=5/sex) (Dreher, 1994d). After 24 hours, the bandage was removed and the animals were observed for 14 days for evidence of toxicity. No deaths or signs of systemic toxicity were observed during this period. After the 14 days, necropsy macroscopic examination of the abdominal and thoracic cavities showed no abnormalities. It was concluded that the acute dermal LD_{50} of Lyc-O-Mato® Oleoresin 5% is greater than 2000 mg/kg in rats.

In male Wistar rats (N=8/group) fed 300 mg/kg lycopene in their diet for 16 days, no adverse effects were observed on growth, liver weight, lung weight, kidney weight or small intestine cytochrome P450 expression and activity (Jewell and O'Brien, 1999).

Mice (N=30/group) fed a diet containing 700 ppm lycopene (approximately 90 mg/kg body weight *per* day) for 2 weeks had no reported adverse effects or changes in liver weight (Black, 1998).

Milani *et al.* (1970) reported lycopene to be non-toxic to: (1) rats at 50 mg/kg orally and subcutaneously at 50 mg/kg and 100 mg/kg; (2) guinea pigs at 20 mg/kg subcutaneously and; (3) mice at 3 g/kg administered orally, subcutaneously or intraperitoneally.

6.2. Subchronic Studies

CD rats (N=20/sex/group; 96-132 g) were given 0, 2.25, 22.5, 225 mg/kg/day lycopene (0, 45, 450 or 4500 mg/kg/day Lyc-O-Mato® Oleoresin 5%, respectively) by gavage for 13 weeks (East, 1995). No deaths occurred during the treatment period. There were no differences in bodyweight gain, food intake, or food conversion efficiency between test and control animals. Test animals had no ocular lesions, changes in hematology, urinalysis changes, changes in organ weights, or macroscopic or microscopic differences from control animals. Test animals did exhibit low alkaline phosphatase blood levels in comparison to controls, but the toxicological significance of this finding is unclear. Plasma levels of lycopene did not increase for the 22.5 mg/kg/day lycopene dosage over those found with the 2.25 mg/kg/day lycopene indicating lycopene absorption was saturated at higher doses. Thus, oral administration of lycopene from Lyc-O-Mato® Oleoresin 5% was well tolerated with no evidence of toxicity at doses of 2.25, 22.5 and 225 mg/kg/day lycopene. The No Observed Adverse Effect Level (NOAEL) of lycopene was 225 mg/kg/day.

In an extensive carotenoid feeding study, carotenoids, including lycopene, were fed to rats, rabbits and dogs (Zbinden and Studer, 1957). The lycopene studies had four groups:

(1) Rat (N=10F/10M), 1000 mg/kg body weight/day, direct feeding, 100 days---authors claim that the animals ate about 10 g lycopene total (each)

(2) Rat (N=15F/15M), 1000 mg/kg diet/day, feed additive, 200 days---authors claim that the animals ate about 2.5 g lycopene total (each)

(3) Rat (N=18F/13M, second generation), 1000 mg/kg diet/day, feed additive---authors claim that the animals ate approx. 0.8 g lycopene total (each)

(4) Dog (N=1F), 100 mg/kg body weight/day, direct feeding, 192 days---authors claim that the animal ate approx. 272 g lycopene total

During the first weeks of the study, two spontaneous deaths occurred in group #1 that were not reported to be treatment related. Otherwise, all rats grew at same pace as controls. No significant changes were observed in hematology; or in histopathology on liver, kidneys, adrenal glands, spleen, pancreas, testis, ovaries, skin, bone and bone marrow.

For groups #2 and #3, the authors observed no significant differences between test and control animals with respect to food intake or body weight. There were neither spontaneous deaths nor the need to sacrifice any animals due to disease in either group. Hematology was normal in both test and control groups. No significant differences were observed in reproduction (gestation period, litter size, average pup weight, *etc.*). Histopathology showed that females (but not males) stored lycopene in the liver as coarse-granulated pigment; otherwise the liver was normal. Also, no significant changes were observed in the kidneys, adrenal glands, spleen, pancreas, testes, epididymis, ovaries, lungs, heart, bones and bone marrow. No pigment storage (outside of the liver) was observed. The authors noted that based on consumption of lycopene, the rats ate about 50 mg/kg *per* day which translates to a daily dose of 3 g/day of lycopene in a 60 kg human or about the amount found in 20 kg of concentrated tomato paste.

For the single dog in group #4, lycopene was administered in gelatin capsules, orally. No intolerance symptoms were observed. Body weight increased normally during the experiment. No significant changes in blood chemistry were observed. All organs appeared normal at termination. The authors noted that liver contained 22.6 mg/g tissue and kidneys 0.6 mg/g tissue of lycopene at termination of the experiment. They also noted that in the 192 day test, the dog ate a lycopene amount equivalent to that found in 10,000 to 15,000 kg of tomatoes.

6.3. Topical application studies

The effects from topical application of lycopene to the eyes and skin in animal models are summarized below. The test material used in these studies was Lyc-O-Mato® Oleoresin 5%, which contains on average 5% lycopene. Thus, any effects following topical application of Lyc-O-Mato® Oleoresin 5% may have been derived from constituents other than lycopene.

6.3.1. Eyes

Two separate eye irritation studies using different batches of Lyc-O-Mato® Oleoresin 5% were conducted (Dreher, 1994c). Lyc-O-Mato® Oleoresin 5% (0.1 mL, approximately 5% lycopene by weight) was applied into the conjunctival sac of the right eye of New Zealand white rabbits (N=6) pretreated with a local anesthetic (Ophthaine) to minimize pain (Dreher, 1994c). Ocular damage/irritation was assessed at 1, 24, 28 and 72 hours; and 7 days following treatment using Draize evaluation criteria. In both studies, Lyc-O-Mato® Oleoresin 5% was scored as a Moderate Eye Irritant (class 5 on a 1 to 8 scale).

6.3.2. Skin

Two separate skin irritation studies using different batches (Nos. 620106, 620207) of Lyc-O-Mato® Oleoresin 5%, were conducted (Dreher, 1994e, f). In each test, Lyc-O-Mato® Oleoresin 5% was applied directly to the shaved skin (dorsal/flank area; 0.5 mL oleoresin under a 2.5 x 2.5 cm gauze patch) of New Zealand white rabbits (N=6). The patch was removed four hours after oleoresin application and any residual material was removed by swabbing with diethyl ether. Test sites were examined and scored for irritation at 1, 24, 48 and 72 hours after patch removal using the Draize system for erythema and edema formation. Both batches of Lyc-O-Mato® Oleoresin 5% produced very slight to well-defined erythema and slight to moderate edema in all animals. An averaging of the scores for the six animals in each test resulted in a primary irritation index of 4.3 (on a scale of 0 to 8). The two tested batches of Lyc-O-Mato® Oleoresin 5% were classified as a "Moderate Irritants" according to the Draize classification scheme.

A skin irritation study was repeated using the same protocol as the earlier studies, but with a different batch (No. 511008) of tomato oleoresin, Lyc-O-Mato® Oleoresin 6%, that was produced at a later date than the earlier batches (Rees, 1996). However, unlike the earlier studies, application of 0.5 ml of the tested batch of Lyc-O-Mato® Oleoresin 6% did not produce any effects and was classified as a "Non-Irritant" to skin.

In an acute dermal toxicity study, Lyc-O-Mato® Oleoresin 5% (batch No. 620207) was applied with semi-occlusion for 24 hours at 2000 mg/kg to a shaved area of intact skin on Sprague-Dawley rats (N=5/sex) (Dreher, 1994d). After 24 hours, the bandage was removed and the animals were observed for 14 days for evidence of primary irritation according to the standard Draize scale. Incidents of hemorrhage of the dermal capillaries were noted in one male and one female animal, two to four days after treatment, however no erythema or edema formation was observed in any animal. It was concluded that the Lyc-O-Mato® Oleoresin 5% tested was not a skin irritant.

The results from these skin irritation studies are inconsistent and suggest that irritation may be species specific with irritation in the rabbit, but not in the rat. Alternatively, irritation in rabbits from application of the earlier batches of Lyc-O-Mato® Oleoresin might have been due to the adventitious presence of lactic acid, which was not present in the latter material[5] that was tested in rats.

The skin contact sensitization potential of Lyc-O-Mato® Oleoresin 5% (Batch No. 620207) was evaluated in the albino guinea pig (N=20/test group; N=10 controls) (Dreher, 1994g). Shaved shoulder regions areas of the animals received three intradermal injections (0.1 mL each) of Freund's Complete Adjuvant, a 5% (wt/vol) dilution of oleoresin in arachis oil, and a 5% (wt/vol) dilution of the oleoresin in a 1:1 mixture of Freund's Complete Adjuvant plus arachis oil. On day 7, the same area on each animal was treated with a topical application of 25% (wt/wt) Lyc-O-Mato® Oleoresin 5% in petroleum jelly and a dressing was applied for 48 hours. Observations for erythema and edema were made at 1 and 24 hours following removal of the dressing. Control animals were injected with carriers only and challenged with 5% (wt/wt) Lyc-O-Mato® Oleoresin 5% in petroleum jelly. Animals were scored according to reactions of test *vs* control animals. The Lyc-O-Mato® Oleoresin 5% produced a 35% (7 out of 20 test animals) sensitization rate and was classified as a "Moderate Sensitizer" to guinea pig skin in these studies. This effect might have been due to the lactic acid present in the batch of oleoresin used in the study.

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[5] LycoRed Natural Product Industries Ltd., personal communication.

6.4. Genotoxicity

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and *Escherichia coli* strain WP2uvrA$^-$ were treated with five dilutions of Lyc-O-Mato® Oleoresin 5% (up to 250 μg lycopene *per* plate) (Batch No. 620207) with and without metabolic activation according to the Ames plate incorporation method (Thompson, 1994). Lyc-O-Mato® Oleoresin 5% was found to be non-mutagenic under the conditions of the test.

6.5. Carcinogenesis

Animal studies have reported anti-carcinogenic effects from lycopene. For example, feeding tomato juice containing up to 17 ppm lycopene to rats for up to 35 weeks significantly protected the animals from nitrosamine-induced bladder cancer and N-methylnitrosourea-induced colon cancer (Narisawa *et al.*, 1998; Okajima *et al.*, 1998). In another study, addition of 50 ppm lycopene in the drinking water of mice for 21 weeks resulted in a significant reduction in nitrosourea-induced lung adenomas and carcinomas in male mice (Kim *et al.*, 1997).

6.6. *In vitro* studies

In vitro studies have shown that lycopene can inhibit cell proliferation in human mammary and lung cancer cells (Furhrmann *et al.*, 1997) and the production of transformed loci in methylchloranthrene-treated C3H/10T1/2 mouse embryo fibroblasts (Araujo *et al.*, 1995; Bertram *et al.*, 1991; Levy *et al.*, 1995). Lycopene caused a concentration-dependent reduction in HL-60 promyelocytic leukemia cell growth accompanied by inhibition of cell cycle progression in the GO/G1 growth phase (Amir *et al.*, 1999). The lycopene effect was enhanced, synergistically, by 1,25-dihydroxyvitamin D3, a known anticancer agent. In a related study, the lycopene inhibition of MCF7 mammary cancer cells appears due to lycopene interference with IGF-I (insulin-like growth factor I) receptor signaling and cell growth cycle progression (Karas *et al.*, 2000).

6.7. Observations in Humans

Fruits and vegetables that contain lycopene have been a normal part of the human diet since antiquity. Moreover, numerous clinical studies using tomato products have demonstrated that consumption of these tomato products and lycopene is safe and well tolerated. A reported side effect from excessive lycopene consumption is lycopenemia, which is when an excess of lycopene in the blood leads to deposition in the liver forming "fatty cysts". The skin takes on the red color found in tomatoes. It is considered harmless and is readily reversible when lycopene ingestion is discontinued. The following is a summary of two clinical studies that carefully documented the safety of lycopene from Lyc-O-Mato® Oleoresin 6% and two case reports of lycopenemia.

No lycopene-induced toxicity was observed in Spanish volunteers that were enrolled in a multicenter, placebo-controlled intervention study in healthy male and female volunteers (N=400) recruited from five European regions designed to study the serum response of carotenoids and tocopherols (Olmedilla *et al.*, 2002). Subjects were given ~13.3 mg/day lycopene (~222 mg/day Lyc-O-Mato® Oleoresin 6%) for 20 weeks. Plasma lycopene levels increased 2-fold (~1.2 μmol/L) compared with placebo controls. No significant changes in biochemical (plasma glucose,

cholesterol, triacylglycerol, uric acid, albumin, aspartate aminotransferase (AST), total bilirubin, calcium, creatinine, alkaline phosphatase, low density lipoprotein (LDL), total protein, urea, iron) or hematological indices (hemoglobin concentration, red cell (RBC Count, HGB, HCT, MCV, MCH, MCHC)[6], white cell (number and % of neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count and mean platelet volume) were observed throughout the study[7]. Carotenodermia[8] developed in 25% of the subjects, but this is considered harmless and is readily reversible when carotene ingestion is discontinued.

Lycopene was given to prostate cancer patients as part of an ongoing National Institutes of Health funded dose escalating phase II trial of lycopene for biochemical relapse of prostate cancer (Hall, 2003). Patients (N=6/group) will be given 15, 30, 45, 60, 90, or 120 mg/day lycopene (250, 500, 750, 1000, 1500 or 2000 mg/day Lyc-O-Mato® Oleoresin 6%, respectively) for one year. Patients will be evaluated monthly and every three months laboratory studies will be conducted on electrolytes, liver function and complete blood count. To date, patients in the high dose group have completed between 4 and 10 months of treatment. Results from the high dose group indicate that 120 mg/day lycopene was well tolerated and no clinically significant toxicity was observed. One subject given an unreported dose of Lyc-O-Mato® Oleoresin 6% developed treatment-related diarrhea that subsided after the Lyc-O-Mato® Oleoresin 6% supplementation was stopped.

Reich *et al.*(1960) reported a case of lycopenemia in a woman who consumed 2 liters of tomato juice daily for "several years," equivalent to a daily dosage of up to 160 mg of lycopene. She had a previous history of the same condition. The woman was admitted to the hospital with chest pains and apparent jaundice, but an examination showed no indication of jaundice, so the physicians looked to carotenoid intake to explain the coloration of the skin.

After three weeks on a diet free of tomato juice, total blood carotenoid levels were 3.7 μg/mL (α- and β-carotene=1.5 μg/mL; lycopene=1.1 μg/mL; lutein=1.1 μg/mL). The expected total carotenoid levels were ~1 μg/mL. It was estimated that the total carotenoid levels had dropped about 19% during the 3 weeks of tomato juice deprivation. Thus, the approximate level of the four carotenoids in the serum at the time of admission was approx. 4.4 μg/mL, or approximately 4X the expected level in normal serum.

The woman was also diagnosed with cholelithiasis and a cholecystectomy was performed. During this process, there was an opportunity to examine the patient's bile for carotenoid content. By colorimetry, the bile contained 191 units/100mL or approximately 7.6 μg carotenoids/mL. The patient's liver was enlarged and had a "strange" orange-yellow color. A biopsy for found indications of carotenoid (lycopene) accumulation as masses of butter-yellow, non-doubly refractile material within the liver cells.

The authors of this study distinguish this first reported case of lycopenemia from carotenemia by the much deeper orange skin hue observed in the patient; and due to the fact that, unlike cases of carotenemia reported to date, the patient did not have diabetes, hypothyroidism, nephrosis or lipemia---conditions which have been associated with carotenemia in other cases.

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[6] RBC=red blood cell; HGB=hemoglobin; HCT=hematocrit; MCV= mean corpuscular volume; MCH= mean corpuscular HGB; MCHC=mean corpuscular HGB concentration.

[7] These specific endpoints were not published with the article, but were provided in response to an inquiry in an e-mail from Begoña Olmedilla (bolmedilla.hpth@salud.madrid.org).

[8] The authors of this study used the term carotenodermia, however this was in all likelihood lycopenemia.

Also, the liver from the lycopenemic patient was orange yellow and gave histologic evidence of storage of carotenoid pigments (the livers of patients with carotenemia have been reported as normal in color).

Reich *et al.* (1960) concluded that, in spite of the observations made, lycopene was neither toxic nor beneficial to the patient, and they characterized lycopene as simply an "adventitious visitor" to her body.

Lycopenemia was reported in a 19-year old Italian woman that sought medical attention after developing a cutaneous discoloration lasting 3 months (La Placa *et al.*, 2000). Her diet for the past 3 years consisted of four to five big red tomatoes and pasta with tomato sauce daily. A "yellow-orange" pigmentation was observed on the forehead, nasolabial folds, palms and soles. She reported recurrent abdominal pain. Hepatic echographia revealed a digitate area relatively hypoechogenic, measuring 2 cm in diameter, in the upper portion of the parenchyma, which the authors suggested consisted of deposits of lycopene. Blood cell count and laboratory tests, including liver enzymes, were normal. Restricting the diet of tomatoes resulted in a complete regression of pigmentation within 6 weeks and disappearance of the abdominal pain.

7. β-CAROTENE HUMAN INTERVENTION TRIALS

The Expert Panel considered whether reported results of studies of β-carotene have any relevance to the safety of lycopene. Randomized clinical trials of β-carotene supplementation as a chemopreventive agent have reported contradictory results. In two of four intervention trials [U.S. Beta Carotene and Retinol Efficacy Trial (CARET) Omen *et al.*, 1996a,b; Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) 1994], increased lung cancer risk was measured among heavy smokers who received pharmacologic doses of β-carotene either alone (20 mg/day; ATBC) or β-carotene (30 mg/day) plus retinyl palmitate (25,000 IU/day; CARET). No increased risk for other types of cancers was observed. In contrast, no increases in lung cancer or any other cancer incidences were observed in any subjects, including smokers, consuming high doses of β-carotene (50 mg on alternate days; ~25 mg/day) from the U.S. Physician's Health Study (Hennekens *et al.,* 1996). Moreover, a large study conducted in a high-risk population in Linxian, China found that supplementation with 15 mg β-carotene, 50 μg selenium and 30 mg vitamin E daily for 5 years reduced the number of deaths from gastric cancer (Blot *et al.,* 1993). The results from these human intervention studies are difficult to interpret given their different designs and study populations, but one possible explanation is that physiological doses (<20 mg/day) of β-carotene have no adverse effects, whereas pharmacological doses (>20 mg/day) may cause a slight increase in lung cancer risk in heavy smokers. At this time, however, the data are inconclusive and the risk, if any, from β-carotene consumption will require further study.

The specific molecular and cellular mechanism(s) underlying the reported effects of β-carotene in these studies has not been identified. While several hypotheses have been put forward, the most credible of these relates to β-carotene's pro-vitamin A activity and altered retinoid signaling. Because lycopene is not a pro-vitamin A carotenoid, lycopene will not affect these retinoid pathways.

7.1. Hypothesis for β-Carotene Effects: Altered Retinoid Signaling

Wang *et al.* (1999) studied ferrets that were given a β-carotene supplement (at a dose equivalent to those used in the clinical trials) or exposed to cigarette smoke, or both for 6 months. They chose ferrets as a model because ferrets metabolize β-carotene in much the same way as humans (Wang and Krinsky, 1997). The results showed a proliferative response in lung tissue in all β-carotene-supplemented animals and this response was enhanced by exposure to tobacco smoke. Histological analysis revealed localized keratinized squamous metaplasia (a precancerous lesion) in all of the ferrets in the high-dose groups of β-carotene, with or without exposure to smoke. The β-carotene treated groups had significantly lower concentrations of retinoic acid in lung tissue and they exhibited 18% to 73% reductions in retinoic acid receptor beta (RARβ) gene expression. The authors proposed that the increased production of β-apocarotenals (from eccentric cleavage of β-carotene) in the ferret lung might promote lung tumorigenesis through interference with retinoid signaling *via* depression of retinoic acid levels (required for normal cell growth and regulation) and downregulation of RARβ (a tumor suppressor gene).

A subsequent study using the same ferret model reported that the β-carotene effects were dose-dependent (Liu *et al,* 2000). Physiological doses of β-carotene (equivalent to 6 mg/day in humans) were not harmful, and instead protected against lung damage induced by cigarette smoke. No protection from smoke-induced lung tissue damage was observed in the ferrets given high doses of β-carotene (equivalent to 30 mg/day in humans). At the end of the study, β-carotene levels in lung tissue increased 25-fold in the low-dose group, and 202-fold in the high-dose group. Thus, it appears that the most plausible explanation for the results of these studies is that β-carotene may interfere with retinoid signaling at high doses.

7.2. β-Carotene *vs.* Lycopene

It is apparent from the studies summarized above that there are significant differences between β-carotene and lycopene. Whereas β-carotene alters retinoid signaling, this activity has not been reported for lycopene, a non-provitamin A carotenoid. In addition, Liu *et al.* (2003) demonstrated that both a low dose (1.1 mg/kg/day; equivalent to 15 mg/day lycopene in humans) and a high dose (4.3 mg/kg/day; equivalent to 60 mg/day in humans) of lycopene supplementation (for nine weeks) partially or completely prevented smoke-induced changes in the lungs of ferrets exposed to cigarette smoke. Cigarette smoke-induced lesions (squamous metaplasia, PCN overexpression and diminished apoptosis) were associated with reduced plasma insulin-like growth factor-binding protein-3 (IGFBP-3) concentrations and increased insulin-like growth factor-I (IGF-I)/IGFBP-3 ratios. Lycopene supplementation at either a low or a high dose reversed the reduction in plasma IGFBP-3 and lung cellular apoptosis, as well as hyperproliferation induced by smoke exposure, in contrast to the effects of β-carotene described in Section 7.1. Therefore, it is the Expert Panel's view that the data described above with respect to β-carotene and altered retinoid signaling are not relevant to a safety assessment of lycopene.

8. EVALUATION

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are produced from tomatoes and contain an average of 70% and 1.5% lycopene, respectively. Tomatoes are a normal component of the American diet with an estimated average annual consumption of processed tomato products equal to nine million metric tons. Tomato lycopene extracts are approved food colorants in the EU and Japan. In the US, all of the major constituents in Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are either approved food ingredients (food additives, GRAS) or are normal constituents found in commonly consumed foods at similar concentrations.

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are stable at the recommended storage conditions and as added ingredients to a variety of foods.

Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are produced from Lyc-O-Mato® Oleoresin 6% and several safety studies on Lyc-O-Mato® Oleoresin 6% were assessed in support of the safety of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract.

Topical application of Lyc-O-Mato® Oleoresin 6% produced equivocal results. Initial tests indicated that Lyc-O-Mato® Oleoresin 6% was moderately irritating to rabbit skin and eyes and was a moderate sensitizer to guinea pig skin. A later study on a new batch of Lyc-O-Mato® Oleoresin 6% indicated that it was not a skin irritant to rabbits. The earlier results were most likely due to the adventitious presence of lactic acid in that batch of Lyc-O-Mato® Oleoresin 6%. The current method of manufacturing described in this document produces Lyc-O-Mato® Oleoresin 6% without lactic acid.

Lycopene and Lyc-O-Mato® Oleoresin 6% were found to be non-toxic in acute and subchronic animal studies. In separate tests, a single oral administration of 5000 mg/kg Lyc-O-Mato® Oleoresin 6% (containing 300 mg/kg lycopene) or single dermal application of 2000 mg/kg Lyc-O-Mato® Oleoresin 6% (containing 120 mg/kg lycopene) to rats resulted in no lethality or toxicity by two weeks. A ninety-day subchronic study in rats identified the NOAEL from oral exposure to Lyc-O-Mato® Oleoresin 6% to be the highest dose tested, 4500 mg/kg/day (containing 270 mg/kg/day lycopene). Lyc-O-Mato® Oleoresin 6% was not mutagenic in an Ames assay and reports indicate that lycopene–rich tomato extracts are anti-carcinogenic in animal studies.

Lycopene is fat-soluble and absorbed in parallel with over-all fat digestion and absorption. Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract contain predominantly all-*trans* lycopene (greater than 90% of the lycopene present). However, the proportions of the *cis/trans* isomers in serum appear constant regardless of the isomer distribution in the supplement/diet, thus serum isomer distribution appears to be independent of that in the supplement/diet. Serum steady-state levels following lycopene supplementation are reached at about four weeks. Lycopene is found predominantly in the testes and adrenals with significant amounts found in the liver, adipose tissue, prostate, kidney and ovary. The majority (>50%) of tissue and serum lycopene consist of the 9-*cis*-, 13-*cis*- and 15-*cis*-isomers, while the 5-*cis*- and 9-*cis* are the main *cis*-isomers in plasma. Lycopene is eliminated by first-order kinetics with a plasma half-life of 2 to 33 days.

Human clinical intervention studies indicate that long-term consumption of lycopene is well tolerated. No clinically significant toxicity was observed in an ongoing clinical intervention study in which subjects consumed up to 120 mg/day lycopene (2000 mg/day Lyc-O-Mato® Oleoresin 6%)

supplements for 4 to 10 months, although one subject developed treatment-related diarrhea that subsided after the lycopene supplementation was stopped. In a multicenter, placebo-controlled intervention study, no clinically significant toxicity was reported following 20 weeks consumption of 13.3 mg/day lycopene.

Reported side effects from excessive consumption of lycopene are carotenodermia[9] and lycopenemia[10], which are not considered health hazards and are reversible conditions. Carotenodermia[11] was observed in 25% of the subjects in one arm of the multicenter study. However, there were no reports of carotenodermia developing in subjects from the other arms of this study nor was carotenodermia reported in the ongoing study in which subjects consumed 120 mg/day lycopene supplements for up to ten months. Case reports of lycopenemia indicate that the condition was not considered adverse and was reversed upon reduction of excessive lycopene from the diet.

Lycopene is a non-provitamin A carotenoid, which does not alter retinoid signaling like the provitamin A carotenoid, β-carotene. Therefore, it is the Expert Panel's view that the data reported with respect to β-carotene are not relevant to a safety assessment of lycopene.

The NOAEL for lycopene in rats is 225 mg/kg/day (equivalent to 13,500 mg/day in a 60 kg human) and the highest tolerable intake of lycopene in humans identified is at least 120 mg/day. Thus, based on the generally available data establishing the lycopene NOAEL at 225 mg/kg/day, the Panel has used a safety factor of at least 100 and established a conservative acceptable daily intake (ADI) of lycopene 2 mg/kg/day or 120 mg/day for a 60 kg individual.

Combining the 90th percentile lycopene consumption levels from foods supplemented with Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract (15.3 mg/day) with the 90th percentile current consumption level of lycopene from conventional foods (15.7 mg/day), the estimated daily intake of lycopene from conventional foods with the addition of Lyc-O-Mato® 70% Concentrate or Lyc-O-Mato® 1.5% Extract is 31.0 mg/day. The 90th percentile consumption of lycopene as a color additive (in the foods reported here) is proposed to be 9.2 mg/day. In addition, the potential lycopene consumption from dietary supplements may add an additional maximum intake of 60 mg/day[12]. Thus, the potential theoretical maximum lycopene consumption at the 90th percentile may reach 100.2 mg/day. This theoretical intake level represents a conservative estimate because it is unlikely that an individual would consume lycopene from both conventional foods and dietary supplements at the 90th percentile level. Even this conservative estimate, however, is well within the ADI for lycopene, 120 mg/day.

A color additive petition (CAP) has been submitted for a tomato lycopene extract (*e.g.*, Lyc-O-Mato® Oleoresin 6%) and may have an additive effect to lycopene consumption. In realistic terms, however, saturation of the diet with lycopene could not be achieved for a number of technical

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[9] Carotenodermia is characterized by a yellowish discoloration of the skin. It is considered harmless and is readily reversible when carotene ingestion is discontinued.

[10] A similar condition as carotenodermia – an excess of lycopene in the blood leads to deposition in the liver forming "fatty cysts". The skin takes on the red color found in tomatoes. It is considered harmless and is readily reversible when lycopene ingestion is discontinued.

[11] The authors of this study used the term carotenodermia, however this was in all likelihood lycopenemia.

[12] This estimate is based on current labeled information rather than on a statistical analysis of consumption because consumption data are unavailable.

and aesthetic reasons (see section on consumption) and, as a result, the use of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract are largely self-limiting. The self-limiting nature of the Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract provides some realistic boundaries for a still conservative estimate for lycopene ingestion (as a color) up to 38 mg. The addition of 38 mg/day as a color to the 90th percentile of 91 mg/day for all other purposes (excluding the earlier CAP of 9.2 mg/day), would yield a total exposure of approximately 129 mg/day (2.15 mg/kg/day) – an amount slightly greater than the ADI (120 mg/day or 2 mg/kg/day), but within the NOAEL (225 mg/kg/day), still allowing a safety factor >100. Lastly, and importantly, the only adverse events that have been reported from high intakes of lycopene (*i.e.*, one case study reported a calculated dose of 160 mg/day lycopene for several years) were skin discoloration and deposits of lycopene in the liver, both of which are reversible upon cessation of lycopene-containing foods. Therefore, even at high doses of lycopene consumption, toxicity would not be expected.

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9. CONCLUSION

After critically evaluating the information available, the Expert Panel has determined that, based on common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food, there is reasonable certainty that Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract, produced in accordance with current Good Manufacturing Practice (cGMP), is Generally Recognized As Safe (GRAS), by scientific procedures, when used as an ingredient to provide consumers with a supplementary source of lycopene in their diets, so that total daily consumption of lycopene from all sources does not exceed 120 mg lycopene.

10. SIGNATURES

Date

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Burdock Group

20 July 04
Date

Walter H. Glinsmann, M.D.
Glinsmann Incorporated

22 July 2004
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11. REFERENCES

Amir, H.; Karas, M.; Giat, J.; Danilenko, M.; Levy, R.; Yermiahu, T.; Levy, J. and Sharoni, Y. (1999) Lycopene and 1,25-dihydroxyvitamin D3 cooperate in the inhibition of cell cycle progression and induction of differentiation in HL-60 leukemic cells. *Nutrition and Cancer* 33:105-112.

Araujo, F. B.; Barbosa, D. S.; Hsin, C. Y.; Maranhao, R. C. and Abdalla, D. S. (1995) Evaluation of oxidative stress in patients with hyperlipidemia. *Atherosclerosis* 117:61-71.

Ascherio, A.; Stampfer, M. J.; Colditz, G. A.; Rimm, E. B.; Litin, L. and Willett, W. C. (1992) Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. *Journal of Nutrition* 122:1792-1801.

BASF (2002) *GRAS Notification Number 119: Synthetic Lycopene as an Ingredient in Food in General, Except Meat and Poultry Products*. BASF Corporation, Mount Olive, NJ. (visited on March 21, 2003), URL: http://www.cfsan.fda.gov/~rdb/opa-gn02.html.

Bertram, J.; King, T.; Fukishima, L. and Khachik, F. (2000) Enhanced activity of an oxidation product of lycopene found in tomato products and human serum relevant to cancer provention. In *Antioxidant and Redox Regulation of Genes*, (C. K. Sen, H. Sies and P. A. Baeuerle, Eds.), Academic Press, San Diego, CA, pp. 409-425.

Bertram, J. S.; Pung, A.; Churley, M.; Kappock, T. D.; Wilkins, L. R. and Cooney, R. V. (1991) Diverse carotenoids protect against chemically induced neoplastic transformation. *Carcinogenesis* 12:671-678.

Bierer, T. L.; Merchen, N. R. and Erdman, J. W., Jr. (1995) Comparative absorption and trans-port of five common carotenoids in preruminant calves. *Journal of Nutrition* 125:1569-1577.

Black, H. S. (1998) Radical interception by carotenoids and effects on UV carcinogenesis. *Nutrition and Cancer* 31:212-217.

Böhm, V. and Bitsch, R. (1999) Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. *European Journal of Nutrition* 38:118-125.

Böhm, V. (2002) Intestinal absorption of lycopene from different types of oleoresin capsules. *Journal of Food Science* 67:1910-1913.

Boileau, T. W.; Boileau, A. C. and Erdman, J. W., Jr. (2002) Bioavailability of all-*trans* and *cis*-isomers of lycopene. *Experimental Biology and Medicine* 227:914-919.

Brown, E. D.; Micozzi, M. S.; Craft, N. E.; Bieri, J. G.; Beecher, G.; Edwards, B. K.; Rose, A.; Taylor, P. R. and Smith, J. C., Jr. (1989) Plasma carotenoids in normal men after a single ingestion of vegetables or purified beta-carotene. *American Journal of Clinical Nutrition* 49:1258-1265.

Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E. and Kinneary, J. F. (1996) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.* 12th Edition, Merck & Co., Inc., Whitehouse Station, NJ.

Burri, B. J.; Neidlinger, T. R. and Clifford, A. J. (2001) Serum carotenoid depletion follows first-order kinetics in healthy adult women fed naturally low carotenoid diets. *Journal of Nutrition* 131:2096-2100.

Burton, G. W. and Ingold, K. U. (1984) *beta*-Carotene: an unusual type of lipid antioxidant. *Science* 224:569-573.

Clinton, S. K.; Emenhiser, C.; Schwartz, S. J.; Bostwick, D. G.; Williams, A. W.; Moore, B. J. and Erdman, J. W., Jr. (1996) *cis-trans* Lycopene isomers, carotenoids, and retinol in the human prostate. *Cancer Epidemiology, Biomarkers and Prevention* 5:823-833.

Clydesdale, F.M. (1997a) Canthaxanthin. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997b) Caramel. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997c) Carmine (*Coccus Cacti* L.). *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997d) Citrus Red No. 2. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997e) Cochineal Extract (*Coccus Cacti* L.). *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997f) Grape Skin Extract. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997g) FD&C Red No. 3. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997h) FD&C Red No. 40. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

Clydesdale, F.M. (1997i) FD&C Red No. 40 aluminum lake. *Food Additives: Toxicology, Regulation, and Properties.* CRC Press, Boca Raton, FL. CD-ROM.

CSFII 1994-96 (2000) *Continuing Survey of Food Intakes by Individuals (CSFII) 1994-96, 1998*, Agricultural Research Service, U.S. Department of Agriculture, Washington, D.C, CD-ROM.

Dreher, D. (1994a) *Lycopene Batch No. 620207: Acute Oral Toxicity (Limit Test) in the Rat.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/203.

Dreher, D. (1994b) *Lycopene Batch No. 620106: Acute Oral Toxicity (Limit Test) in the Rat.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/209.

Dreher, D. (1994c) *Lycopene Batch No. 620207: Acute Eye Irritation Test in the Rabbit.* Safepharm Laboratories Limited, Derby, UK, May 16, 1994, Project Number: 306/206.

Dreher, D. (1994d) *Lycopene Batch No. 620207: Acute Dermal Toxicity (Limit Test) in the Rat.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/204.

Dreher, D. (1994e) *Lycopene Batch No. 620207: Acute Dermal Toxicity (Limit Test) in the Rabbit.* Safepharm Laboratories Limited, Derby, UK, May 16, 1994, Project Number: 306/205.

Dreher, D. (1994f) *Lycopene Batch No. 620106: Acute Dermal Toxicity (Limit Test) in the Rabbit.* Safepharm Laboratories Limited, Derby, UK, May 16, 1994, Project Number: 306/210.

Dreher, D. (1994g) *Lycopene Batch No. 620207: Magnusson & Kligman Maximisation Study in the Guinea Pig.* Safepharm Laboratories Limited, Derby, UK, May 24, 1994, Project Number: 306/207.

East, P. (1995) *Lycopene: Toxicity Study by Oral (gavage) Administration to CD Rats for 13 Weeks.* Pharmaco LSR Ltd., Suffolk, UK, March 8, 1995, Report No. 94/MAK288/1290.

EU (1995) *EU Commission Directive 95/45/EC.* Official Journal of the European Communities, pp. 1,2 and 35.

EUSCF (1975) *Report of the Committee for Food on the Revision of the Directive on Colouring Matters Authorized for Use in Foodstuffs Intended for Human Consumption.* First Series, Brussels, Belgium.

Fuhrman, B.; Ellis, A. and Aviram, M. (1997) Hypercholesteremic effect of lycopene and *beta*-carotene is related to suppression of cholesterol synthesis and augmentation of LDL reseptor activity in macrophages. *Biochemical and Biophysical Research Communications* 223:658-622.

Gartner, C.; Stahl, W. and Sies, H. (1997) Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *American Journal of Clinical Nutrition* 66:116-122.

Hall, M. (2003) *Letter dated April 9, 2003 from M. Craig Hall, M.D. (Wake Forest School of Medicine) to Dr. Zohar Nir (LycoRed Natural Products Industries, Ltd).* Personal Communication.

Healthy Origins (2003) *Lyc-O-Mato® Lycopene Softgels Product Overview.* Healthy Origins, Pittsburgh, PA. (visited on May 21, 2003), URL: http://www.healthyorigins.com/lycomato.htm.

Holden, J. M.; Eldridge, A. L.; Beecher, G. R.; Buzzard, I. M.; Bhagwat, S. A.; Davis, C. S.; Douglass, L. W.; Gebhardt, S. E.; Haytowitz, D. B. and Schakel, S. (1999) Carotinoid content of US foods: An update of the database. *Journal of Food Composition and Analysis* 12:169-196.

Holloway, D. E.; Yang, M.; Paganga, G.; Rice-Evans, C. A. and Bramley, P. M. (2000) Isomerization of dietary lycopene during assimilation and transport in plasma. *Free Radical Research* 32:93-102.

Jewell, C. and O'Brien, N. M. (1999) Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of the rat. *British Journal of Nutrition* 81:235-242.

Johnson, E. J.; Qin, J.; Krinsky, N. I. and Russell, R. M. (1997) Ingestion by men of a combined dose of beta-carotene and lycopene does not affect the absorption of beta-carotene but improves that of lycopene. *Journal of Nutrition* 127:1833-1837.

Kaplan, L. A.; Lau, J. M. and Stein, E. A. (1990) Carotenoid composition, concentrations, and relationships in various human organs. *Clinical Physiology and Biochemistry* 8:1-10.

Karas, M.; Amir, H.; Fishman, D.; Danilenko, M.; Segal, S.; Nahum, A.; Koifmann, A.; Giat, Y.; Levy, J. and Sharoni, Y. (2000) Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. *Nutrition and Cancer* 36:101-111.

Khachik, F.; Beecher, G. R. and Smith, J. C., Jr. (1995) Lutein, lycopene, and their oxidative metabolites in chemoprevention of cancer. *Journal of Cellular Biochemistry. Supplement* 22:236-246.

Khachik, F.; Spangler, C. J.; Smith, J. C., Jr.; Canfield, L. M.; Steck, A. and Pfander, H. (1997) Identification, quantification, and relative concentrations of carotenoids and their metabolites in human milk and serum. *Analytical Chemistry* 69:1873-1881.

Kim, D. J.; Takasuka, N.; Kim, J. M.; Sekine, K.; Ota, T.; Asamoto, M.; Murakoshi, M.; Nishino, H.; Nir, Z. and Tsuda, H. (1997) Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH. *Cancer Letters* 120:15-22.

La Placa, M.; Pazzaglia, M. and Tosti, A. (2000) Lycopenaemia. *Journal of the European Academy of Dermatology and Venereology* 14:311-312.

Lee, A.; Thurnham, D. I. and Chopra, M. (2000) Consumption of tomato products with olive oil but not sunflower oil increases the antioxidant activity of plasma. *Free Radical Biology and Medicine* 29:1051-1055.

Levy, J.; Bosin, E.; Feldman, B.; Giat, Y.; Miinster, A.; Danilenko, M. and Sharoni, Y. (1995) Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene. *Nutrition and Cancer* 24:257-266.

Liu, C.; Lian, F.; Smith, D.E.; Russell, R.M. and Wang, X.-D. (2003) Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis *via* up-regulating insulin-like growth factor-binding protein 3 in cigarette smoke-exposed ferrets. *Cancer Research* 63:3138-3144.

LycoRed (2003a) *Stability of Lycopene in Lyc-O-Mato® 70% stored at 37 °C (Accelerated Conditions) and 4 °C.* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

LycoRed (2003b) *Stability of Lycopene in Lyc-O-Mato® 70% stored at 37 °C (Accelerated Conditions) Packed under Vacuum in 0.5 and 1Kg (10/10/00 - Beginning of Stability test).* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

LycoRed (2003c) *Recovery of Lycopene from Foods Formulated with Lyc-O-Mato® 70% Concentrate.* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

LycoRed (2003d) *Stability of Lycopene in Lyc-O-Mato® 1-2% stored at 4-6 °C.* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

LycoRed (2003e) *Recovery of Lycopene from Margarine Formulated with Lyc-O-Mato® 1.5% Extract.* LycoRed Natural Product Industries Ltd., Beer-Sheva, Isreal. Personal Communication.

Maruyama, C.; Imamura, K.; Oshima, S.; Suzukawa, M.; Egami, S.; Tonomoto, M.; Baba, N.; Harada, M.; Ayaori, M.; Inakuma, T. and Ishikawa, T. (2001) Effects of tomato juice consumption on plasma and lipoprotein carotenoid concentrations and the susceptibility of low density lipoprotein to oxidative modification. *Journal of Nutritional Science and Vitaminology* 47:213-221.

Micozzi, M. S.; Brown, E. D.; Edwards, B. K.; Bieri, J. G.; Taylor, P. R.; Khachik, F.; Beecher, G. R. and Smith, J. C., Jr. (1992) Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. *American Journal of Clinical Nutrition* 55:1120-1125.

Milani, C.; Maccari, M. and Mosconi, P. (1970) Action of lycopene in the experimental gastric ulcer. *Pharmacology* 4:334-340.

Müller, H.; Bub, A.; Watzl, B. and Rechkemmer, G. (1999) Plasma concentrations of carotenoids in healthy volunteers after intervention with carotenoid-rich foods. *European Journal of Nutrition* 38:35-44.

Narisawa, T.; Fukaura, Y.; Hasebe, M.; Nomura, S.; Oshima, S.; Sakamoto, H.; Inakuma, T.; Ishiguro, Y.; Takayasu, J. and Nishino, H. (1998) Prevention of N-methylnitrosourea-induced colon carcinogenesis in F344 rats by lycopene and tomato juice rich in lycopene. *Japanese Journal of Cancer Research* 89:1003-1008.

Okajima, E.; Tsutsumi, M.; Ozono, S.; Akai, H.; Denda, A.; Nishino, H.; Oshima, S.; Sakamoto, H. and Konishi, Y. (1998) Inhibitory effect of tomato juice on rat urinary bladder carcinogenesis after N-butyl-N-(4-hydroxybutyl)nitrosamine initiation. *Japanese Journal of Cancer Research* 89:22-26.

Olmedilla, B.; Granado, F.; Southon, S.; Wright, A. J.; Blanco, I.; Gil-Martinez, E.; van den Berg, H.; Thurnham, D.; Corridan, B.; Chopra, M. and Hininger, I. (2002) A European multicentre, placebo-controlled supplementation study with alpha-tocopherol, carotene-rich palm oil, lutein or lycopene: analysis of serum responses. *Clin Sci (Lond)* 102:447-456.

O'Neill, M. E. and Thurnham, D. I. (1998) Intestinal absorption of *beta*-carotene, lycopene and lutein in men and women following a standard meal: response curves in the triacylglycerol-rich lipoprotein fraction. *British Journal of Nutrition* 79:149-159.

Orstan, A. (2002) Tomato Lycopene Extract. FDA, Office of Food Additive Safety. Color Additive Petition #1C0273. 3-4. LycoRed, personal communication.

Paetau, I.; Khachik, F.; Brown, E. D.; Beecher, G. R.; Kramer, T. R.; Chittams, J. and Clevidence, B. A. (1998) Chronic ingestion of lycopene-rich tomato juice or lycopene supplements significantly increases plasma concentrations of lycopene and related tomato carotenoids in humans. *American Journal of Clinical Nutrition* 68:1187-1195.

Paetau, I.; Rao, D.; Wiley, E. R.; Brown, E. D. and Clevidence, B. A. (1999) Carotenoids in human buccal mucosa cells after 4 wk of supplementation with tomato juice or lycopene supplements. *American Journal of Clinical Nutrition* 70:490-494.

Palozza, P.; Luberto, C.; Calviello, G.; Ricci, P. and Bartoli, G. M. (1997) Antioxidant and prooxidant role of *beta*-carotene in murine normal and tumor thymocytes: effects of oxygen partial pressure. *Free Radical Biology and Medicine* 22:1065-1073.

Pellegrini, N.; Riso, P. and Porrini, M. (2000) Tomato consumption does not affect the total antioxidant capacity of plasma. *Nutrition* 16:268-271.

Porrini, M.; Riso, P. and Testolin, G. (1998) Absorption of lycopene from single or daily portions of raw and processed tomato. *British Journal of Nutrition* 80:353-361.

Porrini, M. and Riso, P. (2000) Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. *Journal of Nutrition* 130:189-192.

Re, R.; Fraser, P. D.; Long, M.; Bramley, P. M. and Rice-Evans, C. (2001) Isomerization of lycopene in the gastric milieu. *Biochemical and Biophysical Research Communications* 281:576-581.

Rees, P. (1996) *Lyc-O-Pen™: Acute Dermal Irritation Test in the Rabbit.* Huntington Lifr Sciences Ltd., Suffolk, UK, May 2, 1996, Report No. 96/LYN002/0274.

Reich, P.; Shwachman, H. and Craig, J. (1960) Lycopenemia: A variant of carotenemia. *New England Journal of Medicine* 262:263-269.

Rice-Evans, C. A.; Sampson, J.; Bramley, P. M. and Holloway, D. E. (1997) Why do we expect carotenoids to be antioxidants *in vivo*? *Free Radical Research* 26:381-398.

Richelle, M.; Bortlik, K.; Liardet, S.; Hager, C.; Lambelet, P.; Baur, M.; Applegate, L. A. and Offord, E. A. (2002) A food-based formulation provides lycopene with the same bioavailability to humans as that from tomato paste. *Journal of Nutrition* 132:404-408.

Rock, C. L.; Swendseid, M. E.; Jacob, R. A. and McKee, R. W. (1992) Plasma carotenoid levels in human subjects fed a low carotenoid diet. *Journal of Nutrition* 122:96-100.

Sakamoto, H.; Mori, H.; Ojima, F.; Ishiguro, Y.; Arimoto, S.; Imae, Y.; Nanba, T.; Ogawa, M. and Fukuba, H. (1994) Elevation of serum carotenoids after continual ingestion of tomato juice. *Journal of the Japanese Society of Nutrition and Food Science* 47:93-99.

Schmitz, H. H.; Poor, C. L.; Wellman, R. B. and Erdman, J. W., Jr. (1991) Concentrations of selected carotenoids and vitamin A in human liver, kidney and lung tissue. *Journal of Nutrition* 121:1613-1621.

Stahl, W.; Schwarz, W.; Sundquist, A. R. and Sies, H. (1992) *cis-trans* Isomers of lycopene and *beta*-carotene in human serum and tissues. *Archives of Biochemistry and Biophysics* 294:173-177.

Stahl, W. and Sies, H. (1992) Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. *Journal of Nutrition* 122:2161-2166.

Subar, A. F. and Block, G. (1990) Use of vitamin and mineral supplements: demographics and amounts of nutrients consumed. The 1987 Health Interview Survey. *American Journal of Epidemiology* 132:1091-1101.

Sutherland, W. H.; Walker, R. J.; De Jong, S. A. and Upritchard, J. E. (1999) Supplementation with tomato juice increases plasma lycopene but does not alter susceptibility to oxidation of low-density lipoproteins from renal transplant recipients. *Clinical Nephrology* 52:30-36.

Thompson, P. (1994) *Lycopene: Six Strain Reverse Mutation Assay "Ames Test" using Salmonella typhimurium and Escherichia coli.* Safepharm Laboratories Limited, Derby, UK, May 3, 1994, Project Number: 306/208.

Tyssandier, V.; Cardinault, N.; Caris-Veyrat, C.; Amiot, M. J.; Grolier, P.; Bouteloup, C.; Azais-Braesco, V. and Borel, P. (2002) Vegetable-borne lutein, lycopene, and *beta*-carotene compete for incorporation into chylomicrons, with no adverse effect on the medium-term (3-wk) plasma status of carotenoids in humans. *American Journal of Clinical Nutrition* 75:526-534.

van den Berg, H. and van Vliet, T. (1998) Effect of simultaneous, single oral doses of *beta*-carotene with lutein or lycopene on the *beta*-carotene and retinyl ester responses in the triacyl-glycerol-rich lipoprotein fraction of men. *American Journal of Clinical Nutrition* 68:82-89.

van den Berg, H. (1999) Carotenoid interactions. *Nutrition Reviews* 57:1-10.

van het Hof, K. H.; de Boer, B. C.; Tijburg, L. B.; Lucius, B. R.; Zijp, I.; West, C. E.; Hautvast, J. G. and Weststrate, J. A. (2000) Carotenoid bioavailability in humans from tomatoes processed in different ways determined from the carotenoid response in the triglyceride-rich lipoprotein fraction of plasma after a single consumption and in plasma after four days of consumption. *Journal of Nutrition* 130:1189-1196.

Watzl, B.; Bub, A.; Blockhaus, M.; Herbert, B. M.; Luhrmann, P. M.; Neuhauser-Berthold, M. and Rechkemmer, G. (2000) Prolonged tomato juice consumption has no effect on cell-mediated immunity of well-nourished elderly men and women. *Journal of Nutrition* 130:1719-1723.

Wingerath, T.; Stahl, W. and Sies, H. (1995) *beta*-Cryptoxanthin selectively increases in human chylomicrons upon ingestion of tangerine concentrate rich in *beta*-cryptoxanthin esters. *Archives of Biochemistry and Biophysics* 324:385-390.

Yong, L. C.; Forman, M. R.; Beecher, G. R.; Graubard, B. I.; Campbell, W. S.; Reichman, M. E.; Taylor, P. R.; Lanza, E.; Holden, J. M. and Judd, J. T. (1994) Relationship between dietary intake and plasma concentrations of carotenoids in premenopausal women: application of the USDA-NCI carotenoid food-composition database. *American Journal of Clinical Nutrition* 60:223-230.

Zbinden, G. and Studer, F. (1957) *Animal Experimentation Investigations of Chronic Tolerance of beta-Carotene, Lycopene. 7,7'-Dihydro-B-Carotene, and Bixin.* Hoffmann-LaRoche & Co., Medical Research Dept., Basel, Switzerland, Report No. 46780.

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Vero Beach, Florida
Founder and President

Dr. Burdock is an internationally recognized authority on the safety of food ingredients, personal care products and dietary supplements. He has more than twenty years experience dealing with regulatory issues related to product safety and risk assessment. He provides safety and toxicity information on foods, food additives, drug excipients and contaminants to a varied client list, including corporations, law firms and individuals. This information may be in the form of regulatory petitions, Generally Recognized As Safe (GRAS) self-determinations, GRAS notifications and litigation support. He has extensive experience searching and evaluating the scientific literature in a number of subject areas. He provides reviews of the literature on substances and advises clients on safety and regulatory matters concerning their products and procedures. He is also engaged, on an on-going basis, by a publisher to provide reference books on food additives, flavor ingredients and regulatory matters. He is experienced in the generation and submission of Food Additive Petitions and has experience in negotiating with the regulatory authorities.

Flavor and Extract Manufacturers' Association (FEMA) **1986 - 1992**
Washington, D.C.
Director of Scientific Affairs

Dr. Burdock assisted member companies in the preparation of materials for submission to the FEMA Expert Panel for GRAS review, maintained awareness for the Expert Panel and Association of scientific developments in the food and flavor arena and changes in regulatory policy as a result of these developments. He authored and edited comprehensive reviews of the literature on flavor additives. Dr. Burdock also managed the FEMA scientific program, coordinated activities of testing laboratories, consultants and allied industry committees and organizations.

Shulton Research Division, American Cyanamid Corporation **1984 - 1986**
Clifton, New Jersey
Manager of Biological Services

Outlook (March 2004) p. 20 – 26.

G.A. Burdock (2003). Sensory deception: the science of making foods more palatable. Functional Foods and Nutraceuticals (November 2003)

G.A. Burdock (2003). The GRAS process. Food Technology (May 2003)

G.A. Burdock (2002). Status and safety assessment of foods and food ingredients produced by genetically modified microorganisms Chapter 3 in: Biotechology and Safety Assessment, 3rd ed. Thomas, J.A. and Fuchs, R. (eds.). Elsevier Science (USA), (2002) pp 39-83

M.G. Soni, **G.A. Burdock**, S.L. Taylor and N. Greenberg (2002). Evaluation of the health aspects of methyl paraben: a review of published literature. Food and Chemical Toxicology. Volume 40:1335-1373;2002

F. Kotsonis, **G.A. Burdock** and W.G. Flamm (2001). Chapter 31 - Food Toxicology. In: Toxicology: The Basic Science of Poisons. Klaessen, C.D. (ed). Pergamon Press, New York. 2001.

G.A. Burdock (2002). Regulation of Flavor Ingredients. In: Nutritional Toxicology. 2nd edition Target Organ Toxicology Series. Kotsonis, F and Mackey, M (eds.). Taylor and Frances, New York pp. 316-339

G.A. Burdock (2002). Handbook of Flavor Ingredients. 4th edition. CRC Press, Boca Raton, FL. 1834 pp.

G.A. Burdock, I.G. Carabin and M.G. Soni (2001). Safety assessment of Beta-nitropropionic acid: A monograph in support of an acceptable daily intake in humans. Food Chemistry 75/1:1-27.

M.G. Soni, **G.A. Burdock**, S.L. Taylor and N. Greenberg (2001). Safety assessment of propyl paraben. Food and Chemical Toxicology 39:513-532.

G.A. Burdock, M.G. Soni and I.G. Carabin (2001). Evaluation of health aspects of kojic acid in food. Regulatory Toxicology and Pharmacology 33:80-101.

M.G. Soni, S.A. White, W.G. Flamm and **G.A. Burdock** (2001). Safety evaluation of dietary aluminum. Regulatory Toxicology and Pharmacology 33:66-79.

M.G. Soni, H. Kimura and **G.A. Burdock** (2001). Chronic studies on diacylglycerol oil in rats. Food and Chemical Toxicology 39:317-329.

I.G. Carabin, **G.A. Burdock** and C. Chatzidakis (2000). Safety assessment of *Panax* ginseng. International Journal of Toxicology 19:293-301.

G.A. Burdock and W.G. Flamm (2000). Review article: Safety assessment of cyclopiazonic acid. International Journal of Toxicology 19:195-218.

G.A. Burdock, W.G. Flamm, I.G. Carabin (2000). Toxicity and mutagenicity studies of DN-50000® and RP-1® enzymes. Food and Chemical Toxicology. Food and Chemical Toxicology 38:429-442.

G.A. Burdock (2000). Dietary supplements and lessons to be learned from *GRAS*. Journal of

000204.055

furyl)acrolein. Acute Toxic. Data 1(1): 3.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2-mercaptomethylpyrazine. Acute Toxic. Data 1(1): 4.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2,5-diethyltetrahydrofuran. Acute Toxic. Data 1(1): 5.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 2,5-dimethylpyrole. Acute Toxic. Data 1(1): 6.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with difurfuryl ether. Acute Toxic. Data 1(2): 93-94.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with phenoxyacetic acid. Acute Toxic. Data 1(2): 94-95.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 4,5-dimethylthiazole. Acute Toxic. Data 1(2): 95-96.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 3-methyl-4-phenyl-3-buten-2-one. Acute Toxic. Data 1(2): 96-97.

G.A. Burdock, R.A. Ford (1990). Acute oral toxicity (LD50) study in the rat with 3-(2-furylacrolein). Acute Toxic. Data 1(2): 97-98.

G.A. Burdock, B.M. Wagner, R.L. Smith, I.C. Munro and P.M. Newberne (1990). Recent progress in the consideration of flavoring ingredients under the food additives amendment. 15. GRAS substances. Food Technology 44(2):78, 80, 82, 84 & 86.

G.A. Burdock and R.L. Hall (1989). Pro-active flavor safety evaluation and management. In: Trends in food product development. Ghee et al (eds.) Presented at the Seventh World Congress of Food Science and Technology, Singapore, October, 1987. Singapore Institute of Food Science and Technology 1989, pp. 359-366.

G.A. Burdock, R.A. Ford, A.M. Bottomley, and D.M. John (1987). An Evaluation of the Teratogenic Potential of Orally Administered Phenylethyl Alcohol (PEA). The Toxicologist 7(1):176.

G.A. Burdock, R.H. Cox, S.L. Morseth, and L.W. Smith (1986). Teratogenicity Study of 4-Nitro-N-Methylphtalimide (4-NPI). The Toxicologist 6(1):94.

G.A. Burdock, B.A. Kulwich, R.D. Alsakar and P.M. Marshall (1984). 90-Day Dog Study - Caprolactam. In: Proceedings of a Symposium on An Industry Approach to Chemical Risk Assessment. Caprolactam and related compounds as a case study. May 15-17, 1984. Industrial Health Foundation, Pittsburgh, PA 15206.

J.A. Trutter, F.E. Reno, **G.A. Burdock** and D.W. Korte, Jr. (1984). Fertility Study with a Candidate Antimalarial Drug in the Rat. Journal of the American College of Toxicology 3:172.

G.A. Burdock (1983). Diethanolamine-Induced Changes in Liver and Kidney of the Neonatal Rat. The Toxicologist 4(1):491.

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EDUCATION

1956	BA - Columbia College, New York, NY
1960	M.D. - Columbia College of Physicians and Surgeons, NY
1960-1965	Internship and Residency in Medicine - New York Hospital (Cornell Medical School), New York, NY - Training Dept, of Metabolism, Walter Read Army Medical Center and Army Institute of Research, Washington, DC

MEDICAL LICENSE

1961-Current	New York State Physician, No.

EMPLOYMENT HISTORY:

2002 As below with change in academic affiliation: Fellow and Adjunct Professor, Center for Food Safety and Nutrition and Ceres Forum®, Virginia Polytechnic Institute and State University (Virginia Tech), Arlington, VA.

1998-2000 President, Glinsmann, Inc. Evaluations of safety and health effects of foods, the development of nutritional products, and food-related claims.
Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University.
Member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc.
Scientific Advisor to the Technical Committee on Food Components for Health Promotion ("Functional Foods"), International Life Sciences Institute, North America and to U.S. and International Food Companies.

1995-1997 President, Glinsmann, Inc.
Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University.
Advisor to the Committee on Revision (1995) and member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc.
Scientific Advisor to the Technical Committee on Food Components for Health Promotion, International Life Sciences Institute, North America.
Expert Consultant, Office of the Deputy Director for Programs, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration (FDA).

1993-1994 Expert in Nutrition, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services (DHHS)Health. Provided management/technical support for nutrition and dietary guidance-related activities.

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1965-1966 Medical Officer, Research Planning and Program Development, Growth and Development Program, NICHHD, NIH.

1962-1965 Assistant Chief, Department of Metabolism and Attending Physician in Medicine, Walter Reed Army Hospital, and Senior Investigator, Walter Reed Army Institute of Research, Washington, D.C.

PROFESSIONAL MEMBERSHIPS

American Institute of Nutrition, renamed American Society for Nutritional Sciences (Membership Committee, 1986-1991)
American Society for Clinical Nutrition (Membership Committee, 1986-1994: Chair, Publications Management Committee, American Journal of Clinical Nutrition, 1994-1996)
American Physiological Society
New York Academy of Sciences

AWARDS

Fellow, American Society for Nutritional Sciences, 2002.

FDA Commendable Service Award: assessing safety and labeling of monosodium glutamate, 1999.

DHHS Secretary's Award for Excellence in Public Service, Implementing the Food Labeling Initiative, 1993.

PHS Citation for exemplary and creative work as a management clinician in nutrition research and investigative matters, 1989

FDA Award of Merit for Leadership, Health Hazard Evaluations, 1988

PHS Unit Commendation, Food Irradiation Safety Evaluation, 1988

PHS Citations for Outstanding Management Performance in Clinical Nutrition and Food Safety Evaluations, 1986-91

PHS Meritorious Service Medal for sustained high quality leadership and outstanding contributions to Nutrition and Food Safety, 1986

FDA Award of Merit for Leadership, Aspartame Clinical Investigation Team, 1986

FDA Commissioner's Special Citation to the Research Involving Human Subjects Committee for unique and outstanding performance to the Food and Drug Administration by promoting research while ensuring the protection of the human subjects involved, 1984

PHS Commendation Medal for sustained high quality leadership and professional accomplishments in planning, implementing, and evaluating nutrition research at the FDA

SEMINARS, INVITED LECTURES

June 12, 2001 *Is There a Need for Cyclical Third Party Reviews? An Affirmative Assessment,* 10th Annual Conference, Functional Foods for Health, Chicago, IL

Jan. 24, 1996	*Perspective on the Future of Designer and Functional Foods: Definitions, Regulatory Perspective, and Health Claims* Annual Meeting, ILSI, Cancun, Mexico
Oct. 2, 1995 Oct. 3	*Food Labeling and Food Safety Requirements in the United States* and *International Developments in Food Fortification, Foods for Special Dietary Use, and Functional Foods*, Doosan Technical Center, Seoul, Korea
Sept. 26, 1995 Sept. 28	*Functional Foods in North America* *Regulatory Aspects of Functional Foods* First International Conference on East-West Perspectives on Functional Foods, ILSI-Southeast Asia, Singapore

PUBLICATIONS

Carpenter, M.B., Glinsmann, W.H., Fabrega, H. Effects of secondary striatal lesions upon cerebella dyskinesia. Neurology. 8: 352, 1958.

Carpenter, M.D., Fabrega, H., Glinsmann, W.H. Physiological deficits occurring with lesions of labyrinth and fastigial nuclei. J. Neurosphysiol. 22: 22, 1959.

Fiala, S., Glinsmann, W.H., Fiala, A.E. Deoxyribonucleotidase activity during carcinogenesis in rat liver. Naturwiss. 46: 635, 1959.

Swank, R.L., Glinsmann, W.H., Sloop, P. The production of fat embolism in rabbits by feeding high fat meals. Surgery, Gynecology and Obstetrics 110: 9, 1960.

Fiala, S., Fiala, A.E., Glinsmann, W.H. Deoxycytidylic deaminase in carcinogenic rat liver. Naturwiss, 47: 45, 1960.

Fiala, S., Glinsmann, W.H. Acid soluble ribonucleotides in adrenal tissue after hormonal stimulation. Endocrinology 68: 479, 1961.

Fiala, S., Fiala, A., Glinsmann, W.H. Mechanism of carcinogenesis and proliferation of tumor cells in rat liver. Pathologie-Biologie 9: 613, 1961.

Fiala, S., Glinsmann, W.H. A unified concept of cancerogenesis. Neoplasma 10: 1, 1963.

Glinsmann, W.H. Renal micropuncture studies during exsanguination hypotension. Clin. Res. 12: 252, 1964.

Ericsson, J.L.E., Glinsmann, W.H. Focal degenerative cytoplasmic alterations in liver cells induced by hypoxia. Electron microscopic observations. Acta Path. Microbial. Scand. 64: 151, 1965.

Ericsson, J.L.E., Glinsmann, W.H. Observations on the subcellar organization of hepatic parenchymal cells I. golgi apparatus, cytosomes, and cytosegresomes in normal cells. Lab. Invest. 15: 750, 1966.

Glinsmann, W.H., Ericsson, J.L.E. Observations on the subcellular organization of hepatic parenchymal cells II. Evolution of reversible alterations induced by hypoxia. Lab. invest. 15: 762, 1966.

DNA-cellulose. J. Steroid Biochem. 6: 1171, 1975.

Huang, K. P., Huang, F.F., Glinsmann, W.H., Robinson, J.C. Regulation of glycogen synthetase activity by two kinases. Biochem. Biophys. Res. comm. 65: 1163, 1975.

Huang, F.L., Glinsmann, W.H. Inactivation of rabbit muscle phosphorylase phosphatase by cyclic AMP-dependent kinase. Proc. Nat. Acad. Sci. (U.S.A.) 72: 3004, 1975.

Sparks, J.W., Lynch A., Glinsmann, W.H. Regulation of rat liver glycogen synthesis and activities of glycogen cycle enzymes by glucose and galactose. Metabolism 25: 47, 1976.

Sparks, J.W., Lynch A., Chez, R.A., Glinsmann, W.H. Glycogen regulation in isolated perfused near-term monkey liver. Pediat. Res. 10: 51, 1976.

Huang, F.L., Glinsmann, W.H. A second heat-stable protein inhibitor of phosphorylase phosphatase from rabbit muscle. FEBS Lett. 62: 326, 1976.

Eisen, H.J., Glinsmann, W.H. Partial purification of the glucocorticoid receptor from rat liver: a rapid two-step procedure using DNA-cellulose. Biochem, Biophys, Res. Comm. 70: 367, 1976.

Huang, K. P., Huang, F.L., Glinsmann, W.H., Robinson, J.C. Effect of limited proteolysis on activity and phosphorylation of rabbit muscle glycogen synthetase. Arch. Biochem. Biophys. 173: 6, 1976.

Huang, F.L., Glinsmann, W.H. Separation and characterization of two phosphorylase phosphatase inhibitors from rabbit skeletal muscle. European J. Biochem. 70: 419, 1976.

Nakai, C., Glinsmann, W.H. Effects of polyamines on nucleosidediphosphate kinase activity. Biochem. Biosphys. Res. Comm. 74: 1419, 1977.

Nakai, C., Glinsmann, W.H. Inhibition of rabbit skeletal muscle phosphorylase phosphatase by spermine. Molec. Cellular Biochem. 15: 141, 1977.

Nakai, C., Glinsmann, W.H. Protein inhibitors of phosphorylase phosphatase and cyclic AMP-dependent protein kinase from rabbit muscle. Molec. Cellular Biochem. 15: 133, 1977.

Glinsmann, W.H., Huang, F.L., Tao, S., Nakai, C. Control of rabbit muscle phosphorylase phosphatase activity. Proc. FEBS Congress, Copenhagen. Elsevier Press, 1977.

Huang, F., Tao, S., Glinsmann, W.H. Multiple forms of protein phosphatase inhibitors in mammalian tissues. Biochem. Biophys. Res. Comm. 78: 615, 1977.

Eisen, H.J., Glinsmann, W.H. Maximizing purification of the activated glucocorticoid receptor by DNA-cellulose chromatography. The Biochem. J., Molecular Aspects, 17: 1977.

Nakai, C., Glinsmann, W.H. Interaction between polyamines and nucleotides. Biochemistry 16: 5636, 1977.

Buffone, G.J., Sparks, J.W., Johnson, J., Iosefsdin, M., Lewis, S.A., Glinsmann, W.H. Evaluation of an immobilized enzyme electrode system for the monitoring of therapeutic galactose concentrations in neonates. Clin. Chem. 23: 1166, 1977.

Tao, S.H., Huang, F.L., Lynch, A., Glinsmann, W.H. Control of rat skeletal muscle phosphorylase activity by adrenalin. Biochem. J. 176: 347, 1978.

000204.060

Symposium Series, No 484, Food Safety Assessment, Eds. J.W. Finley, S.F. Robinson, and D.J. Armstrong, p. 105-13, Amer. Chem. Society, 1992.

Vanderveen, J.E., Glinsmann, W.H. Fat substitutes: a regulatory perspective. In Ann. Rev. Nutr., Vol. 12, Eds. R.E. Olsen, D.M. Bier, and D.B. McCormick, p. 473-87, Annual Reviews Inc., Palo Alto, California, 1992.

Workshop on Dietary Fatty Acids and Thrombosis, March 1991, Proceedings Eds. J.C. Hoak, W.H. Glinsmann, J.T. Judd. Amer. J. Clin. Nutr. 56 - supplement 4: 7835-8265, 1992.

Hyman, F.N., Sempos, E., Saltsman, J., Glinsmann, W.H. Evidence for success of caloric restriction in weight loss and control: summary of data from industry. *NIH Technology Assessment Conference on Methods for Voluntary Weight Loss and Control.* Ann. Int. Med. 119: 681-87, 1993.

Glinsmann, W.H., Bowman, B. Public health significance of dietary fructose. In *Health Effects of Dietary Fructose*, Eds. A.L. Forbes and B.A. Bowman. Amer. J. Clin. Nutr. 58 - Supplement 5:820-23, 1993.

Glinsmann, W.H., Park, Y.K. Perspective on the 1986 FDA assessment of the safety of carbohydrate sweeteners; uniform definitions and recommendations for future assessments. Amer. J. Clin. Nutr. 62 (suppl): 161S-9S, 1995.

Shank, F.R., Carson, K., Glinsmann, W.H. Putting things in perspective: building on our experience. (1995 Ceres Forum: *Fortifying Policy with Science - The Case for Folate*) J. Nutrition 126 (suppl): 781-87S, 1996.

Glinsmann, W. Focus on substitutes that alter gastrointestinal physiology. (*Proceedings of the Workshop on Safety and Regulatory Aspects of Macronutrient Substitutes,* Nov. 1994, Washington, D.C.) Regulatory Toxicol. and Phamacol. 23(suppl): S27-30, 1996.
Glinsmann, W. H., Bartholmay, S.J., Coletta, F. Dietary guidelines for infants: a timely reminder. Nutrition Reviews 54:50-57, 1996.

Glinsmann, W.H. Functional foods in North America. In *Proceedings of First International Conference on Functional Foods*, Singapore, September 1995. Eds. F.M. Clydesdale and S.H. Chan. Nutrition Reviews, Vol. 54, No. 11, Part II, S33-37, 1996.

Glinsmann, W.H. Perspective on functional food development and commercialization. J. Nutraceuticals, Functional & Medical Foods, 1:89-93, 1997.

Glinsmann, W.H. Functional foods: an overview of regulatory status. Nutrition Today, 34:1-4, 1999.

Glinsmann, W. Functional Foods: Special Considerations in the Pediatric Diet. Pediatric Basics, 92:2-15, 2000.

Flamm, G., Glinsmann, W., Kritchevsky, D., Prosky, L., Roberfroid, M. Inulin and oligofructose as dietary fiber: A review of the evidence. Critical Reviews in Food Science Nutrition, 41:353-62, 2001.

Campbel, E., Rheinhardt, W., Glinsmann, W.H. Claims regarding the health Benefits of foods. Nutrition and the M.D., in press

`BIOGRAPHICAL SKETCH

Give the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Norman I. Krinsky	Professor *Emeritus*

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of Southern California, Los Angeles, CA	B.S.	1948	Biochemistry & Nutrition
University of Southern California, Los Angeles, CA	M.S.	1950	Biochemistry & Nutrition
University of Southern California, Los Angeles, CA	Ph.D.	1953	Biochemistry
Harvard University, Cambridge, MA	Post-doc.	1953-56	Biochemistry of Vision

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience:

1953-56 **Postdoctoral Fellow**, USPHS/National Council to Combat Blindness, Harvard Univ (with George Wald)
1956-60 **Instructor, Lecturer**, Department of Biology, Harvard University
1960-67 **Assistant & Associate Professor**, Department of Pharmacology, Tufts University School of Med.
1967-69 **Associate Professor**, Department of Biochemistry, Tufts University School of Medicine
1969-70 **Professor,** Department of Biochemistry, Tufts University School of Medicine
1969-73 **Chairman**, Molecular Basis of Biological Phenomenon Graduate Program, Tufts University
1970-87 **Professor** of Biochemistry and Pharmacology, Tufts University School of Medicine
1973 **Visiting Professor**, Dept. Physiology/Anatomy, Univ. of Calif./Berkeley (with Lester Packer)
1981-82 **Visiting Scientist**, Boston VA Medical Center, Boston, MA (with Daniel Deykin)
1987-2000 **Professor, Department of Biochemistry,** Tufts University School of Medicine
1993-present **Scientist**, USDA Human Nutrition Research Center on Aging at Tufts University
2000-present **Professor Emeritus, Department of Biochemistry,** Tufts University School of Medicine

Honors, Awards and National Committees:

1966 **Fellow**, American Association for the Advancement of Science
1975-81 **Secretary-Treasurer**, American Society for Photobiology
1978 **Co-Organizer**, 5th International Symposium on CAROTENOIDS & VITAMIN A, Madison, WI
1981 **Chairman**, 1st Gordon Research Conf. on OXYGEN RADICALS IN BIOLOGY & MEDICINE, Ventura, CA
1982-83 **President**, American Society for Photobiology
1987 **Chairman**, 8th International Symposium on CAROTENOIDS, Boston, MA
1988-91 **Councilor**, The Oxygen Society
1989-02 **Executive Council**, International Association for Nutrition and Cancer
1990 **Lotte Arnrich Lecturer**, Department of Food & Nutrition, Iowa State University, Ames, IA
1992 **Chairman,** 1st Gordon Research Conf. on CHEMISTRY AND BIOLOGY OF CAROTENOIDS, Oxnard, CA
1992 **Outstanding Research Paper**, USDA\Agric. Research Service, Biochem. 30:9829-9834,1991
1993 **Co-Chair**, New York Academy of Sciences Conf. on CAROTENOIDS IN HUMAN HEALTH, San Diego, CA
1993 **Honorary Member,** The Vitamin Society of Japan
1994 **Co-Chair**, 2nd Int. Conf. ANTIOXIDANT VITAMINS AND β-CAR. IN DISEASE PREVENTION, Berlin, FRG
1994-01 **President**, New England Free Radical/Oxygen Society
1995 **Co-Chair**, FASEB Summer Research Conf. on ANTIOXIDANT NUTR. IN CELL BIOL. Saxtons River, VT

1995-96 **Secretary-General**, The Oxygen Society
1996-02 **Advisory Committee**, International Antioxidant Research Centre, King's College, London
1997 **Mordechi Avron Memorial Lecturer**, Nikken Sohonsha Corp., Gifu and Tokyo, Japan
1997 **American College of Nutrition Award Lecture**, New York, NY
1997-00 **Chair**, Panel on Antioxidants and Related Nutrients, Food & Nutrition Board, Institute of Medicine/NAS
1998 **Fellow**, American College of Nutrition
1998 **Dozor Visiting Professor**, Ben Gurion University, Beer Sheva, Israel
1999 **Visiting Scholar**, Linus Pauling Institute, Oregon State University, Corvallis, OR
1999 **Lars Ernster Lecturer**, Oxygen Club of California 1999 World Congress, Santa Barbara, CA
1999 **Honorary Member**, Oxygen Club of California 1999 World Congress, Santa Barbara, CA
2001 **Robert S. Harris Lecture**, Mass Inst Tech, Cambridge, MA
2001- **Advisory Board**, Oxygen Club of California
2001 **Chair**, Committee on Examination of the Evolving Science for Dietary Supplements, F&NB, Inst. Med./NAS
2001 **National Associate**, National Academy of Sciences/National Research Council
2003- 07 **Member**, Food Advisory Committee, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, FDA
2003- 07 **Chair**, Nutrition Subcommittee, Food Advisory Committee, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, FDA

Editorial Boards: J. FREE RAD. BIOL MED (1984-6); ADVANCES IN FREE RAD. BIOL. MED. (1984-6); FREE RAD. BIOL. MED. (1984-94); ARCHIVES OF BIOCHEM. & BIOPHYS. (1993-03); FREE RADICAL RESEARCH (1994-02); ENVIRONMENTAL & NUTRITIONAL INTERACTIONS (1997-present); NUTRITION REVIEWS (2002-present)

Member:
AAAS/AmChemSoc/AmCollNutr/AmSocBiochMolBiol/AmSocPhotobiol/InternCarSoc/InternSocNutritionCancer/ NewEnglFreeRad-OxSoc/NewYorkAcadSci/OxygenClubCalif/SocFreeRadBiolMed/SocFreeRadResearch

Peer Reviewed Journal Articles (101) Carotenoid metabolism and function: 2000-2004 papers listed below:

101. Yeum, K.-J., Russell, R.M., Krinsky, N.I. and Aldini, G. Arch. Biochem. Biophys. In press (2004) Biomarkers of Antioxidant Capacity in the Hydrophilic and Lipophilic Compartments of Human Plasma
100. Prakash, P., Liu, C., Hu, K.-Q., Krinsky, N.I., Russell, R.M. and Wang, X.-D., J. Nutr. 134:667-673 (2004) Effects of ß-Carotene, ß-Apo-14' -carotenoic Acid and Benzo[a]pyrene on Retinoic Acid Receptor ß Expression and Growth of Normal Human Bronchial Epithelial Cells.
99. Ferreira, A.L.A., Yeum, K.-Y., Russell, R.M., Krinsky, N,I, and Tang, G., J. Nutr. Biochem. 14:531-540 (2003) Enzymatic and Oxidative Metabolites of Lycopene
98. Yeum, K.-J., Aldini, G., Chung H.-Y., Krinsky N.I. and Russell, R.M., J Nutrition 133:2688-2691 (2003) The Activities of Antioxidant Nutrients Human Plasma Depend on the Localization of Attacking Radical Species
97. Aldini, G., Yeum KJ., Carini M., Krinsky, N.I. and Russell, R.M., Biochem Biophys Res Commun 302:413-418 (2003) (-)-Epigallocatechin-(3)-gallate Spares Carotenoids, Recycles α-Tocopherol and Prevents Oxidative Damage in Both the Aqueous and Lipid Compartments of Human Plasma
96. Tibaduiza, E.C., Fleet, J.C., Russell, R.M. and Krinsky, N.I., J. Nutrition 132:1368-1375 (2002) Excentric Cleavage Products of ß-Carotene Inhibit Estrogen Receptor (ER) Positive and ER negative Breast tumor Cell Growth *in vitro* and Inhibit Activator Protein-1 Mediated Transcriptional Activation.
95. Krinsky, N.I., J. Nutrition 132:540S-542S (2002) Possible biological mechanism for a protective role of xanthophylls
94. Aldini, G., Yeum, K.-J., Russell, R.M. and Krinsky, N.I., Free Radical Biology & Medicine 31:1043-1050 (2001) A Selective Method to Measure the Oxidizability of the Aqueous and Lipid Compartments of Plasma
93. Prakash, P., Russell, R.M. and Krinsky, N.I., J. Nutr. 131:1574-1580 (2001) *In vitro* Inhibition of Proliferation of Estrogen- dependent and Estrogen-independent Human Breast Cancer Cells Treated with Carotenoids or Retinoids

92. Liu, C., Wang, X.-D., Bronson, R.T., Smith, D.E., Krinsky, N.I., Russell, R.M., Carcinogenesis 21:2245-2253 (2000) Effects of Physiological vs. Pharmacological ß-Carotene supplementation on cell proliferation and histopathological changes in the lung of Cigarette Smoke-exposed Ferrets
91. Yeum, K.-Y., Ferreira, A.L.A., Smith, D., Krinsky, N.I. and Russell, R.M., Free Rad. Biol. Med. 29:105-114 (2000) The Effect of α-Tocopherol on the Oxidative Cleavage of ß-Carotene
90. Ferreira, A.L.A., Yeum, K.-Y., Liu, C., Smith, D., Krinsky, N.I., Wang, X.-D. and Russell, R.M., J. Nutr. 130:1256-1260 (2000) Tissue distribution of lycopene in ferrets and rats after lycopene supplementation

Book Chapters & Invited Reviews (65): Carotenoid metabolism and function: 1998-2003 papers listed below:

66. Krinsky, N.I., Mayne, S.T. and Sies, H. in CAROTENOIDS IN HEALTH AND DISEAA3E (Krinsky, N.I., Mayne, S.t. and Sies, H., eds.) in press Marcel Dekker, New York (2004) Carotenoids: Looking Forward
65. Krinsky, NI., Molecular Aspects of Medicine 24:317-324 (2003) Human Requirements for Fat-soluble Vitamins, and Other Things Concerning These Nutrients
64. Krinsky, N.I., Landrum, J.T. and Bone R.A.. Annu. Rev. Nutr. 23:171-201 (2003) Biologic Mechanisms of the Protective Role of Lutein and Zeaxanthin in the Eye
63. Aldini, G., Yeum KJ., Russell, R.M. and Krinsky, N.I., Nutritional Sciences 6:12-19 (2003) A Selective Assay to Measure Antioxidant Capacity in both the Aqueous and Lipid Compartments of Plasma
62. Krinsky, NI and Yeum, K-J., Biochem Biophys Res Commun 305:754-60 (2003) Carotenoid-Radical Interactions
61. Krinsky, N.I. in CRITICAL REVIEWS OF OXIDATIVE STRESS AND AGING: ADVANCES IN BASIC SCIENCE, DIAGNOSTICS, AND INTERVENTION (Cutler, RG and Rodriguez, H, Eds.) pp. 598-611, World Scientific Publishers, New Jersey (2003) Carotenoids and oxidative stress
60. Krinsky, N.I., Nutrition 17:815-817 (2001) Carotenoids as antioxidants

CURRICULUM VITAE

NORMAN I. KRINSKY, Ph.D.

Professor Emeritus, Department of Biochemistry
Tufts University School of Medicine
136 Harrison Avenue
Boston, MA 02111-1837 USA

Scientist,
Jean Mayer USDA Human Nutrition Research
Center on Aging at Tufts University

phone (617) 636-6861 FAX (617) 636-2409
E-mail: norman.krinsky@tufts.edu

Born: [redacted] Iron River, MI, USA
Married:
Children:

EDUCATION

1948 B.S. University of Southern California, Los Angeles, CA
1950 M.S. University of Southern California, Los Angeles, CA (Biochemistry and Nutrition)
1953 Ph.D. University of Southern California, Los Angeles, CA (Biochemistry, with Harry J. Deuel, Jr.)

PROFESSIONAL EXPERIENCE

1953-55 U.S. Public Health Service Post-doctoral Fellow; Harvard University (with George Wald)
1955-56 National Council to Combat Blindness Post-doc. Fellow; Harvard University (with George Wald)
1956-60 Instructor, Lecturer, Department of Biology, Harvard University
1960-64 Assistant Professor, Department of Pharmacology, Tufts University School of Medicine (TUSM)
1964-67 Associate Professor, Department of Pharmacology, TUSM
1967-69 Associate Professor, Department of Biochemistry, TUSM
1969-70 Professor, Department of Biochemistry, TUSM
1970-87 Professor, Department of Biochemistry and Pharmacology, TUSM
1973 Visiting Professor, Department of Physiology/Anatomy, University of California, Berkeley, CA
1981-82 Research Associate, Boston Veterans Administration Medical Center
1987-2000 Professor, Department of Biochemistry, Tufts University School of Medicine
1993-present **Scientist, USDA Human Nutrition Research Center on Aging, Tufts University**
2000-present **Professor Emeritus, Department of Biochemistry, Tufts Univ. School of Medicine**

RESEARCH INTERESTS

Function and metabolism of carotenoids, including antioxidant and anticarcinogenic actions and metabolism to retinoic acid and apocarotenoids. Role of carotenoids in primate macula. Analysis of tissue carotenoids. Biological oxidant damage, and mechanisms of lipophilic and hydrophilic protection.

EDITORIAL BOARDS

1984-1986 Journal of Free Radicals in Biology and Medicine

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PROFESSIONAL SOCIETIES

1948	American Association for the Advancement of Science (Fellow, 1966)
1949	Society of the Sigma Xi
1951	American Chemical Society
1951	New York Academy of Sciences
1959	American Society for Biochemistry and Molecular Biology
1972	American Society for Photobiology
1982	Society for Free Radical Research
1988	The Oxygen Society (2003: Society for Free Radical Biology and Medicine)
1988	International Society for Nutrition and Cancer
1993	European Retinoid Research Group
1994	International Carotenoid Society
1998	American College of Nutrition (Fellow, 1998)
1999	International Society for Coenzyme Q Research

PROFESSIONAL ACTIVITIES/HONORS

1950	Phi Sigma Award in the Biological Sciences, University of Southern California
1952	Phi Lambda Upsilon
1966	Fellow, American Association for the Advancement of Science
1967-1968	President, Tufts University Chapter, Society of the Sigma Xi
1975-1981	Secretary-Treasurer, American Society for Photobiology
1978	Organizing Committee, Fifth International Symp. on Carotenoids and Vitamin A, Madison, WI
1980	Co-Chairman, Workshop on Biological Chemiluminescence, American Society for Photobiology, Colorado Springs, CO
1981	Chairman, 1st Gordon Research Conference on "Oxygen Radicals in Biology and Medicine" Ventura, CA
1981-1984	Teaching Award, Tufts University School of Medicine
1982-1983	President, American Society for Photobiology
1984	Treasurer, Ninth International Congress on Photobiology, Philadelphia, PA
1987	Organizing Committee, Fourth International Congress on Oxygen Radicals, La Jolla, CA
1987	Chairman, Eighth International Symposium on Carotenoids, Boston, MA
1988-1991	Council, The Oxygen Society
1989-2000	Executive Committee, International Society for Nutrition and Cancer
1990	Lottie Arnrich Lecturer, Dept of Food & Nutrition, Iowa State University, Ames, IA May 1. 1990
1992	Chairman, 1st Gordon Research Conf. on "Chemistry and Biology of Carotenoids", Oxnard, CA
1993	Co-Chair, New York Academy of Sciences Conference on "Carotenoids in Human Health ", San Diego, CA
1993	Honorary Member, The Vitamin Society of Japan
1993	Distinguished Faculty Award, Tufts University School of Medicine
1994	Fellow, The Oxygen Society
1994	Co-Chair, Second International Conference on "Antioxidant Vitamins and ß-Carotene in Disease Prevention", October 10-12, Berlin, Germany
1994-1999	President, New England Free Radical/Oxygen Society
1995	Co-Chair, FASEB Summer Research Conference on "Antioxidant Nutrients in the Cellular Biology of Health and Disease", Saxtons River, VT
1995-1996	Secretary-General, The Oxygen Society
1996-1998	Advisory Committee, International Antioxidant Research Centre, King's College, London
1997	Mordechai Avron Memorial Lecturer, Nikken Sohonsha Corp., Gifu and Tokyo, Japan, 2/21/97

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1966-1967	Judith Leff, Ph.D.	Consultant, New York, NY
1971	Joseph J. Cooney, Ph.D.	Chairman, Environmental Sciences Program University of Massachusetts, Boston, MA
1972	Andreja Kornhauser, Ph .D.	Director, Dermal & Ocular Branch Division of Toxicology, Food & Drug Administration, Washington, DC
1977	A.F.P.M. DeGoij, Ph.D.	Research Associate, Sylvius Laboratoria, Univ. of Leiden, Leiden, The Netherlands
1979-1989	S. Welankiwar, Ph.D.	Scientist, Duracell Technology Center, Needham, MA
1988	Florian J. Schweigert, D.V.M.	Professor, Nutrition Physiology Institute für Physiologie, Veterinary Faculty University of Leipzig. D-7010, Leipzig, FRG
1990-1992	Paulo Palozza, M.D.	Institute of General Pathology Catholic University, Rome. Italy
1996-1999	Pankaj Prakash, Ph. D.	USDA HNRCA, Boston, MA
1999-2003	Giancarlo Aldini, Ph. D.	University of Milan, Milan, Italy

RESEARCH TRAINEES - UNDERGRADUATES/MEDICAL STUDENTS

1964-1966 [redacted] TUSM, 1968
1966-1967 [redacted] TUSM, 1968
1973-1974 [redacted], Tufts University, 1973
1974 [redacted] Tufts University, 1974
1974 [redacted] Tufts University, 1974
1974 [redacted], Tufts University, 1974
1974 [redacted], Tufts University, 1974
1974 [redacted], TUSM, 1977
1974 [redacted] Hampshire College, 1975
1974-1975 [redacted] Tufts University, 1975
1975-1976 [redacted], Tufts University, 1979
1977-1978 [redacted], Tufts University, 1979
1979-1980 [redacted] Tufts University, 1981
1980 [redacted], Tufts University, 1980
1980 [redacted], Oberlin College, 1981
1980 [redacted], Tufts University, 1981
1983-1984 [redacted], Tufts University, 1984
1983-1984 [redacted] TUSM, 1987
1984-1985 [redacted] Tufts University, 1985

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FACULTY ACTIVITIES

TUFTS UNIVERSITY SCHOOL OF MEDICINE

1963-1966	Pre-Clinical Curriculum Study (Director)
1963-1967	Curriculum Committee
1967-1969	Faculty Medical Education Group
1968-1971	Committee on Extended Educational Opportunity (Chairman)
1968-1969	Health Information Sciences Committee
1969-1970	Advisory Committee on Medical Education
1970-1972	Committee on Faculty Affairs
1973-1978	Committee on Educational Affairs
1974-1975	Fringe Benefits Subcommittee, Faculty Affairs Committee
1974-1975	Admissions Committee
1977	Medical Bylaws Committee
1978-1979	Faculty Affairs Committee (Chairman)
1979-1981	Budgetary Advisory Subcommittee, Faculty Affairs Committee
1979-1981	Boston Tuition Scholarship Benefits Committee
1980-1983	Curriculum Coordinator, Year I
1980-1983	Student Promotions Committee
1981-1982	Ad Hoc Committee on Student Performance Evaluation
1981	Special Program Development Committee
1981-1983	Library and Educational Spaces Planning Subcommittee
1981-1986	Curriculum Committee
1982-1983	Committee on the Teaching of Nutrition at TUSM (Co-Chairman)
1982-1985	Ad Hoc Grievance Committee
1982-1983	Basic Science Appointment, Promotion and Tenure Committee
1983-1985	Task Force on Curriculum Planning
1983-1985	Faculty Advisor
1984-1987	Course Director, Biochemistry
1984-1987	Faculty Affairs Committee
1985-1987	Curriculum Committee Sub-Committee on Curriculum Planning and Implementation
1985-1990	Problem-Based Learning Committee
1988-1989	Curriculum Committee
1989-1992	Faculty Affairs Committee (Chairman, 1990-1992)
1991-1992	Self-Study Sub-Committee on Governance and Administration, LCME, (Chairman)
1992-1993	Steering Committee, RWJ Foundation Generalist Physician Initiative Program
1993-1994	Member, Faculty Senate
1994-1995	Member, Core Curriculum Collaborators Group
1994-1996	Member, Faculty Prizes/Awards Committee
1996-1998	Self-Study Sub-Committee on Governance and Administration, LCME

TUFTS-NEW ENGLAND MEDICAL CENTER

1963	Committee on the Role of the Basic Scientist in the Medical Center, (Chairman)
1968-1969	Audio-visual Task Force
1970-1971	Advisory Committee on Minority Opportunity and Planning
1982-1984	Board of Directors, Women's Resource Center

TUFTS UNIVERSITY

1966-1968	Policy and Program Committee, Graduate School of Arts and Sciences

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SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

1983-1984 Faculty Secretary
1983-1987 Nominating Committee (Chairman)

TUFTS UNIVERSITY SCHOOL OF DENTAL MEDICINE

1964-1965 Curriculum Committee

JEAN MAYER HUMAN NUTRITION RESEARCH CENTER ON AGING AT TUFTS UNIVERSITY

1995-2000 Promotions Committee

TEACHING EXPERIENCE

HARVARD UNIVERSITY

1956-1960 Biology 191 (Experimental Biochemistry)
1956-1960 Undergraduate Advisor, Department of Biology
1958 Biology 190 (General Biochemistry, with George Wald)

TUFTS UNIVERSITY SCHOOL OF MEDICINE

1960-1967 Pharmacology
1967-1999 Biochemistry (Course Director, 1984-1987, 1994)
1968-1986 Neuropharmacology
1974-1979 Biochemistry of Disease
1980-1985 Principles of Pharmacology
1985-1991 Problem-Based Learning Facilitator
1990 Nutrition and Medicine Facilitator

TUFTS UNIVERSITY SCHOOL OF DENTAL MEDICINE

1960-1966 Pharmacology
1966-1968 Basic Health Sciences
1968-1988 Pharmacology
1984-1993 Biochemistry

TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE

1979-1985 Biochemistry
1980-1985 Neuropharmacology
1980-1985 Pharmacology

TUFTS UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

1960-1967 Graduate Pharmacology
1970 Mitochondrial Membranes and Bacterial Envelopes (BCM 294)
1972 Energy Flow in Biological Systems (BCM 214)
1974, 1978 Metabolic Pathways (BCM 213)
1978, 1982 Membranes (BCM 211)
1981- 1982 Advanced Biochemistry (BCM 223)

TUFTS UNIVERSITY SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

1984 Membranes (BCM 221)

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SCIENTIFIC CONFERENCES AND MEETINGS: INVITED PARTICIPATION

1. Invited Speaker: The Lipoprotein Nature of Rhodopsin Symposium on "Visual Mechanisms" (Sponsored by National Institutes of Health) Bethesda, Maryland, September 11-12, 1957.

2. Invited Speaker: The Role of Carotenoid Pigments as Protective Agents against Photosensitized Oxidations in Chloroplasts. Symposium on "Biochemistry of Chloroplasts" NATO Advanced Study Institute, Aberystwyth, Wales, U.K., August 5-9, 1965.

3. Invited Speaker: A Biochemical Basis for Carotenoid Function in Green Plants and Algae. Joint Japan-U.S. Seminar on "Carotenoid Biosynthesis and Related Topics" National Science Foundation/Japan Society for the Promotion of Science, Kyoto, Japan, November 29 - December 1, 1965.

4. Invited Speaker: Carotenoid De-epoxidation Reactions. Conference on "Photosynthetic Pigments" in honor of Harold H. Strain, Argonne National Laboratory, Argonne, Illinois, November 7-8,1968.

5. Invited Speaker: Minority Programs at Tufts University School of Medicine. Conference on "Minority Groups in Professional Schools" American Personnel and Guidance Association, Las Vegas, Nevada, March 30 - April 2, 1969.

6. Invited Participant: Minority Enrollment at Tufts University School of Medicine. Conference on "The Impact of Cultural and Economic Background on Programs to Recruit Negroes for Medicine" Macy Foundation, Princeton, NJ, April 13-16, 1969.

7. Invited Speaker: Evolution of Photosensitive Pigments in Microbes. Colloquium on "Photosynthetic Organisms: Origin and Evolution on Early Earth" 123rd meeting of the American Association for the Advancement of Science, Boston, MA, December 26, 1969.

8. Invited Speaker: The Protective Function of Carotenoid Pigments against Aerobic Photosensitivity. Colloquium on "Molecular Mechanisms of Photodynamic Action with and without Molecular Oxygen" VIth International Congress on Photobiology, Bochum, W. Germany, Aug. 21-25, 1972.

9. Sigma Xi Lecturer: Function of Carotenoids. University of Rhode Island, Kingston, RI, October 10, 1973.

10. Invited Speaker: Photosensitization and Protection of Biomembranes and Model Systems. Colloquium on "Photochemistry of Biomembranes" at the 2nd Meeting of the American Society for Photobiology, Vancouver, British Columbia, Canada, July 24, 1974.

11. Theme Speaker: Light and Life: Biochemical Responses to Light. New England Association of Chemistry Teachers 36th Summer Conference, St. Anselem's College, Manchester, New Hampshire, Aug. 20-24, 1974.

12. Invited Speaker: Singlet Oxygen Production in Biological Systems, Workshop on "The Role of Oxygen in the Production of Excited States in Biological Systems" Photobiology Group, Biophysical Society, Philadelphia, PA, February 18, 1975.

13. Invited Speaker: Damage and Protection against Singlet Oxygen. Workshop on "Free Radical Damage and Protection" Bioenergetics Group, Biophysical Society Seattle, WA, February 24, 1976.

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28. Invited Speaker: Introduction to Photobiology and Photosensitization. Symposium on "Photobiology" Chosun University, Gwang Ju, Korea, June 2, 1982.

29. Invited Speaker: Free Radicals as Possible Mutagens and Carcinogens. Symposium on "Free Radicals and Cancer" Council for Tobacco Research, New York, NY, June 21, 1982.

30. Invited Speaker: Mutagenic and Carcinogenic Effects of Oxygen Radicals Symposium on "Possible Roles of Free Radicals in Aging" Gerontological Society of America, Boston, MA, Nov. 21, 1982.

31. Invited Speaker: Biology and Photobiology of Singlet Oxygen 3rd International Conference on Oxygen Radicals, Munich, FRG, July 10-15, 1983.

32. Invited Speaker: Comparison of the Oxidant Mechanisms of Myeloperoxidase and UV-B Irradiation EMBO Workshop on "Oxidative Enzymes-Damage and Consequences" Grottoferrata, Italy, October 2-7, 1983.

33. Public Lecture: New Findings on the Role of Provitamin A in Health and Disease. Institute for Research on Aging, University of California, San Diego, CA, September 13, 1984.

34. Invited Speaker: The Action of Carotenoids In vitro as Compared to their Function In vivo. Symposium on "Nutrition and Disease: Cancer" Helicon Foundation, San Diego, CA, September 15, 1984.

35. Invited Speaker: Detection and Biological Function of Active Oxygen Species School Lecture, American Society for Photobiology, New Orleans, and LA, June 27, 1985.

36. Invited Speaker: The Unique Singlet Oxygen Quenching Properties of Carotenoids. FASEB Summer Research Conference on "Micronutrients Retinoids" Saxtons River, VT, June 22-27, 1986.

37. Invited Speaker: Mechanisms of Inactivation of Oxygen Species by Carotenoids. 2nd International Conference on Anticarcinogenesis and Radiation Protection, National Bureau of Standards, Gaithersburg, MD, March 9-12, 1987.

38 Invited Speaker: Beta-carotene and Cancer: Overview and Rationale. VNIS Health Communications Conference: Beta-Carotene, Boca Raton, FL, April 11-12, 1987.

39. Invited Speaker: Overview of Carotenoids in Medicine. Eighth International Symposium on Carotenoids, Boston, MA, July 26-31, 1987.

40. Invited Speaker: Enzymic and Pigment Protection from Photodynamic Damage. FEMS/Society for Applied Bacteriology Symposium on "Homeostatic Mechanisms in Micro-organisms." Warwick University, Coventry, UK, September 14-18, 1987.

41. Invited Speaker: The Evidence for the Role of Carotenes in Preventive Health Symposium on "Carotenes in Food and Health" Department of Food Science and Office of Continuing Professional Education, Rutgers, The State University of New Jersey, Iselin, NJ, December 3, 1987.

42. Invited Speaker: Carotenoids as Chemopreventive Agents. Third International Conference on "The Prevention of Human Cancer: Chemoprevention" Arizona Cancer Center, Tucson, AZ, January 12-15,

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58. Invited Speaker: Carotenoids as Biological Antioxidants. Symposium on "Active Oxygens, Lipid Peroxides and Antioxidants" 5th International Congress on Oxygen Radicals, Kyoto, Japan, November 17-21, 1991.

59. Invited Speaker: Excentric Cleavage Mechanism(s) for Carotenoid Metabolism. Gordon Research Conference on "Chemistry and Biology of Carotenoids" Oxnard, CA, March 9-13, 1992

60. Invited Speaker: Nutritional Factors an Their Influence on Mutagenicity and Malignant Transformation. Tobacco and Health Research Institute, University of Kentucky Symposium on "Tobacco Smoking and Nutrition: Influence of Nutrition on Tobacco Associated Health Risks" Lexington, KY, September 14-16, 1992

61. Invited Speaker: Excentric Cleavage of Carotenoids. New York Academy of Sciences Conference on "Carotenoids in Human Health" San Diego, CA, February 6-9, 1993.

62. Invited Speaker: Antioxidant Effects of Carotenoids. International Conference on "Critical Aspects of Free Radicals in Chemistry, Biochemistry and Medicine" Vienna, Austria, February 14-17, 1993.

63. Invited Speaker: Antioxidant Properties of Carotenoids. The Kurashiki Symposium for Medical Science, Kurashiki, Japan, May 21-22, 1993.

64. Invited Speaker: ß-Carotene: Disease Prevention and Its Health Impact. Japan Vitamin Society, Gifu City, Japan, May 25-27, 1993.

65. Invited Speaker: Function, Actions, and Associations of Carotenoids. Tenth International Symposium on Carotenoids, Trondheim, Norway, June 20-25, 1993.

66. Invited Speaker: Antioxidants: Classification and Mode of Action. Symposium on "Antioxidants and Disease Prevention: Biochemical, Nutritional, and Pharmacological Aspects" Stockholm. Sweden, June 30-July 3, 1993.

67. Invited Speaker: Carotenoid Metabolism. Symposium on "Retinoids: New Trends in Research and Clinical Applications" Genoa, Italy, October 4-7, 1993.

68. Invited Speaker: The Effects of Carotenoids on Cells. Workshop on "Cell Proliferation and Differentiation: Modulation by Free" Rome, Italy, October 8, 1993.

69. Invited Discussant: Antioxidant Nutrients. Symposium on "Nutritional Assessment of Elderly Populatio Measure and Function" Boston, MA, October 11-13, 1993.

70. Invited Speaker: Clinical and Experimental Studies of ß-Carotene and Cancer. FDA Public Conference on Antioxidant Nutrients and Cancer and Cardiovascular Disease. Washington, DC, November 1-3, 1993.

71. Invited Speaker: Recent Research Findings on Beta-Carotene. Henkel Symposium on Vitamin E Palm Beach, FL, June 7-8, 1994.

72. Invited Speaker: Comments on Antioxidant Vitamins and ß-Carotene. "Second International Conference on Antioxidant Vitamins and Beta Carotene in Disease Prevention" Berlin, Germany, October 10-12, 1994.

88. Invited Lecturer: The Properties of Carotenoids that Define Their Actions (June 1) and The Actions of Carotenoids in Biology and Medicine (June 3), NATO Advanced Study Institute on Free Radicals, Oxidative Stress and Antioxidants. Pathological and Physiological Significance, Antalya, Turkey, May 24-June 4, 1997

89. Invited Speaker: Carotenoids and Chronic Degenerative Diseases, International Conference on Nutrition and Cancer, Irvine, CA July 16-July 19, 1997

90. Invited Speaker: The Antioxidant and Biological Properties of the Carotenoids, 7th Congress of the International Association of Biomedical Gerontology, Adelaide, Australia, August 15-August 18, 1997

91. Invited Speaker: Biochemistry of Carotenoids: Actions and Functions. American College of Nutrition Award Lecture, American College of Nutrition Annual Meeting, New York, NY, September 26-28, 1997

92. Invited Speaker: Measurement of Carotenoids, WORKSHOP on Quantitative Methods for Determination of Hydroxyl Radicals, Oxidation of Biological Molecules and Antioxidants, The Oxygen Society, San Francisco, CA, November 20-24, 1997.

93. Invited Speaker: Actions of Carotenoids, Oxygen Club of California, Santa Barbara, CA, February 7, 1998

94. Plenary Lecture: Carotenoids in Health and Disease, Gordon Research Conference on Oxygen Radicals in Biology, Ventura, CA, February 12, 1998

95. Invited Speaker: Role of Carotenoids in Health and Disease, The First Regional Meeting on Medical Sciences: "The Roles of Free Radicals in Health and Disease" Jerusalem and Amman, March 22-27, 1998

96. Invited Speaker: Activity of ß-Carotene Oxidation Products, European Conference on Biomedical Research and Peace, Paralimni, Cyprus, October 17-21, 1999

97. Invited Speaker: What is the Scientific Evidence for Establishing Carotenoids as Recommended Nutrients? Symposium on Dietary Antioxidants: the New Dietary Reference Indices; The Oxygen Society, New Orleans, LA, November 21, 1999

99. Invited Speaker: The Relationship Between Antioxidant and Chronic Disease Symposium on Dietary Reference Intakes, Experimental Biology '00, San Diego, CA April 17, 2000

100. Invited Speaker Carotenoids, Smoking and Cancer, 3rd International Conference on Antioxidants and Free Radicals in Health and Disease, Vancouver, BC, Canada July 23, 2000

101. Invited Speaker: Antioxidants and Chronic Diseases: How Much Science is Enough? Symposium on Dietary Reference Intakes, American Dietetic Association, Denver, CO October 18, 2000

102. Invited Speaker: Antioxidants and Chronic Diseases, Symposium on Dietary Reference Intakes, American Public Health Association, Boston, MA Nov. 13, 2000

NORMAN I. KRINSKY, Ph. D. PUBLICATIONS

A. Peer Reviewed Journal Articles (99)

1. Ganguly, J, Krinsky, NI, Mehl, JW and Deuel, HJ Jr, Studies of the Distribution of Vitamin A as Ester and Alcohol and of Carotenoids in Plasma Proteins of Several Species. Arch. Biochem. Biophys. 38:275-282 (1952).

2. Krinsky, NI and Ganguly, J, Intracellular Distribution of Vitamin A Ester and Vitamin A Alcohol in Rat Liver. J. Biol. Chem. 202:227-232 (1953).

3. Ganguly, J and Krinsky, NI, Absence of Relationship between Vitamin A Alcohol Levels in Plasma and Liver of Rats. Biochem. J. 54:177-181 (1953).

4. Ganguly, J, Krinsky, NI, Pinckard, JH and Deuel, HJ, Jr., Untersuchungen über den Carotinoid-Stoffwechsel, XIV. Biologische Wirksamkeit von Echinenon. Z. Physiol. Chem. 295:61-66 (1953).

5. Ganguly, J, Krinsky, NI and Pinckard, JH, Isolation and Nature of Echinenone, a Provitamin A. Arch. Biochem. Biophys. 60:345-351 (1956).

6. Stefanini, M, Krinsky, NI and Magalini, SI, Studies on Platelets, XIX. Carotenoid Pigments in Human Platelets. J. Lab. Clin. Med. 50:225-228 (1957).

7. Krinsky, NI, Cornwell, DG and Oncley, JL, The Transport of Vitamin A and Carotenoids in Human Plasma. Arch. Biochem. Biophys. 73:233-246 (1958).

8. Krinsky, NI, Enzymatic Esterification of Vitamin A. J. Biol. Chem. 232:881-894 (1958).

9. Krinsky, NI, The Lipoprotein Nature of Rhodopsin. Arch. Ophthal. 60:688-694 (1958).

10. Goldsmith, TH and Krinsky, NI, The Epoxide Nature of the Carotenoid Neoxanthin. Nature (London) 188:491-493 (1960).

11. Krinsky, NI and Goldsmith, TH, The Carotenoids of the Flagellated Alga, Euglena gracilis. Arch. Biochem. Biophys. 91:271-279 (1960).

12. Krinsky, NI, A Relationship between Partition Coefficients of Carotenoids and their Functional Groups. Anal. Biochem. 6:293-302 (1963).

13. Krinsky, NI, Gordon, A and Stern, AI, The Appearance of Neoxanthin During the Re-greening of Dark-grown Euglena. Plant Physiol. 39:441-445 (1964).

14. Krinsky, NI and Levine, RP, Carotenoids of Wild Type and Mutant Strains of the Green Alga, Chlamydomonas reinhardi. Plant Physiol. 39:680-687 (1964).

15. Krinsky, NI, Carotenoid De-epoxidations in Algae. I. Photochemical Transformation of Antheraxanthin to Zeaxanthin. Biochim. Biophys. Acta 88:487-491 (1964).

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33. Anderson, SM, Krinsky, NI, Stone, MJ and Clagett, DC, Effect of Singlet Oxygen Quenchers on Oxidative Damage to Liposomes Initiated by Photosensitization or by Radiofrequency Discharge. Photochem. Photobiol. 20:65-69 (1974).

34. Krinsky, NI, Singlet Excited Oxygen as a Mediator of the Antibacterial Action of Leukocytes. Science 186:363-365 (1974).

35. Levine, PH, Weinger, RS, Simon, J, Scoon, KL and Krinsky, NI, Leukocyte-Platelet Interaction. Release of Hydrogen Peroxide by Granulocytes as a Modulator of Platelet Reactions. J. Clin. Investigation 57:955-963 (1976).

36. Deneke, CF and Krinsky, NI, Enhanced Dimol Emission of Singlet Oxygen by Cyclic Tertiary Amines. J. Am. Chem. Soc. 98:3041-3042 (1976).

37. Deneke, CF and Krinsky, NI, Inhibition and Enhancement of Singlet Oxygen ($^1\Delta_g$) Dimol Chemiluminescence. Photochem. Photobiol. 25:299-304 (1977).

38. Deneke, CF and Krinsky, NI, A Cheap and Durable Cuvet Washer. J. Chem. Educ. 54:257 (1977).

39. Krinsky, NI, Scoon, KL, Hardin, JC and Levine, PH, The Source of Hydrogen Peroxide and of Chemiluminescence Observed in Activated Human Platelet Preparations. Blood 50:597-602 (1977).

40. Lederman, DM, Cumming, RD, Petschek, HE, Levine, PH and Krinsky, NI, The Effect of Temperature on the Interaction of Platelets and Leukocytes with Materials Exposed to Flowing Blood. Trans. Am. Soc. Artif. Intern. Organs. 24:557-560 (1978).

41. Levine, PH, Hardin, JC, Scoon, KL and Krinsky, NI, Effect of Corticosteroids on the Production of Superoxide and Hydrogen Peroxide and the Appearance of Chemiluminescence by Phagocytosing Polymorphonuclear Leukocytes. Inflammation 5:19-27 (1981).

42. Andrews, PC and Krinsky, NI, The Reductive Cleavage of Myeloperoxidase in Half, Producing Enzymically Active Hemi-Myeloperoxidase. J. Biol. Chem. 256:4211-4218 (1981).

43. Krinsky, NI, Sladdin, DG, Levine, PH, Taub, IA and Simic, MG, Modification of Platelet Function by Radical Species Produced During Irradiation of Oxygenated Water. Thromb. Haemostasis 45:116-120 (1981).

44. Levine, PH, Sladdin, DG and Krinsky, NI, Superoxide, Xanthine Oxidase and Platelet Reactions. Further Studies on Mechanisms by which Oxidants Influence Platelets. Thromb. Haemostasis 45:290-293 (1981).

45. Krinsky, NI and Deneke, SM, The Interaction of Oxygen and Oxy-Radicals with Carotenoids. JNCI 69:205-210 (1982).

46. Andrews, PC and Krinsky, NI, A Kinetic Analysis of the Interaction of Human Myeloperoxidase with Hydrogen Peroxide, Chloride Ions and Protons. J. Biol. Chem. 257:13240-13245 (1982).

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61. Mathews-Roth, MM, Lausen, N, Drouin, G, Richter, A and Krinsky, NI, Effects of Carotenoid Administration on Bladder Cancer Prevention. Oncology 48:177-179 (1991).

62. Handelman, GJ, van Kuijk, FJGM, Chatterjee, A and Krinsky, NI, Characterization of Products Formed During the Autoxidation of ß-Carotene. Free Radical Biol. Med. 10:427-437 (1991).

63. Palozza, P and Krinsky, NI, The Inhibition of Radical-Initiated Peroxidation of Microsomal Lipids by both α-Tocopherol and ß-Carotene. Free Radical Biol. Med. 11:407-414 (1991).

64. Tang, G, Wang, X-D, Russell, RM and Krinsky, NI, Characterization of ß-Apo-13-Carotenone and ß-apo-14'-Carotenal as Enzymatic Products of the Excentric Cleavage of ß-Carotene. Biochemistry 30:9829-9834 (1991).

65. Wang, X-D, Krinsky, NI, Tang, G and Russell, RM, Retinoic Acid can be Produced from Excentric Cleavage of ß-Carotene in Human Intestinal Mucosa. Arch. Biochem. Biophys. 293:293-304 (1992).

66. Palozza, P and Krinsky, NI, ß-Carotene and α-Tocopherol are Synergistic Antioxidants. Arch. Biochem. Biophys. 297:184-187 (1992).

67. Palozza, P, Moualla, S and Krinsky, NI, Effects of ß-Carotene and α-Tocopherol on Radical-Initiated Peroxidation of Microsomes. Free Radical Biol. Med. 13:127-136 (1992).

68. Palozza, P and Krinsky, NI, Astaxanthin and Canthaxanthin are Potent Antioxidants in a Membrane Model. Arch. Biochem. Biophys. 297:291-295 (1992).

69. Wang, XD, Krinsky, NI, Marini, R, Tang, G, Yu, J, Fox, JG and Russell, RM, Intestinal Uptake and Lymphatic Absorption of ß-Carotene in Ferrets: A Model for Human ß-Carotene Metabolism. Am. J. Physiol. 263:G480-G486 (1992).

70. Wang, X-D, Russell, RM, Marini, R, Tang, G, Dolnikowski, G, Fox, JG and Krinsky, NI, Intestinal Perfusion of ß-Carotene in the Ferret Raises Retinoic Acid Levels in Portal Blood. Biochim. Biophys. Acta 1167:159-164 (1993).

71. Wang, X-D, Krinsky, NI and Russell, RM, Retinoic Acid Regulates Retinol Metabolism via Feedback Inhibition of Retinol Oxidation and Stimulation of Retinol Esterification in Ferret Liver. J. Nutr. 123:1277-1286 (1993).

72. Palozza, P and Krinsky, NI, Antioxidant Effects of Carotenoids on Biological Membranes. Acta Medica Romano 31:131-140 (1993).

73. Wang, X-D, Krinsky, NI, Benotti, PN and Russell, RM, Biosynthesis of 9-*cis*-retinoic acid from 9-*cis*-ß-carotene in human intestinal mucosa in vitro. Arch. Biochem. Biophys. 313:150-155 (1994).

74. Kennedy, AR and Krinsky, NI, Effects of retinoids, ß-carotene and canthaxanthin on UV and X-ray-induced transformation of C3H10T1/2 cells *in vitro*. Nutr. Cancer 22:219-232 (1994).

000204.076

87. Johnson, EJ, Qin, J, Krinsky, NI and Russell, RM, ß-Carotene Isomers in Human Serum, Breast Milk and Buccal after Continuous Oral Doses of all-*trans* and 9-*cis* ß-Carotene J. Nutr. 127: 1993-1999 (1997).

88. Yeum, K-J, Ahn, S-H, de Paiva, SAR, Lee-Kim, YC, Krinsky, NI and Russell, RM, Correlations between Carotenoid Concentrations in Serum and Breast Adipose Tissue of Women with Benign Breast Tumor or Breast Cancer. J. Nutrition, 128: 1920-1926 (1998)

89. Wang, X-D, Liu, C, Bronson, RT, Smith, DE, Krinsky, NI and Russell, RM Altered Retinoid Signaling and AP-1 Expression by ß-Carotene and Smoking Leads to Lung Metaplasia. J. Natl. Cancer Inst., 91: 60-66 (1999)

90. Ferreira, A.L.A., Yeum, K.-Y., Liu, C., Smith, D., Krinsky, N.I., Wang, X.-D. and Russell, R.M. Tissue distribution of lycopene in ferrets and rats after lycopene supplementation J. Nutr., 130:1256-1260 (2000)

91. Yeum, K.-Y., Ferreira, A.L.A., Smith, D., Krinsky, N.I. and Russell, R.M. The Effect of α-Tocopherol on The Mechanisms of ß-Carotene Cleavage. Free Radic. Biol. Med. 29:105-114 (2000)

92. Liu, C., Wang, X.-D., Bronson, R.T., Smith, D.E., Krinsky, N.I. and Russell, R.M. Effects of Physiological versus Pharmacological ß-Carotene Supplementation on Cell Proliferation and Histopathological Changes in the Lungs of Cigarette Smoke-exposed Ferrets. Carcinogenesis 21:101-110 (2000)

93. Prakash, P., Russell, R.M. and Krinsky, N.I. *In vitro* Inhibition of Proliferation of Estrogen-dependent and Estrogen-independent Human Breast Cancer Cells Treated with Carotenoids or Retinoids. J. Nutr. 131:1574-1580 (2001)

94. Aldini, G, Yeum, K-J, Russell, RM and Krinsky, NI, A selective Method to Measure the Oxidizability of the Aqueous and Lipid Compartments of Plasma. Free Radic. Biol. Med. 31:1043-1050 (2001)

95. Krinsky, NI, Possible Biological Mechanisms for a Protective role of Xanthophylls. J. Nutrition 132:540S-542S (2002)

96. Tibaduiza, EC, Fleet, JC, Russell, RM and Krinsky, NI, Excentric Cleavage Products of ß-Carotene Inhibit Estrogen Receptor Positive and Negative Breast Tumor Cell Growth in Vitro and Inhibit Activator Protein-1-Mediated Transcriptional Activation. J. Nutrition 132:1368-1375 (2002)

97. Aldini, G., Yeum KJ., Carini M., Krinsky, N.I. and Russell, RM, (-)-Epigallocatechin-(3)-gallate Spares Carotenoids, Recycles α-Tocopherol and Prevents Oxidative Damage in Both the Aqueous and Lipid Compartments of Human Plasma. Biochem Biophys Res Commun 302:413-418 (2003)

98. Yeum, K.-J., Aldini, G., Chung H.-Y., Krinsky N.I. and Russell, R.M., J Nutrition 133:2688-2691 (2003) The Activities of Antioxidant Nutrients Human Plasma Depend on the Localization of Attacking Radical Species

99. Ferreira, A.L.A., Yeum, K.-Y., Russell, R.M., Krinsky, N,I, and Tang, G., J. Nutr. Biochem. 14:531-540 (2003) Enzymatic and Oxidative Metabolites of Lycopene

000204.077

13. Krinsky, NI, Photosensitization and Singlet Oxygen Damage **in:** Topics In Photobiology (Kim, H-O and Song, PS, Eds.) pp. 67-71, Jeju National University, Jeju, Korea (1983)

14. Krinsky, NI and Welankiwar, S, Assay of Carotenoids. Meth. Enzymol. 105:155-162 (1984).

15. Krinsky, NI, Biology and Photobiology of Singlet Oxygen **in:** Oxygen Radicals In Chemistry And Biology (Bors, W, Saran, M and Tait, D, Eds.) pp. 453-464, Walter de Gruyter & Co., Berlin (1984)

16. Andrews, PC and Krinsky, NI, Myeloperoxidase Activity **in:** Handbook of Methods for Oxygen Radical Research (Greenwald, RA, Eds.) pp. 297-302, CRC Press, Boca Raton, FL (1985)

17. Andrews, PC and Krinsky, NI, Human Myeloperoxidase and Hemi-myeloperoxidase **in:** Immunochemical Techniques, Part J. Phagocytosis and Cell-Mediated Cytotoxicity. (Di Sabato, G and Everse, J, Eds.) pp. 369-378, Academic Press, New York (1986), vol. 132,

18. Krinsky, NI, Mechanisms of Inactivation of Oxygen Species by Carotenoids **in:** Anticarcinogenesis and Radiation Protection (Cerutti, PA, Nygaard, O and Simic, MG, Eds.) pp. 41-46, Plenum Press, New York (1987)

19. Krinsky, NI, The Evidence for the Role of Carotenes in Preventive Health. Clin. Nutr. 7:107-114 (1988).

20. Krinsky, NI, Theoretical Basis for Anticarcinogenic Effects of Retinoids. J. Cutan. Aging Cosm. Derm. 1:53-58 (1988).

21. Krinsky, NI, Membrane Antioxidants. Ann. N.Y. Acad. Sci. 551:17-33 (1988).

22. Krinsky, NI, Carotenoids and Cancer in Animal Models. J. Nutr. 119:123-126 (1989).

23. Krinsky, NI, Beta-Carotene: Functions **in:** New Protective Roles for Selected Nutrients (Spiller, GA and Scala, J, Eds.) pp. 1-15, Alan R. Liss, New York (1989)

24. Krinsky, NI, Carotenoids as Chemopreventive Agents. Prev. Medicine 18:592-602 (1989).

25. Krinsky, NI, Antioxidant Functions of Carotenoids. Free Radical Biol. Med. 7:617-635 (1989).

26. Krinsky, NI, Carotenoids in Medicine **in:** Carotenoids: Chemistry and Biology (Krinsky, NI, Mathews-Roth, MM and Taylor, RF, Eds.) pp. 279-292, Plenum Press, New York and London (1989)

27. Krinsky, NI, Effects of Carotenoids in Cellular and Animal Systems. Am. J. Clin. Nutr. 53:238S-246S (1991).

28. Krinsky, NI, Photooxidative Stress and Photodynamic Therapy: An Overview **in:** Oxidative Damage & Repair. Chemical, Biological and Medical Aspects (Davies, KJA, Eds.) pp. 298-299, Pergamon Press, Oxford (1991)

29. Krinsky, NI, Mechanism of Action of Biological Antioxidants. Proc. Soc. Exp. Biol. Med. 200:248-254 (1992).

000204.078

46. Krinsky, NI, Selected actions of micronutrient antioxidants **in:** Nutritional Assessment of Elderly Populations: Measure and Function (Rosenberg, IH, ed.) pp. 205-211, Raven Press, New York (1994)

47. Krinsky, NI, Plant Carotenoids and Related Molecules: Important Dietary Antioxidants **in**: Free Radicals and Oxidative Stress: Environment, Drugs and Food Additives (Rice-Evans, C., Halliwell, B. and Lunt, G.G., Eds.) Biochem. Soc. Symp. 61: 117-126, Portland Press, London (1995).

48. Krinsky, NI and Sies, H, The present status of antioxidant vitamins and beta-carotene. Am. J. Clin. Nutr. 62 (Suppl): 1299S-1300S (1995).

49. Olson, J.A. and Krinsky, N.I., The Colorful Fascinating World of the Carotenoids. FASEB J., 9: 1547-1550 (1995)

50. Krinsky, NI, Cellular aspects of carotenoids **in:** Handbook of Antioxidants (Cadenas, E and Packer, L, Eds.) pp. 315-336, Marcel Dekker, New York (1996)

51. Wang, X-D and Krinsky, NI, Identification and Quantification of Retinoic Acid and other Metabolites from ß-Carotene Excentric Cleavage in Human Intestine *in vitro* and Ferret Intestine *in vivo.* **in** METHODS IN ENZYMOLOGY (Suttie, JM and McCormack, D, eds.) 282: 117-130 (1997).

52. Omaye, ST, Krinsky, NI, Kagan, VE, Mayne, ST, Liebler, DC and Bidlack, WR, ß-Carotene: Friend or Foe? Fundam. Appl. Toxicol. 40: 163-174 (1997)

53. Krinsky, NI, Carotenoid Properties Define Primary Biological Actions And Metabolism Defines Secondary Biological Actions, **in** FREE RADICALS, OXIDATIVE STRESS, AND ANTIOXIDANTS: PATHOLOGICAL AND PHYSIOLOGICAL SIGNIFICANCE (Õzben, T, ed.) pp. 323-332, NATO Advanced Study Institute (1998).

54. Wang, X-D and Krinsky, NI, The Bioconversion of ß-Carotene into Retinoids **in** SUBCELLULAR BIOCHEMISTRY, VOL. 30: FAT-SOLUBLE VITAMINS (Quinn, PJ and Kagan, V, eds.) pp. 159-180, Plenum/London (1998)

55. Krinsky, NI, Overview of Lycopene, Carotenoids, and Disease Prevention. Proc. Soc. Exp. Biol. Med. 218: 95-97 (1998)

56. Krinsky, NI, The Antioxidant and Biological Properties of the Carotenoids. Annals, New York Academy of Sciences 854: 443-447 (1998)

57. Krinsky, NI and Rock. C L, Carotenoids (a) Chemistry, sources and physiology **in** ENCYCLOPEDIA OF HUMAN NUTRITION (Sadler, M, Strain, S and Caballero, B eds.) pp. 304-314, Academic Press, London (1998)

58. Krinsky, NI and Mayne, ST, Current Views on Carotenoids: Biology, Epidemiology and Trials **in** VITAMIN A AND RETINOIDS: AN UPDATE OF BIOLOGICAL ASPECTS AND CLINICAL APPLICATIONS, (Livrea, MA, ed.) pp. 45-57, Birkhäuser, Basel (2000)

000204.079

E. Letters

1. Krinsky, NI and Leff, J, Visible Light: Mutagen or Killer? Science 160:1255-1256 (1968).

2. Krinsky, N.I., Peacocke, M. and Russell, R.M. Antioxidant Vitamins, Cancer and Cardiovascular Disease. New Engl. J. Med. 335: 1066-1067 (1996).

3. Krinsky, NI and Russell, RM, Regarding the Conversion of ß-Carotene to Vitamin A. Nutr. Rev. 59: 309 (2001).

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AMENDMENT TO THE DOSSIERS IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® 6% AND 1.5%/70% OLEORESINS AS FOOD INGREDIENTS

09-24-07P04:36 RCVD

September 12, 2007

Panel Members

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AMENDMENT OT THE GRAS DOSSIERS IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® 6%, 1.5%/70% OLEORESINS AS FOOD INGREDIENTS

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AMENDMENT TO THE DOSSIERS IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF LYC-O-MATO® 6% OLEORESIN AND LYC-O-MATO® 1.5%/70% AS FOOD INGREDIENTS

1. EXECUTIVE SUMMARY

On a prior occasion, this independent expert GRAS panel critically evaluated the available information on Lyc-O-Mato® Oleoresin 6%, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate (common names: tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract, respectively)[1] meeting food grade specifications and produced in accordance with current Good Manufacturing Practice (cGMP), were GRAS by scientific procedures for supplementing the diet with lycopene. These GRAS determinations were requested by LycoRed Ltd. [LycoRed Natural Products Industries, Ltd.], Hebron Road – Industrial Zone, P.O. Box 320, Beer Sheva – 84102 Israel, and notified to the FDA (GRN 000156).[2] In these GRAS determinations, the literature was through April of 2003 was evaluated for information relevant to the GRAS determinations. On this occasion, the Expert Panel was requested to assess the current literature relevant to the GRAS determination of Lyc-O-Mato® Oleoresin 6%, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate in response to the proposed use as ingredients in products previously determined to be medical foods, in addition to current uses. The Expert Panel members independently evaluated the additional published safety information and confirmed that the available information supports the GRAS status of Lyc-O-Mato® Oleoresin 6%, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate as currently used. The Expert Panel also determined the proposed use as ingredients in products previously defined as medical foods is also GRAS, on the basis of scientific procedures.

2. INTRODUCTION

Lycopene is a natural constituent of the typical U.S. diet, with mean lycopene consumption at approximately 8 mg/day. The available information indicates that current commercial enteral formulas do not provide lycopene to patients comparable to that which would be derived from a typical diet (Olmedilla *et al.*, 1996). LycoRed, Ltd. intends to market Lyc-O-Mato® Oleoresin 6%, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate as ingredients for addition

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[1]Dossier in support of the Generally Recognized As Safe (GRAS) status of Lyc-O-Mato® Oleoresin 6% as a food ingredient; Dossier in support of the Generally Recognized As Safe (GRAS) status of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract as food ingredients

[2]GRN 000156, http://www.cfsan.fda.gov/~rdb/opa-gras.html; site visited September 6, 2007

to products previously determined to be medical foods at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day.[3,4]

The term "medical food" means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Medical foods are in some cases, the sole source of calories and nutrients for a patient, but as often as not, certain medical foods are consumed as a caloric and nutritive supplement (*i.e.*, may be taken to supplement the typical diet), as a result of the patient not eating or being able to eat normally due to the patient's specific disease or condition.[5]

3. ESTIMATED DAILY INTAKE

Lyc-O-Mato® Oleoresin 6%, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate (as indicated in GRN 000156), are intended to be used to increase the consumption of lycopene in the diet of the general population, when incorporated into specific food products as food ingredients. These foods are identified in the original GRAS dossiers, according to food codes given in the U.S. Department of Agriculture (USDA) 1994-1996, 98 Continuing Survey of Food Intakes by Individuals (CSFII, 94-96, 98), and these codes have been used to calculate the Estimated Daily Intake (EDI) values for lycopene consumption (Table 1). Other GRAS Notices concerning lycopene have also been filed with the FDA, but due to the self-limiting nature of lycopene addition to food (*i.e.*, an undesirable red color or tomato-like taste), lycopene from

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[3]The energy content of a supplemental product is typically in the range of 200 – 400 kcal *per* serving, with a suggested intake of 1 to 3 servings *per* day, depending on the product. The maximum daily intake of lycopene from products previously determined as medical foods taken as a supplement to the typical diet would be 36 mg/day.

[4] Because there is no specific deficiency, disease, syndrome or symptom arising from an absence of lycopene, the addition of lycopene, in and by itself, cannot render a food a "medical food" simply as the result of its addition to the food. In this GRAS Notification, tomato extract of lycopene is to be added to foods already determined to be medical foods.

[5] 21 CFR 101.9(j)(8) Nutrition labeling of food. Medical foods as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)). A medical food is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. A food is subject to this exemption only if: (i) It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube; (ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone; (iii) It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation; (iv) It is intended to be used under medical supervision; and (v) It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

more than one source would not likely be added to a food product. The GRAS dossiers for Lyc-O-Mato® Oleoresin 6% and for Lyc-O-Mato® 1.5%/70% identified the Acceptable Daily Intake (ADI) of lycopene at 120 mg/day.

Table 1. Current lycopene intake, predicted lycopene intake following supplementation of selected foods at the levels indicated in GRN 000156 and total lycopene intake (predicted + current) for individuals consuming selected supplemented foods

	Per User (mg/day)	
Lycopene intake from:	**Mean**	**90th Percentile**
A. Current consumption from food[a]	8.2	15.7
B. Possible maximum consumption with Tomato extracts (1.5%, 6%) or crystallized tomato lycopene extract as an added ingredient to food[a]	10.4	17.7
C. Consumption as a color additive[b]	5.3	9.2
D. Total consumption from conventional food (current + added)	23.9	42.6
E. Potential consumption from dietary supplement use	30.0	60.0
F. Total consumption from all sources (food + dietary supplements)	53.9	102.6

[a]Levels calculated using consumption values from CSFII 1994-1996, 1998 (2000) and food lycopene concentrations from Holden *et al.* (1999).
[b]GRN 000156

The addition of Lyc-O-Mato® Oleoresin 6%, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate to products previously determined as medical foods intended to supplement the patient's diet at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day. While there is no question that patients receiving such a medical food as a sole source of nutrition would not exceed the ADI of lycopene because of the absence of other lycopene sources, the Expert Panel determined supplemental uses to the typical diet to also be consistent with the safe use of lycopene the following reasons:

- The original lycopene consumption calculation (see table above), indicating a potential total consumption of lycopene from all sources was 53.9 mg/day (mean) and 102.6 mg/day (90th percentile). This total stipulated that consumption from food [*i.e.*, as a natural constituent of food, as an added ingredient (with limitations to specific foods) and as a color additive] was 23.9 mg/day (mean) and 42.6 at the 90th percentile. The Expert Panel reasoned that if a patient is receiving medical food to supplement his/her caloric intake, it is unlikely that the patient will be consuming enough conventional food to achieve the mean or 90th percentile intakes of lycopene.

- This total (above, 53.9 and 102.6 mg/day) also assumed an exaggerated consumption of lycopene as a dietary supplement at 30 mg/day (mean) and 60 mg/day (90th percentile). Because medical foods are administered under supervision of a physician, the Expert Panel reasoned that patients who receive medical food to supplement their caloric and nutritive intake would be unlikely to consume dietary supplements, at least to the extent of the exaggerated estimates identified above.
- Lastly, the only documented effect of over-consumption of lycopene is a skin color change and to this extent, consumption of lycopene is self-limiting. In addition, because a patient consumes medical foods under the supervision of a physician, the physician, as a trained observer, would notice the skin color change, investigate this phenomenon and subsequently caution the patient about over consumption of lycopene.

4. PRECLINICAL AND CLINICAL STUDIES

The following is a summary of additional preclinical and clinical studies published since the initial GRAS determinations conducted in 2003 that evaluate the effects of lycopene or tomato extract consumption.

Zaripheh and Erdman (2005) investigated the biodistribution of lycopene in groups of twelve male F344 rats through the use of radiolabeling techniques. For 30 days, the rats consumed lycopene-enriched (LP) (250 mg lycopene/kg/day) or control (CP) diets. The control diet provided an estimated daily dietary lycopene intake of 8 mg/day.[6] The rats were then gavaged with 0.152 mg lycopene; 50% of which was ^{14}C-labeled. Five or 24 hours following radiolabel administration, the rats were euthanized and examined for lycopene biodistribution. No adverse effects of diet or dose administration were apparent. A red color was observed in the liver and feces of the lycopene-fed rats. Serum total lycopene increased over time in both dietary groups, with the concentration greater in LP rats, than in CP rats ($P<0.05$). The *percentage* of the ^{14}C dose absorbed at 24 hours was lower (5.5±0.5%) in the rats fed lycopene, when compared to control-fed rats (6.9±0.4%, $P<0.05$). The total recovery of the ^{14}C dose from all tissues, intestinal contents, urine, and feces was higher in LP rats (75±6%) than in CP rats (57±6.5%) ($P<0.05$). Of the tissues analyzed, an increase in the *percentage* of ^{14}C-polar products occurred between 5 and 24 hours only in the prostate and seminal vesicles regardless of diet. Feeding lycopene also decreased the absorption of the single oral ^{14}C-lycopene dose. Overall, Zaripheh and Erdman (2005) found that lycopene absorption, tissue uptake, and catabolism were altered by previous

[6] At the start of the study, the rats weighted 113 g so their initial daily intake was approximately 70 mg/kg/day (*i.e.*, 8 mg/0.113 kg). However, final body weights were not reported so an estimated range of daily intake cannot be calculated.

lycopene consumption, and that lycopene is taken up by extrahepatic tissues from the postprandial triglyceride-rich fraction.

Commercially-available lycopene is processed from several different sources, including a fungal biomass (*Blakeslea trispora*). A 90-day feeding study of *B. trispora*-derived lycopene at dietary levels of 0, 0.25, 0.5, and 1.0% in male and female Wistar rats (n=20 *per* group) found no evidence of lycopene toxicity at the highest dietary concentration as determined by clinical chemistry and neurobehavioral observations, assessment of motor activity, body weight and food consumption, ophthalmoscopic examinations, hematology, urinalysis, organ weights, histopathology and gross pathology. Mean lycopene intake was estimated to be 0, 145, 291, and 586 mg/kg/day for males and 0, 156, 312, and 616 mg/kg/day for females. The authors reported that the No-Observed-Effect-Level (NOEL) was 1.0% dietary lycopene, the highest dose tested (Jonker *et al.*, 2003).

The effects of lycopene on adriamycin (ADR)-induced Sprague-Dawley rat cardiotoxicity and nephrotoxicity were evaluated by Atessahin *et al.* (2006b) and Yilmaz *et al.* (2006). Gavage treatment with lycopene at 4 mg/kg/day either ten days before intraperitoneal (*i.p.*) injection of 10 mg/kg ADR; or two days before and three days after *i.p.* ADR administration reduced ADR-induced cardiotoxicity and nephrotoxicity (Yilmaz *et al.*, 2006; Atessahin *et al.*, 2006b). Compared to controls not administered lycopene, treatment with lycopene normalized ADR-induced increases in plasma creatinine and urea as well as levels of cardiac and kidney catalase, and also inhibited the formation of cardiac and histopathological changes. In addition, lycopene pretreatment inhibited ADR-induced reductions in testes and epididymis weights, and sperm motility, restored an ADR-induced increase in malondialdehyde levels, and reduced glutathione concentrations back to control level status. Lycopene treatment also reverted ADR-induced histopathological alterations back to control parameters (Yilmaz *et al.*, 2006; Atessahin *et al.*, 2006b).

A 31-day oral pretreatment with lycopene (1 mg/kg/day) significantly prevented myocardial damage and lipid peroxidation induced by ischemia and reperfusion (I-R) injury in a Wistar albino rat animal model, and preserved antioxidant status and hemodynamic parameters (Bansal *et al.*, 2006). In addition, gavage administration of lycopene or tomato juice for three weeks to Sprague Dawley rats prior to I-R injury reportedly reduced I-R-induced lipid peroxidation, but only tomato juice ingestion improved post-ischemic ventricular function, reduced myocardial infarct size and reduced cardiomyocyte apoptosis (Das *et al.*, 2005).

Lycopene consumption has been linked with decreased oxidative damage. Sendao *et al.* (2006) investigated the cytogenetic effects of a single dose or four daily gavage administrations of lycopene on chromosomal damage induced by the anti-tumor drug cisplatin in Wistar rat bone marrow cells. In the single dose study, 24 hours prior to *i.p.* cisplatin (or saline control) treatment, lycopene (LycoRed) was administered at 0, 4, and 6 mg/kg. One day later, the rats were euthanized, and bone marrow slides prepared for chromosomal aberration analysis. For the repeated dose analysis, rats were treated with lycopene (0.5, 1.0, and 1.5 mg/kg) 72, 48, 24, and one hour before a single *i.p.* cisplatin or saline treatment. Rats exposed to cisplatin alone showed 22% and 22.6% abnormal metaphases, respectively, for the acute and subacute dosing regimens,

whereas comparative saline treated controls showed only 2.6% and 2% abnormal metaphases. Single or repeated dose lycopene treatment alone did not increase chromosomal aberrations ($P>0.01$); however, those treatments significantly decreased incidences of cisplatin-induced chromosomal damage at all dose levels ($P<0.01$). The results of this study indicate that lycopene was not clastogenic, and that low doses of lycopene reduce cisplatin-induced chromosome damage in the bone marrow (Sendao *et al.*, 2006).

Lycopene (approximately 4 mg/kg/day) has also been reported to inhibit oxidative stress in rats (as seen by a reduction in xanthine oxidase and myeloperoxidase activities[7] in skeletal muscle tissue) due to muscle exhaustion and gentamycin-induced nephrotoxicity, as determined by renal failure in rats, as well as reduced malondialdehyde and glutathione levels, and reduced glutathione peroxidase and catalase activities in rat kidney tissue, when compared with gentamycin treatment alone (Kim *et al.*, 2004; Karahan *et al.*, 2005; Liu *et al.*, 2005).

Gavage administration of Lyc-O-Mato® 6% oleoresin to male Swiss mice at 1.25 mg/kg/day for five days prior to gastric *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) administration protected against MNNG-induced genotoxicity and oxidative stress at 27 hours post-MNNG administration (Velmurugan *et al.*, 2005). Carbon tetrachloride-induced hepatic toxicity in male Sprague Dawley rats was partially inhibited by a diet containing 10% tomato powder (approximately equivalent to 10,000 mg/kg bodyweight/day), based on serum sorbitol dehydrogenase and serum aspartate aminotransferase activities (Kim *et al.*, 2004). Dietary lycopene at 40 mg/kg/day for 43 weeks significantly ($P<0.05$) inhibited the number and size of azoxymethane-induced colon tumors in Fisher 344 male weanling rats (Martinez-Ferrer *et al.*, 2006).

Turk *et al.* (2007) reported that daily gavage administration of lycopene along with daily subcutaneous (*s.c.*) injection of cyclosporine A (CsA) resulted in a marked amelioration of CsA-induced testicular toxicity.[8] Over a period of 21 days, male Sprague-Dawley rats were administered (*via* gavage) lycopene (10 mg/kg/day) and CsA (15 mg/kg/day) with subsequent evaluation of testicular toxicity and comparison of results to controls treated with CsA only (Turk *et al.*, 2007). The effects of daily lycopene gavage administration on cisplatin-induced testicular and spermatozoal toxicity were studied in male Sprague-Dawley rats. After being administered an acute *i.p.* dose of 7 mg/kg cisplatin, rats were administered lycopene at 4 mg/kg/day for five days, followed by evaluation of sperm concentration, sperm motility, total sperm abnormalities and, malondialdehyde and glutathione levels. When compared to the cisplatin-treated control group, the values of all examined parameters were normalized in the lycopene-treated rats (Atessahin *et al.*, 2006a).

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[7] Xanthine oxidase and myeloperoxidase have been indicated as responsible for exhaustive exercise-induced oxidative stress in several tissues, including muscle, liver, and heart (Liu *et al.*, 2005).

[8] Significant decreases in seminal vesicle weight, epidiymal sperm concentration, motility, testicular tissue glutathione (GSH), glutathione peroxidase and catalase activity, diameter of seminiferous tubules and germinal cell thickness, while it increased malondialdehyde levels and abnormal sperm rates (as determined by the visual evaluation of forward progressive sperm motility) along with degeneration, necrosis, and appearance of desquamative germ cells.

Lycopene consumption has also been evaluated for an ability to decrease cigarette smoke-induced changes in a preclinical gastric cancer ferret model (Liu *et al.*, 2006). Ferrets that either were exposed or not exposed to cigarette smoke were administered daily gavage doses of lycopene at 0, 1.1, or 4.3 mg/kg for nine weeks. After exposure, the ferrets were euthanized, and gastric mucosal cells were isolated and analyzed for p53, Bax-1, cleaved caspase 3, and p21Cip1/Waf1 levels. Lycopene treatment attenuated a smoke-induced elevation in total p53 and phosphorylated p53 levels in the gastric mucosa. Smoke-induced changes in p53 target genes p21Waft/Cip1, Bax-1, as well as the cell proliferation and apoptosis markers of cleaved caspase 3, cylin D1, and proliferating cellular nuclear antigen (PCNA), were reduced in a dose-dependent fashion after lycopene consumption (Liu *et al.*, 2006).

Rao (2004) evaluated the effects of a four-week consumption of a tomato-rich diet on lycopene bioavailability and antioxidant properties. Healthy human subjects (n=17) first followed a diet low in lycopene content (*i.e.*, washout period), after which the subjects consumed a tomato-rich diet[9] that provided 30 mg lycopene/day. Compared to the washout period, daily consumption of 30 mg lycopene resulted in significant increases in serum lycopene (181.79±31.25 *vs.* 684.7±113.91 nmol/L, respectively) and the total antioxidant potential[10] (2.26±0.015 *vs.* 2.38±0.17 mmol/L Trolox equivalents, respectively), while serum lipid and protein oxidation was significantly reduced (all levels of significance at $P<0.05$). As reported in an English abstract of a Spanish paper by Madrid *et al.* (2006), a seven-day supplementation with pure tomato juice (119.9 μM; approximately 0.64 μg/L) to healthy volunteers (n=17) resulted in significant increases in plasma lycopene and HDL cholesterol levels, when compared to basal levels ($P<0.05$). Total antioxidant capacity,[11] and enzymatic antioxidants catalase and superoxide dismutase were not altered with lycopene consumption.

Porrini *et al.* (2005) evaluated the consumption of a beverage prototype (250 ml) containing Lyc-O-Mato® six *percent* (containing approximately 6 mg lycopene) by healthy volunteers for 26 days on the ability to improve protection against DNA damage in lymphocytes. Lyc-O-Mato®-containing beverage consumption for 26 days significantly increased plasma lycopene levels, and significantly reduced DNA damage in lymphocytes subjected to oxidative stress, as determined by the single-cell gel electrophoresis (COMET) assay ($P<0.0001$). This data is supported by *in vitro* data in the Hep3B human hepatoma cell line, which indicated that lycopene treatment inhibited tumor cell growth in a dose-dependent manner (0.2 – 50 μM lycopene after a 24-hour incubation period), and that lycopene-treated cells showed less DNA damage (*via* the COMET assay) than did placebo-treated cells (Yun *et al.*, 2005). Consumption of lycopene in a beverage containing 5.7 mg lycopene was also evaluated by Riso *et al.* (2006), who reported that production of the inflammatory mediator tumor necrosis factor (TNF)-*alpha* in whole blood was 34.4% lower after 26 days of treatment. No other effects were noted. In addition, a study evaluating the effects of tomato-based carotenoids on ultraviolet light-induced erythema reported that consumption of a Lyc-O-Mato®-containing drink that provided 10 mg

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[9] Tomato juice, tomato sauce, tomato paste, ketchup, spaghetti sauce, and ready-to-serve tomato soup.
[10] The overall antioxidant potential of serum was estimated using the ABTS decoloration assay (Re *et al.*, 1999).
[11] Total antioxidant capacity was measured by a luminol-enhanced chemiluminescence measurement (Lissi *et al.*, 1995).

lycopene *per* day for twelve weeks prevented erythema formation and was well tolerated (Aust *et al.*, 2005; Stahl *et al.*, 2006).

Mohanty *et al.* (2005) reported that daily consumption of 8 mg lycopene for one year delayed or prevented high grade prostate intraepithelial neoplasia from developing into occult prostate cancer, with an inverse relationship found between lycopene and prostate-specific antigen (PSA) levels. Good patient tolerance and no toxicity were reported from lycopene ingestion. In evaluating the efficacy of lycopene in the treatment of oral leukoplakia,[12] Singh *et al.* (2004) administered placebo, 4, or 8 mg lycopene/day (Lyc-O-Mato® tomato extract) for three months to 58 patients both histologically and clinically diagnosed with oral leukoplakia. Histological analysis of the oral lesions after lycopene treatment found that both 4 and 8 mg lycopene/day treatment had significant positive responses (*i.e.*, $P<0.05$ and $P<0.001$, respectively) as measured by reversed hyperkeratosis and decreased lesion size on the oral lesions, compared with control treatment ($P<0.001$). The authors indicated that no side effects or toxicity of the lycopene treatment was encountered during the study duration. Lyc-O-Mato® tomato extract was also administered for eight weeks at approximately 15 mg lycopene/day to grade-1 hypertensive patients ($n=31$). It was well tolerated, and resulted in significantly decreased systolic and diastolic blood pressure ($P<0.01$ and $P<0.05$, respectively) (Engelhard *et al.*, 2006). Clark *et al.* (2006) administered lycopene at up to 120 mg/day (dose-escalating Phase I/II trial of 15, 30, 45, 60, 90, and 120 mg/day) to patients for one year, which did not result in any discernible response in serum PSA levels in biochemically relapsed prostate cancer patients ($n=36$). Toxicity was mild, with one patient discontinuing therapy because of diarrhea. Plasma lycopene levels significantly increased during the first three months, and then plateaued for all six dose levels.

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[12] A pre-cancerous lesion in the oral cavity, in which a white patch or plaque on the oral mucosa develops that cannot be scraped off and cannot be attributed to any diagnosable disease, but tobacco consumption is always present (Singh *et al.*, 2004).

5. CONCLUSION

We, the Expert Panel, have individually and collectively critically evaluated information generated since the first GRAS review summarized in this amendment for the GRAS dossiers (Dossier in support of the Generally Recognized As Safe (GRAS) status of Lyc-O-Mato® Oleoresin 6% as a food ingredient; Dossier in support of the Generally Recognized As Safe (GRAS) status of Lyc-O-Mato® 70% Concentrate and Lyc-O-Mato® 1.5% Extract as food ingredients). This information is consistent with that provided in the initial GRAS determinations and fully supports the GRAS status of Lyc-O-Mato® 6% Oleoresin, Lyc-O-Mato® 1.5% Extract, and Lyc-O-Mato® 70% Concentrate, respectively. We conclude that the use of Lyc-O-Mato® 6% Oleoresin, Lyc-O-Mato® 1.5% Extract, or Lyc-O-Mato® 70% Concentrate as ingredients when added to medical foods are Generally Recognized As Safe by scientific procedures. It is our opinion that other qualified experts qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

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6. REFERENCES

Atessahin, A., Karahan, I., Turk, G., Gur, S., Yilmaz, S and Ceribasi (2006a) Protective role of lycopene on cisplatin-induced changes in sperm characteristics, testicular damage and oxidative stress in rats. *Reproductive Toxicology* 21:42-47.

Atessahin, A., Turk, G., Karahan, I., Yilmaz, S., Ceribasi, A. O. and Bulmus, O. (2006b) Lycopene prevents adriamycin-induced testicular toxicity in rats. *Fertility and Sterility* 85:1216-1222.

Aust, O., Stahl, W., Sies, H., Tronnier, H. and Heinrich, U. (2005) Supplementation with tomato-based products increases lycopene, phytofluene, and phytoene levels in human serum and protects against UV-light-induced erythema. *International Journal for Vitamin and Nutrition Research* 75:54-60.

Bansal, P., Gupta, S. K., Ojha, S. K., Nandave, M., Mittal, R., Kumari, S. and Arya, D. S. (2006) Cardioprotective effect of lycopene in the experimental model of myocardial ischemia-reperfusion injury. *Molecular and Cellular Biochemistry* 289:1-9.

Clark, P. E., Hall, M. C., Borden Jr..L.S., Miller, A. A., Hu, J. J., Lee, W. R., Stindt, D., D'Agostino Jr., R., Lovato, J., Harmon, M. and Torti, F. M. (2006) Phase I-II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. *Urology* 67:1257-1261.

CSFII 1994-96 (2000) *Continuing Survey of Food Intakes by Individuals (CSFII) 1994-96, 98.* Agricultural Research Service, US Department of Agriculture, Washington, DC. CD-ROM.

Das, S., Otani, H., Maulik, N. and Das, D. K. (2005) Lycopene, tomatoes, and coronary heart disease. *Free Radical Research* 39:449-455.

Engelhard, Y. N., Gazer, B. and Paran, E. (2006) Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study. *American Heart Journal* 151:100e1-100e6.

Holden, J. M., Eldridge, A. L., Beecher, G. R., Buzzard, I. M., Bhagwat, S. A., Davis, C. S., Douglass, L. W., Gebhardt, S. E., Haytowitz, D. B. and Schakel, S. (1999) Carotenoid content of U.S. foods: an update of the database. *Journal of Food Composition and Analysis* 12: 169-196.

Jonker, D., Kuper, C. F., Fraile, N., Estrella, A. and Rodriguez Otero, C. (2003) Ninety-day oral toxicity study of lycopene from *Blakeslea trispora* in rats. *Regulatory Toxicology and Pharmacology* 37:396-406.

000244

Karahan, I., Atessahin, A., Yilmaz, S., Ceribasi, A. O. and Sakin, F. (2005) Protective effect of lycopene on gentamicin-induced oxidative stress and nephrotoxicity in rats. *Toxicology* 215:198-204.

Kim, Y., DiSilvestro, R. and Clinton, S. (2004) Effects of lycopene-beadlet or tomato-powder feeding on carbon tetrachloride-induced hepatotoxicty in rats. *Phytomedicine* 11:152-156.

Lissi, E., Salim-Hanna, M., Pascual, C. and del Castillo, M. D. (1995) Evaluation of total antioxidant potential (TRAP) and total antioxidant reactivity from luminol-enhanced chemiluminescence measurements. *Free Radical Biology and Medicine* 18: 153-158.

Liu, C., Russell, R. M. and Wang, X. D. (2006) Lycopene supplementation prevents smoke-induced changes in p53, p53 phosphorylation, cell proliferation, and apoptosis in the gastric mucosa of ferrets. *Journal of Nutrition* 136:106-111.

Liu, C. C., Huang, C. C., Lin, W. T., Hsieh, C. C., Huang, S. Y., Lin, S. J. and Yang, S. C. (2005) Lycopene supplementation attenuated xanthine oxidase and myeloperoxidase activities in skeletal muscle tissues of rats after exhaustive exercise. *The British Journal of Nutrition* 94:595-601.

Madrid, E., Vasquez, D., Leyton, F., Mandiola, C. and Escobar, J. A. (2006) Short-term lycopersicum esculentum consumption may increase plasma high density lipoproteins and decrease oxidative stress. *Revista Medica De Chile* 134:855-862. (in Spanish)

Martinez-Ferrer, M., Verghese, M., Walker, L. T., Shackelford, L., Chawan, C. B. and Jhala, N. (2006) Lycopene reduces azoxymethane-induced colon tumors in Fisher 344 rats. *Nutrition Research* 26:84-91.

Mohanty, N. K., Saxena, S., Singh, U. P., Goyal, N. K. and Arora, R. P. (2005) Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. *Urologic Oncology* 23:383-385.

Olmedilla, B., Granado, F., Blanco, I. and Rojas-Hidalgo, E. (1996) Evaluation of retinol, *alpha*-tocopherol, and carotenoids in serum of men with cancer of the larynx before and after commercial enteral formula feeding. *Journal of Parenteral and Enteral Nutrition* 20:145-149.

Porrini, M., Riso, P., Brusamolino, A., Berti, C., Guarnieri, S. and Visioli, F. (2005) Daily intake of a formulated tomato drink affects carotenoid plasma and lymphocyte concentrations and improves cellular antioxidant protection. *The British Journal of Nutrition* 93:93-99.

Rao, A. V. (2004) Processed tomato products as a source of dietary lycopene: bioavailability and antioxidant properties. *Canadian Journal of Dietetic Practice and Research* 65:161-165.

Re, R., Pellegrini, N., Proteggente, A., Pannala, A., Yang, M. and Rice-Evans, C. (1999) Antioxidant activity applying an improved ABTS radical cation decolorization assay. *Free Radical Biology & Medicine* 26: 1231-1237.

Riso, P., Visioli, F., Grande, S., Guarnieri, S., Gardana, C., Simonetti, P. and Porrini, M. (2006) Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. *Journal of Agricultural and Food Chemistry* 54:2563-2566.

Sendao, M. C., Behling, E. B., Alves dos Santos, R., Greggi Antunes, L. M. and Pires Bianchi, M. (2006) Comparative effects of acute and subacute lycopene administration on chromosomal aberrations induced by cisplatin in male rats. *Food and Chemical Toxicology* 44:1334-1339.

Singh, M., Krishanappa, R., Bagewadi, A. and Keluskar, V. (2004) Efficacy of oral lycopene in the treatment of oral leukoplakia. *Oral Oncology* 40:591-596.

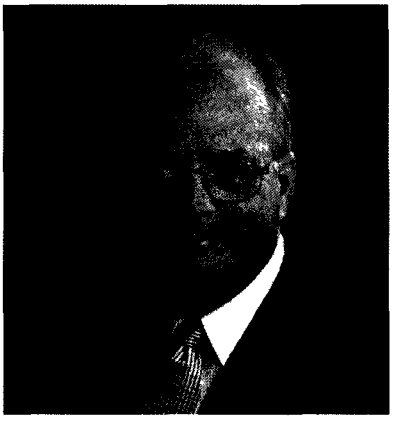
Stahl, W., Heinrich, U., Aust, O., Tronnier, H. and Sies, H. (2006) Lycopene-rich products and dietary photoprotection. *Photochemical & Photobiological Sciences: Official journal of the European Photochemistry Association and the European Society for Photobiology* 5:238-242.

Turk, G., Atessahin, A., Sonmez, M., Yuce, A. and Ceribasi, A. O. (2007) Lycopene protects against cyclosporine A-induced testicular toxicity in rats. *Theriogenology* 67:778-785.

Velmurugan, B., Mohan, C., Abraham, S. K. and Nagini, S. (2005) Combination of *S*-allylcysteine and lycopene protects against *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-induced genotoxicity and oxidative stress in mice. *Nutrition Research* 25:577-586.

Yilmaz, S., Atessahin, A., Sahna, E., Karahan, I. and Ozer, S. (2006) Protective effect of lycopene on adriamycin-induced cardiotoxicity and nephrotoxicity. *Toxicology* 218:164-171.

Zaripheh, S. and Erdman Jr., J. W. (2005) The biodistribution of a single oral dose of [C-14]-lycopene in rats prefed either a control or lycopene-enriched diet. *Journal of Nutrition* 135:2212-2218.



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Burdock Group **1988-Present**
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Dr. Burdock is an internationally recognized authority on the safety of food ingredients, personal care products, and dietary supplements. He has more than twenty years experience dealing with regulatory issues related to product safety and risk assessment. As the President of Burdock Group, Dr. Burdock provides safety and toxicity information on food, food and feed additives, drug excipients, and contaminants to a varied client list, including Fortune 100 corporations, start-up companies, law firms, and trade associations. This information may be in the form of confidential reviews, regulatory petitions, Generally Recognized As Safe (GRAS) self determinations, GRAS notifications, product contamination, and litigation support. As a leading scientist in the food industry, Dr. Burdock is sought by scientific publishers to author journal articles and edit reference books on food additives, flavor ingredients, and regulatory matters and by clients to comment on proposed regulations or respond to communications from regulatory agencies including the FDA and the USDA.

Flavor and Extract Manufactures' Association (FEMA) **1986-1992**
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Dr. Burdock managed the FEMA scientific programs, coordinated the research activities of the testing laboratories, and communicated with external consultants and allied industry committees working with FEMA. As the primary scientific liaison, Dr. Burdock guided member companies with the preparation of submissions to the FEMA Expert Panel for GRAS review, alerted Expert Panel and Association members to scientific developments in the food and flavor industry, and identified

changes in the regulatory policies as a result of these developments. He authored and edited comprehensive literature reviews on flavor additives and other topics relevant to the Association's interests.

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Manger of Biological Services

Dr. Burdock directed the Product Safety section, Microbiological Research Services, the Clinical Evaluation Laboratory and the Product Evaluation Center. As the senior toxicologist, he was responsible for the toxicological laboratories and microbiologic safety of products applied to the test groups in clinical evaluation laboratories and for those products released for public use. Dr. Burdock served as a corporate member of the Pharmacology/Toxicology Committee and the Cosmetic Ingredient Review Subcommittee of the Cosmetic, Toiletries and Fragrance Association. He represented the Consumer Products Division on toxicology issues within the corporation, and externally, with vendors, government agencies, and trade associations.

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As a Study Director, Dr. Burdock designed and managed toxicological oversight for compliance with regulatory requirements, quality assurance, budgetary monitoring, testing of pharmaceuticals, food additives, pesticides, and evaluated the performance of subcontractors. He negotiated program design and individual toxicity study requirements for the registration of substances with FDA, EPA, and other regulatory agencies. Dr. Burdock supervised two laboratory sections -Teratology/Reproduction and Sub-Chronic Rodent Toxicology.

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PUBLICATIONS

G.A. Burdock, and I.G. Carabin (2007). Safety assessment of ylang-ylang oil as a food ingredient. *Food and Chemical Toxicology* (submitted to the editor).

G.A. Burdock, and I.G. Carabin (2007). Safety assessment of 2-ethyl-3,(5 or 6)-dimethylpyrazine as a food ingredient. *Regulatory Toxicology and Pharmacology* (submitted to editor).

G.A. Burdock and I.G. Carabin (2007). Safety assessment of sandalwood oil as a food ingredient. *Food and Chemical Toxicology* (submitted to editor).

I.G. Carabin and **G.A. Burdock** (2007). Safety assessment of β-ionone as a food ingredient. *Food and Chemical Toxicology* (submitted to editor).

G.A. Burdock and I.G. Carabin (2007). Safety assessment of hydroxypropylmethyl cellulose as a food ingredient. *Food and Chemical Toxicology* (submitted to editor).

G.A. Burdock, I.G. Carabin and J.C. Griffiths (2007) Breaking Down the Barriers to Functional Foods, Chapter XX. In: *Nutraceutical And Functional Food Regulation In The United States and Around The World*, a volume of the *Foodscience and Technology Series*. D. Bagchi (ed). Elsevier, NY (accepted and in press).

G.A. Burdock and L. Williams (2007) Nanotechnology and the potential nanotoxicity of food ingredients. *Agro Food Industry* (accepted by publisher)

F. Kotsonis, and **G.A. Burdock** (2007) Chapter 30: Food Toxicology. In: *Toxicology: The Basic Science of Poisons*. 8th edition C.D. Klaassen (Ed.) Pergamon Press, New York. (accepted and in press)

B.A. Magnuson, **G.A. Burdock**, J. Doull, R.M. Kroes, G.M. Marsh, M.W. Pariza, P.S. Spencer, W.J. Waddell, R. Walker, and G.M. Williams (2007). Aspartame: A safety evaluation based on current use levels, regulations, toxicological and epidemiological studies. Submitted to *Critical Reviews in Toxicology* (accepted and in press).

G.A. Burdock (2007) Safety assessment of castoreum extract as a food ingredient. *International Journal of Toxicology* 26:51 – 55.

G.A. Burdock and S. Teske (2007). Nanotechnology: benefits vs. toxic risks. *Functional Foods and Nutraceuticals. Pp. 18 & 20.*

G.A. Burdock, and I.G. Carabin (2006). Safety assessment of mystic acid as a food ingredient. *Food and Chemical Toxicology* 45:517-529.

G.A. Burdock, I.G. Carabin and J.C. Griffiths (2006). Toxicology and pharmacology of sodium ricinoleate. *Food and Chemical Toxicology* 44, 1689-1698.

R.A. Isbrucker and **G.A. Burdock** (2006). Risk and safety assessment on the consumption of Licorice root (Glycyrrhiza sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. *Regulatory Toxicology and Pharmacology* 46, 167-192.

M.G. Soni, **G.A. Burdock**, M.S. Christian, C.M. Bitler and R. Crea (2006). Safety Assessment of Aqueous Olive Pulp Extract as an Antioxidant or Antimicrobial Agent in Foods. *Food Chemical Toxicology* 221, 17-27.

G.A. Burdock and B. Magnuson (2006) Small threat? *World of Food Ingredients. Pp 61-62.*

G.A. Burdock, I.G. Carabin and J.C. Griffiths (2006). The Importance of GRAS to the Functional Food and Nutriceutical Industries *Toxicology* 221: 12-27.

G.A. Burdock and J.C. Griffiths (2006). Aflatoxin basics: Penicillins deadly cousin – past and present. Petfood Industry Pp. 28-29.

M.G. Soni, I.G. Carabin and **G.A. Burdock**. (2005) Safety assessment of esters of *p*-hydroxybenzoic acid (Parabens) *Food and Chemical Toxicology* 43(7):985-1015.

I.G. Carabin and **G.A. Burdock**. (2005) Overweight and obesity in the United States – an overview. *Update: Food and Drug Law, Regulation and Education* 42(9), 2004: 1513-29.

G.A. Burdock. (Ed) (2004) *Fenaroli's Handbook of Flavor Ingredients.* Fifth Edition. CRC Press, Boca Raton, FL. 2040 pp.

G.A. Burdock and I.G. Carabin (2004) Generally recognized as safe (GRAS): History and description. *Toxicology Letters*. 150(1):3-18.

M.G. Soni, I.G. Carabin, J.C. Griffiths, and **G.A. Burdock.** (2004) Safety of ephedra: lessons learned. *Toxicology Letters.* 2004 150(1): 97-110.

M.G. Soni, **G.A. Burdock**, H.G. Preuss, S.J. Stohs, S.E. Ohia, D. Bagchi (2004) Safety assessment of (-)-hydroxycitric acid and Super CitriMax®, a novel calcium/potassium salt, *Food and Chemical Toxicology* 42, 1513-1529

G.A. Burdock, and I.G. Carabin. (2004) Warning letters, recalls and elixir of death. *Nutritional Outlook* p. 20 – 26.

G.A. Burdock. (2003) Sensory deception: the science of making foods more palatable. *Functional Foods and Nutraceuticals* p. 34-36.

G.A. Burdock. (2003) The GRAS process. *Food Technology* 57(5):17.

G.A. Burdock. (2002) Chapter 3: Status and safety assessment of foods and food ingredients produced by genetically modified microorganisms. In *Biotechnology and Safety Assessment.* Third Edition. (J.A. Thomas and R. Fuchs, Eds.) Elsevier Science, New York. P. 39-83.

M.G. Soni, **G.A. Burdock**, S.L. Taylor, and N. Greenberg. (2002) Evaluation of the health aspects of methyl paraben: a review of published literature. *Food and Chemical Toxicology*. 2002 10: 1335-73.

F. Kotsonis, **G.A. Burdock,** and W.G. Flamm. (2001) Chapter 31: Food Toxicology. In: *Toxicology: The Basic Science of Poisons*. 7th edition C.D. Klaassen (Ed.) Pergamon Press, New York. P. 1049-1088

G.A. Burdock. (Ed.) (2002) *Fenaroli's Handbook of Flavor Ingredients*. Fourth Edition. CRC Press, Boca Raton, FL. 1834 pp.

G.A. Burdock. (2002) Regulation of flavor ingredients. In: *Nutritional Toxicology.* Second Edition. Target Organ Toxicology Series. (F. Kotsonis and M. Mackey, Eds.). Taylor and Frances, New York. p. 316-339.

G.A. Burdock, I.G. Carabin, and M.G. Soni. (2001) Safety assessment of beta-nitropropionic acid: A monograph in support of an acceptable daily intake in humans. *Food Chemistry* 75(1): 1-27.

M.G. Soni, **G.A. Burdock**, S.L. Taylor, and N. Greenberg. (2001) Safety assessment of propyl paraben. *Food and Chemical Toxicology* 39:513-532.

G.A. Burdock, M.G. Soni, and I.G. Carabin. (2001) Evaluation of health aspects of kojic acid in food. *Regulatory Toxicology and Pharmacology* 33:80-101.

M.G. Soni, S.A. White, W.G. Flamm, and **G.A. Burdock.** (2001) Safety evaluation of dietary aluminum. *Regulatory Toxicology and Pharmacology* 33:66-79.

M.G. Soni, H. Kimura, and **G.A. Burdock.** (2001) Chronic studies on diacylglycerol oil in rats. *Food and Chemical Toxicology* 39:317-329.

I.G. Carabin, **G.A. Burdock,** and C. Chatzidakis. (2000) Safety assessment of *Panax* ginseng. *International Journal of Toxicology* 19:293-301.

G.A. Burdock and W.G. Flamm. (2000) Review article: Safety assessment of the mycotoxin cyclopiazonic acid. *International Journal of Toxicology* 19:195-218.

G.A. Burdock, W.G. Flamm, and I.G. Carabin. (2000) Toxicity and mutagenicity studies of DN-50000® and RP-1® enzymes. *Food and Chemical Toxicology* 38:429-442.

G.A. Burdock. (2000) Dietary supplements and lessons to be learned from GRAS. *Journal of Regulatory Toxicology and Pharmacology.* 31:68-76.

G.A. Burdock. (1999) The line between generally recognized as safe and dietary supplements. *Proceedings of the 25th Annual Summer Meeting, July 12-16, 1999.* The Toxicology Forum, Aspen, CO.

G.A. Burdock and W.G. Flamm. (1999) A review of the studies of the safety of polydextrose in food. *Food and Chemical Toxicology* 37:233-264.

G.A. Burdock. (1998) Review of the biologic properties and toxicity of bee propolis (propolis). *Food and Chemical Toxicology* 36:347-363.

G.A. Burdock. (1997) *Encyclopedia of Food and Color Additives*. Volumes I-III. CRC Press, Boca Raton, FL. 3153 pp.

G.A. Burdock. (Ed.) (1995) *Fenaroli's Handbook of Flavor Ingredients,* Volume I - Natural Flavoring Ingredients. Third. Edition. CRC Press, Boca Raton, FL. pp. 1-350

G.A. Burdock, (Ed.) (1995) *Fenaroli's Handbook of Flavor Ingredients,* Volume II - Synthetic Flavoring Ingredients. Third Edition. CRC Press, Boca Raton, FL. pp. 1-990

F. Kotsonis, **G.A. Burdock,** and W.G. Flamm. (1995). Chapter 30: Food Toxicology. In: *Toxicology: The Basic Science of Poisons*. 6th edition C.D. Klaassen (Ed.). Pergamon Press, New York. p. 909-949.

G.A. Burdock and R.A. Ford. (1992). Safety evaluation of dibenzyl ether as a flavoring ingredient. *Food Chemical Toxicology* 30 (7): 559-566.

G.A. Burdock, D.H. Pence, and R.A. Ford. (1992). Safety evaluation of benzophenone. *Food Chemical Toxicology* 29 (11): 741-750.

G.A. Burdock. (Ed.) (1991) *Flavor and Fragrance Materials*. Fifth Edition. Allured Publishing Corporation, Wheaton, IL.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with isobutyl 3-(2-furypropionate). *Acute Toxicology Data* 1(1): 1.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 3-benzyl-4-heptanone. *Acute Toxicology Data* 1(1): 2.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 2-methyl-3-(2-furyl) acrolein. *Acute Toxicology Data* 1(1): 3.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 2-mercaptomethylpyrazine. *Acute Toxicology Data* 1(1): 4.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 2,5-diethyltetrahydrofuran. *Acute Toxicology Data* 1(1): 5.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 2,5-dimethylpyrole. *Acute Toxicology Data* 1(1): 6.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with difurfuryl ether. *Acute Toxicology Data* 1(2): 93-94.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with phenoxyacetic acid. *Acute Toxicology Data* 1(2): 94-95.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 4,5-dimethylthiazole. *Acute Toxicology Data* 1(2): 95-96.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 3-methyl-4-phenyl-3-buten-2-one. *Acute Toxicology Data* 1(2): 96-97.

G.A. Burdock and R.A. Ford. (1990) Acute oral toxicity (LD50) study in the rat with 3-(2-furylacrolein). *Acute Toxicology Data* 1(2): 97-98.

G.A. Burdock, B.M. Wagner, R.L. Smith, I.C. Munro, and P.M. Newberne. (1990) Recent progress in the consideration of flavoring ingredients under the food additives amendment. 15. GRAS substances. *Food Technology* 44(2): 78, 80, 82, 84 & 86.

G.A. Burdock, and R.L. Hall. (1989) Pro-active flavor safety evaluation and management. In: *Trends in Food Product Development, Seventh World Congress of Food Science and Technology, Singapore, October 1987.* A.H. Ghee, T.C. Yam and C. Tan. (Eds.). Singapore Institute of Food Science and Technology, Singapore. p. 359-366.

G.A. Burdock, R.A. Ford, A.M. Bottomley, and D.M. John. (1987). An evaluation of the teratogenic potential of orally administered Phenylethyl Alcohol (PEA). *The Toxicologist* 7(1): 176.

G.A. Burdock, R.H. Cox, S.L. Morseth, and L.W. Smith. (1986). Teratogenicity study of 4-Nitro-N-Methylphthalimide (4-NPI). *The Toxicologist* 6(1): 94.

G.A. Burdock, B.A. Kulwich, R.D. Alsakar, and P.M. Marshall. (1984). 90-Day dog study: Caprolactam. In *Proceedings of a Symposium on an Industry Approach to Chemical Risk Assessment: Caprolactam and related compounds as a case study*, May 15-17, 1984. Industrial Health Foundation, Pittsburgh, PA.

J.A. Trutter, F.E. Reno, **G.A. Burdock,** and D.W. Korte, Jr. (1984). Fertility study with a candidate antimalarial drug in the rat. *Journal of the American College of Toxicology* 3:172.

G.A. Burdock. (1983). Diethanolamine-induced changes in liver and kidney of the neonatal rat. *The Toxicologist* 4 (1): 491.

G.A. Burdock, R. B. Hackett, and L.W. Masten. (1980). A comparison of hepatic microsomal enzyme induction by methadone, phenobarbital and 3-methylcholanthrene in the mouse. *Biochemical Pharmacology* 28:3476-3482.

J.C. Kapeghian, **G.A. Burdock,** and L.W. Masten. (1980). The effect of the route of administration of microsomal enzyme induction following repeated methadone administration in the mouse. *Biochemical Pharmacology* 28:3021-3025.

G.A. Burdock. (1980). Some Toxic Effects of Diethanolamine in the Neonatal Rat. Doctoral Dissertation. School of Pharmacy, University of Mississippi.

G.A. Burdock and L.W. Masten. (1979). Diethanolamine-induced changes in the neonatal rat. *Toxicology and Applied Pharmacology* 48:A30.

J.C. Kapeghian, **G.A. Burdock,** and L.W. Masten. (1977). Effect of the route of administration on microsomal enzyme induction following repeated administration of methadone in the mouse. *Toxicology and Applied Pharmacology* 41:159.

G.A. Burdock, R. B. Hackett, and L.W. Masten. (1976). Dose-response relationship of oral methadone administration and liver microsomal enzyme activity. *Federation Proceedings* 35:469.

J.D. Catravas, I.W. Waters, **G.A. Burdock,** and W.M. Davis. (1975). Haloperidol and propanolol in the treatment of acute amphetamine intoxication in the dog. *Toxicology and Applied Pharmacology* 33:185.

REPORTS

G.A. Burdock. (1993). High Dose Irradiation of Food. Report submitted to the Food Safety Unit, World Health Organization.

W.G. Flamm, P. Lombardo, A. Forbes, W. Nichols, J.B. Little, **G.A. Burdock,** and J.A. Flamm. (1992). Review of the wholesomeness of irradiated food. Report submitted to the Food Safety Unit, World Health Organization.

Dr. Burdock was the author of numerous technical reports while serving as a consultant and a scientist for the Flavor and Extract Manufacturers' Association, Hazleton Laboratories and American Cyanamid. The content of these reports is proprietary and confidential to the sponsoring organizations.

EDITORIAL REVIEW

Regulatory Toxicology and Pharmacology. (1997 to present) Elsevier Science. Manuscript reviews.

Journal of Agricultural and Food Chemistry. (1998 to present) American Chemical Society. Manuscript reviews.

Bee World. (1999 to present) International Bee Research Association. Manuscript reviews.

Italian Journal of Food Science. (1999 to present) Istituto di Industrie Agrarie, University of Perugia Manuscript reviews.

Journal of Agricultural Research. (1999 to present) Agricultural Research Service. Manuscript reviews.

Food and Chemical Toxicology. (1999 to present) Elsevier. Manuscript reviews.

International Journal of Toxicology. (2000 to present) Taylor & Francis. Manuscript reviews,

Update (2005) Food and Drug Law Institute. Editorial Board Member.

INVITED PRESENTATIONS AND ABSTRACTS

G.A. Burdock. Functional Foods: Session I – Functional Foods – What are they? Who wants them? Who regulates them? 4th Inventages Life Venture Summit, Great Exuma, Bahamas, June, 2007.

G.A. Burdock. Functional Foods: Session II - How can Functional Ingredients be Added to Food? 4th Inventages Life Venture Summit, Great Exuma, Bahamas, June, 2007.

G.A. Burdock. Functional Foods – Session IV – Getting to market: Costs, timelines and frequent mistakes. 4th Inventages Life Venture Summit, Great Exuma, Bahamas, June, 2007.

G.A. Burdock. Practical applications of toxicology. University of Mississippi School of Pharmacy, University, MS, May, 2007.

G.A. Burdock. Nanotechnology and Nanotoxicology of Food and Feed Ingredients. Alltech International Feed Industry Symposium, Lexington, KY, May 23, 2007.

G.A. Burdock. Food and Supplement Nanotechnology. Nutracon, Anaheim, CA, March, 2007.

G.A. Burdock. Food Toxicology: An Applied Science. University of Florida, Nutritional Science Department. Gainesville, FL, February, 2007

G.A. Burdock. Nanotechnology: Implications for food and food ingredients. Annual ILSI Meeting. Cancún, México, January, 2007.

G.A. Burdock. Conventional Foods as "Functional Foods," FDA Public Hearing. Washington, DC, 2006.

G.A. Burdock. Nanotechnology in Food and Nanotoxicology. Nano4Food Conference. Atlanta, GA, 2006.

G.A. Burdock. New Dietary Ingredient Notifications. Council of Responsible Nutrition (CRN). Boston, Mass, 2006

G.A. Burdock. Nanotoxicology: a small science or the (big) science of small things? Institute of Food Technologists (IFT). Orlando, FL, 2006

G.A. Burdock. Nutraceuticals & Functional Foods – Strategies for Moving Forward. Nestlé Foods Technical Centre. Lausanne, Switzerland, June, 2006.

G.A. Burdock. Qualified Health Claims: A Critical Juncture. 2005 Institute of Food Technologists Annual Meeting and Food Expo. New Orleans, LA, 2005.

G.A. Burdock. Why Efficacy Trials for Dietary Supplements? Association of Clinical Research Professionals 2005 Conference and Exhibition – North America. Orlando, FL. 2005.

G.A. Burdock. Dietary Supplements and a Method for Determining Safety and Efficacy. Botanical Dietary Supplements: Scientific Perspectives and Public Health Pitfalls Congressional Science Briefings. Washington, DC. 2005.

G.A. Burdock Approving Preservatives: Not a 'Natural' Process. International Symposium on Natural Preservatives in Food Systems. Princeton, NJ. 2005.

G.A. Burdock. Regulatory Issues and the Effect on Your Bottom Line. South Florida Regional Chapter, Institute of Food Technologists. Fort Lauderdale, FL. 2004.

G.A. Burdock. The Dichotomy of Structure Function Claims. Food and Drug Law Institute, Qualified Health Claims Conference. 2004.

G.A. Burdock. Qualified Health Claims and the Role of Independent Experts (and a few other items). 2004 Institute of Food Technologists Annual Meeting and Food Expo. Las Vegas, NV. 2004.

G.A. Burdock. Premarket Notification for New Dietary Ingredient Notifications, Public Meeting. Food and Drug Administration/Center for Food Safety and Nutrition. College Park, MD. 2004.

G.A. Burdock. Efficacy Assessment of Functional Ingredients by Independent Experts. Institute of Food Technologists. Chicago, IL. 2003.

G.A. Burdock. When Accidents Happen – Risk Assessment for the Processing Plant. American Meat Institute. Chicago, IL. 2003.

G.A. Burdock. The GRAS status of Pycnogenol®. Vitafoods International. Geneva, Switzerland. 2003.

G.A. Burdock. Risk Assessment at the Processing Plant. Food Safety Inspection Service, U.S. Department of Agriculture. Washington, DC. 2003.

G.A. Burdock. Hot Topics (Dietary Supplements). Food and Drug Law Institute, Washington, DC 2003.

G.A. Burdock. Overview: Nutraceuticals, Dietary Supplements and Functional Food Ingredients. American College of Toxicology 23rd Annual Meeting. Hershey, PA. 2002.

G.A. Burdock. Pycnogenol®. SupplySide East International Trade Show and Conference. Seacacus, NJ. 2003.

G.A. Burdock. When Accidents Happen – Risk Assessment for the Processing Plant. American Meat Institute, Chicago, IL July, 2002.

G.A. Burdock. Safety Assessment of Foods Derived From Biotech Crops. 42nd Annual Meeting of the Society of Toxicology. Nashville, TN. 2002.

G.A. Burdock. Dietary Supplements at a Crossroads. Food and Drug Law Institute Food Week. Washington, DC. 2002.

G.A. Burdock. Determining the Safety of a Dietary Supplement (Ingredient). Food and Drug Law Institute. Washington, DC. 2002.

G.A. Burdock. Safety Assessment of Botanicals. Worldnutra 2002 3rd Annual International Conference and Exhibition on Nutraceuticals and Functional Foods. San Diego, CA. 2002.

G.A. Burdock. Safety Assessment of Botanicals. ILSI Workshop on Principles for the Safety Assessment of Botanicals and Botanical Preparations in Food and Food Supplements. Marseille, France. 2002.

G.A. Burdock. Ephedra, Is It As Toxic As Reported? 43rd Annual Meeting of the American College of Toxicology. San Antonio, TX. 2002.

G.A. Burdock. The Line Between Generally Recognized As Safe (GRAS) and Dietary Supplements. Toxicology Forum, Aspen, CO. 1999.

G.A. Burdock. DSHEA, GRAS and Functional Foods: Regulatory and Safety Criteria. American Chemical Society. 224th ACS National Meeting. Boston, MA. 2002.

CONTINUING EDUCATION

Clinical Pathology-The Granddaddy of Biomarkers. Society of Toxicology 44th Annual Meeting and Toxexpo. New Orleans, LA. March, 2005

Herbals and Dietary Supplements in Athletic Performance Enhancement: Fact vs. Fiction. Society of Toxicology 43rd Annual Meeting and Toxexpo. Baltimore, MD. March, 2004.

The Safety Assessment of Proteins: Applications to Agricultural Biotechnology. Society of Toxicology 43rd Annual Meeting and Toxexpo. Baltimore, MD. March, 2004.

Choice and Application of Classical, Population or Physiologically-Based PK for Chemical Assessment and Pharmaceutical Development. Society of Toxicology 42nd Annual Meeting and Toxexpo. Salt Lake City, UT, March,2003.

Medicinal Herbals and Dietary Supplements. Society of Toxicology 42nd Annual Meeting and Toxexpo. Salt Lake City, UT, March, 2003.

Dietary Supplement Use in the Elderly. American College of Nutrition Continuing Education Program. NIH Campus, Bethesda, MD. January, 2003.

International Regulatory Approval of Ingredients and Dietary Supplements. Institute of Food Technologists Annual Meeting. Chicago, IL. July, 2003.

Labeling of FDA Regulated Foods. Institute of Food Technologits. Orlando, FL. February, 2001.

Dietary Ingredients or Drugs? Food and Drug Law Institute. Washington, DC. July, 2000.

Reproductive Toxicology. American College of Toxicology – 20th Annual Meeting, Washington, DC. November, 1999

PROFESSIONAL ACHIEVEMENT AND RECOGNITION

Institute of Food Technologists, *Toxicology and Safety Evaluation Division*, (2006 Member at Large); Professional Member (2004 to present).

Society of Toxicology, *Food Safety Specialty Section*, (2005 – 2006 Vice President, 2004 – 2005 Vice President-Elect).

International Society of Regulatory Toxicology and Pharmacology (2005 - 2006 President; 2004 – 2005 Past Vice-President; Councilor)

FDA Advisory Committee Member, *Additives and Ingredients Subcommittee*. 2004 to present.

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EDUCATION:

1956	B.A. - Columbia College, New York, NY
1960	M.D. - Columbia College of Physicians and Surgeons, New York, NY
1960-1965	Internship and Residency in Medicine - New York Hospital (Cornell Medical School), New York, NY Service and Training in Endocrinology and Metabolism at Walter Reed Army Medical Center, Department of Metabolism, Army Medical Center and Army Institute of Research, Washington, DC

MEDICAL LICENSE:

1961-Current	New York State Physician, No.

EMPLOYMENT HISTORY:

2005-present	Principal activities are as President, Glinsmann, Inc.
2000-2005	As below, with change in academic affiliation to Fellow, Center for Food Safety and Nutrition Policy, re-located to Virginia Polytechnic Institute and State University (Virginia Tech), Alexandria, VA. (Completed term as Scientific Advisor to Technical Committee, International Life Sciences Institute.) Appointed as Fellow, American Society for Nutrition.
1998-2000	President, Glinsmann, Inc. Evaluations of safety and health effects of foods, the development of nutritional products, and food-related claims. Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Medical College and Graduate School of Public Policy, Georgetown University, Washington, DC Member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc. Scientific Advisor to Technical Committee on Food Components for Health Promotion ("Functional Foods" or "Nutraceuticals"), International Life Sciences Institute, North America; to the International Food Information Council; and to U.S. and International Food Companies.

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1995-1997 President, Glinsmann, Inc. Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy and Medical School, Georgetown University.
Advisor to the Committee on Nutrition and Electrolytes, United States Pharmacopeial Convention.
Scientific Advisor to the Technical Committee on Food Components for Health Promotion, International Life Sciences Institute, North America.
Expert Consultant, Office of the Deputy Director for Programs, Center for Food Safety and Applied Nutrition (CFSAN or the Center), U.S. Food and Drug Administration (FDA).

1993-1994 Expert in Nutrition, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Department of Health and Human Services (DHHS). Provided management/technical support and coordination for nutrition and dietary guidance-related activities for DHHS among U.S. government agencies, e.g., USDA and National Institute of Health Components.

1992-1993 Visiting Fellow, Georgetown Center for Food and Nutrition Policy and Ceres Forum®, Georgetown Medical School.
Director, Nutrition Policy Staff, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Public Health Service (PHS), DHHS. Provided leadership and coordination among DHHS agencies for Nutrition Policy Board functions; implementation of year 2000 nutrition objectives; development of dietary guidance with U.S. Department of Agriculture; and initiatives in food labeling, safety, and fortification: included program coordination for nutrition monitoring and related research; DHHS representative at international nutrition conferences and committees on interagency nutrition research initiatives; preparation of nutrition and health reports and briefing materials for Congress.

1987-1991 Associate Director for Clinical Nutrition, Division of Nutrition, CFSAN, FDA. Provided program direction for human clinical and population-based research on: food safety; special dietary use and medical food products; novel food ingredients; health impacts of dietary behaviors of select populations; nutrient imbalances that relate to human morbidity and mortality; and techniques for assessing and monitoring nutritional status and adverse reactions to foods, food additives, and contaminants. Chaired the Center's Health Hazard Evaluation Board and Task Force for developing Guidelines for Clinical Testing for Food Additives and served as Senior Center Medical Officer for developing Medical Foods Regulations. Represented Center or Agency interests and positions and provided guidance on human food safety evaluations to industry.

1983-1987 Chief, Clinical Nutrition Branch, Division of Nutrition, CFSAN, FDA. Developed and managed clinical nutrition activities, human food safety assessment programs, and supervised the revision of Nutrition Monitoring Programs. Special assignments included: FDA Research in Human Subjects Committee; CFSAN Health Hazards Evaluation Board;

primary responsibility for Center programs dealing with Clinical Nutrition, Clinical Investigations, Foods for Special Dietary Use, and Health-and Injury-Related Surveillance; Chairperson, Task Forces on Medical Foods Regulation and Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners; and member Task Forces on Research Priorities in Biotechnology, Food Monitoring, Nutrition, and Toxicology.

1978-1983 Chief, Experimental Nutritional Branch and Director of Research, Division of Nutrition, CFSAN, FDA. Developed, managed, and conducted research based on CFSAN priorities; Special assignments included: FDA Research Involving Human Subjects Committee; Center/FDA Science Liaison; Center Health Hazards Evaluation Committee; and Task Forces on Nitrates-Nitrosamines, Research and Research Facilities Plans, Medical Foods Regulations, and the Coordinated Use of Databases to Estimate Exposures.

1965-1978 Chief, Section on Physiological Controls, Laboratory of Biomedical Sciences, National Institute of Child Health and Human Development (NICHHD), National Institutes of Health (NIH), Bethesda, Maryland. Developed and managed research; Chief Intramural Research Contracts Officer (NICHHD); Institute Safety Officer; Member/Chair of Clinical Research Review and Grants and Contracts Review Committees.

1967-1968 Senior Research Investigator, Laboratory of Biomedical Sciences, NICHHD, NIH.

1966-1967 Guest Investigator, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, NIH.

1965-1966 Medical Officer, Research Planning and Program Development, Growth and Development Program, NICHHD, NIH.

1962-1965 Assistant Chief, Department of Metabolism and Attending Physician in Medicine, Walter Reed Army Hospital, and Senior Investigator, Walter Reed Army Institute of Research, and Institute of Pathology, Washington, DC.

PROFESSIONAL MEMBERSHIPS

American Institute of Nutrition, renamed American Society for Nutritional Sciences (Membership Committee, 1986-1991, Fellow, 2002)
American Society for Clinical Nutrition (Membership Committee, 1986-1994: Chair, Publications Management Committee, American Journal of Clinical Nutrition, 1994-1996)
American Physiological Society
Institute of Food Technologists
American Association for the Advancement of Science
American Diabetes Association
New York Academy of Sciences

AWARDS

Fellow, American Society for Nutritional Sciences, 2002

FDA Commendable Service Award: assessing safety and labeling of monosodium glutamate, 1999.

DHHS Secretary's Award for Excellence in Public Service, Implementing the Food Labeling Initiative, 1993.

PHS Citation for exemplary and creative work as a management clinician in nutrition research and investigative matters, 1989

FDA Award of Merit for Leadership, Health Hazard Evaluations, 1988

PHS Unit Commendation, Food Irradiation Safety Evaluation, 1988

PHS Citations for Outstanding Management Performance in Clinical Nutrition and Food Safety Evaluations, 1986-91

PHS Meritorious Service Medal for sustained high quality leadership and outstanding contributions to Nutrition and Food Safety, 1986

FDA Award of Merit for Leadership, Aspartame Clinical Investigation Team, 1986

FDA Commissioner's Special Citation to the Research Involving Human Subjects Committee for unique and outstanding performance to the Food and Drug Administration by promoting research while ensuring the protection of the human subjects involved, 1984

PHS Commendation Medal for sustained high quality leadership and professional accomplishments in planning, implementing, and evaluating nutrition research at the FDA, 1982.

EXAMPLES OF SEMINARS, INVITED LECTURES

July 12, 2003 **Clinical Investigations for Establishing Safety and Efficacy for Food, Annual Meeting of Institute of Food Technologists, Chicago, IL**

June 12, 2001 ***Is There a Need for Cyclical Third Party Reviews? An Affirmative Assessment,*** **10th Annual Conference, Functional Foods for Health, U. Illinois, Chicago, IL**

April 29, 2001 ***Orientation to Functional Foods*****, Pediatric Academic Societies' Annual Meeting, Baltimore, MD**

April 3, 2001 ***Safety Regulation for Dietary Supplements: The System Needs a Significant Change*** **- Toxicology Roundtable, Experimental Biology, Orlando, FL**

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August 3, 2000 *Communicating Benefits to the Consumer: FTC, FDA, and Claim Substantiation.* Warner-Lambert-Pfizer Nutrition Symposium, Morris Plains, NJ

Jan. 27, 2000 *Concepts, Standards, and Substantiation of Effects of Functional Foods* Workshop on Functional Foods, Kappel am Albis, Switzerland

June 14, 1999 *Scientific Concepts, Standards, and Substantiation* American Association of Cereal Chemists Annual Meeting, Functional Foods – Strategies for the Food Industry, Newport Beach, CA

March 30,1999 *Distinguishing a Nutrient from a Drug* Ceres Forum® on What is a Nutrient? Georgetown University Conference Center, Washington, DC

June 19, 1998 *The Role of Clinical Investigations in Establishing Safety and Efficacy for Functional Foods* Course: A Global Perspective on Regulatory Approval for Food Ingredients, Nutraceuticals, and Dietary Supplements. Institute of Food Technologists Annual Meeting '98, Atlanta, GA

April 18, 1998 *Functional Foods: Regulatory Considerations* Symposium: Functional Foods for Health Promotion: A Public Health Opportunity? Experimental Biology '98, San Francisco, CA

Oct. 27, 1997 *Functional Foods: Regulatory Considerations* Panel: Are Consumers Ready for Functional Foods? American Dietetic Association Annual Meeting, Boston, MA

March 13, 1997 *Overview of Research on Health Benefits from Specific Phytochemicals* Panel on Demystifying Functional Foods, Public Voice 20th Annual National Food Policy Conference, Washington, DC

Nov. 28, 1996 *Dietary Guidance and the U.S. Food Supply: Focus on Infants and Young Children* Health Visitors Association Centenary Conference, Harrogate, England

Oct.17, 1996 *U.S. Health Claims: Rational and Lessons Learned* Symposium on Health Claims for Foods in Canada, U. Toronto, Ontario, Canada

Feb. 26, 1996 *Statements of Nutritional Support: Claim Substantiation* Symposium on the New Structure/Function Claims Frontier Under DSHEA, National Nutritional Foods Association, Washington, DC

Feb. 9, 1996 *Regulatory Framework: United States* Workshop on Antioxidants, ILSI-Europe, Brussels, Belgium

000263

Jan. 24, 1996 *Perspective on the Future of Designer and Functional Foods: Definitions, Regulatory Perspective, and Health Claims*
Annual Meeting, ILSI, Cancun, Mexico

Oct. 2, 1995
Oct. 3 *Food Labeling and Food Safety Requirements in the United States* and *International Developments in Food Fortification, Foods for Special Dietary Use, and Functional Foods*, Seminars, Doosan Technical Center, Seoul, Korea

Sept. 26, 1995
Sept. 28 *Functional Foods in North America and Regulatory Aspects of Functional Foods*
First International Conference on East-West Perspectives on Functional Foods, ILSI-Southeast Asia, Singapore

PUBLICATIONS

Carpenter, M.B., Glinsmann, W.H., Fabrega, H. Effects of secondary striatal lesions upon cerebella dyskinesia. Neurology. 8: 352, 1958.

Carpenter, M.D., Fabrega, H., Glinsmann, W.H. Physiological deficits occurring with lesions of labyrinth and fastigial nuclei. J. Neurosphysiol. 22: 22, 1959.

Fiala, S., Glinsmann, W.H., Fiala, A.E. Deoxyribonucleotidase activity during carcinogenesis in rat liver. Naturwiss. 46: 635, 1959.

Swank, R.L., Glinsmann, W.H., Sloop, P. The production of fat embolism in rabbits by feeding high fat meals. Surgery, Gynecology and Obstetrics 110: 9, 1960.

Fiala, S., Fiala, A.E., Glinsmann, W.H. Deoxycytidylic deaminase in carcinogenic rat liver. Naturwiss, 47: 45, 1960.

Fiala, S., Glinsmann, W.H. Acid soluble ribonucleotides in adrenal tissue after hormonal stimulation. Endocrinology 68: 479, 1961.

Fiala, S., Fiala, A., Glinsmann, W.H. Mechanism of carcinogenesis and proliferation of tumor cells in rat liver. Pathologie-Biologie 9: 613, 1961.

Fiala, S., Glinsmann, W.H. A unified concept of cancerogenesis. Neoplasma 10: 1, 1963.

Glinsmann, W.H. Renal micropuncture studies during exsanguination hypotension. Clin. Res. 12: 252, 1964.

Ericsson, J.L.E., Glinsmann, W.H. Focal degenerative cytoplasmic alterations in liver cells induced by hypoxia. Electron microscopic observations. Acta Path. Microbial. Scand. 64: 151, 1965.

Ericsson, J.L.E., Glinsmann, W.H. Observations on the subcellar organization of hepatic parenchymal cells I. golgi apparatus, cytosomes, and cytosegresomes in normal cells. Lab. Invest. 15: 750, 1966.

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Glinsmann, W.H., Ericsson, J.L.E. Observations on the subcellular organization of hepatic parenchymal cells II. Evolution of reversible alterations induced by hypoxia. Lab. Invest. 15: 762, 1966.

Glinsmann, W.H., Mertz, W. Effect of trivalent chromium on glucose tolerance. Metabolism 15: 510, 1966.

Glinsmann, W.H., Feldman, F.J., Mertz, W. Plasma chromium during glucose loading. Science 152: 1243, 1966.

Mortimore, G., Mondon, C.E., King, E., Glinsmann, W.H. Effect of insulin on alterations in liver glycogen. Am. J. Physiol. 212: 179, 1967.

Glinsmann, W.H., Mertz, W. Studies on the relationship between chromium and glucose tolerance in man. Proc. VIIth Internat. Cong. Nutrition, Vol. 5, p. 714, 1967.

Glinsmann, W.H., Mortimore, G.E. Influence of glucagon and 3', 5'-AMP on insulin responsiveness of the perfused rat liver. Am. J. Physiol. 216: 698, 1969

Glinsmann, W.H., Hern, E.P., Linarelli, L.G., Farese, R.V. Similarities between effects of adenosine 3', 5'-monophosphate and guanosine 3', 5'-monophosphate on liver and adrenal metabolism. Endocrinology 85: 711, 1969.

Farese, R.V., Linarelli, L.G., Glinsmann, W.H., Ditzion, B.R., Paul, M.I., Pauk, G.L. Persistence of the steroidogenic effect of adenosine-3', 5'-monophosphate in vitro: Evidence for a third factor during the steroidogenic effect of ACTH. Endocrinology 85: 867, 1969.

Linarelli, L.G., Weller, J.L., Glinsmann, W.H. Stimulation of fetal rat liver tyrosine aminotransferase activity in utero by 3', 5'-cyclic nucleotides. Life Sciences 9: 535, 1970.

Klein, D.C., Berg, G.R., Weller, J., Glinsmann, W.H. Pineal gland: dibutyryl cyclic adenosine monophosphate stimulation of labelled melatonin production. Science 167: 1738, 1970.

Glinsmann, W.H., Pauk, G., Hern E. Control of rat liver glycogen synthetase and phosphorylase activities by glucose. Biochem. Biophys. Res. Comm. 39: 774, 1970.

Berg, G., Glinsmann, W.H. Cyclic AMP in depression and mania. Lancet 1: 834, 1971.

Sherline, P., Lynch, A., Glinsmann, W.H. Cyclic AMP and adrenergic receptor control of rat liver glycogen metabolism. Endocrinology 91: 680, 1972.

Eisen, H.J., Glinsmann, W.H., Sherline, P. Effect of insulin on glycogen synthesis in fetal rat liver in organ culture. Endocrinology 92: 584, 1973.

Zieve, F.J., Glinsmann, W.H. Activation of glycogen synthetase and inactivation of phosphorylase kinase by a single phosphoprotein phosphatase. Biochem. Biophys. Res. Comm. 50: 872, 1973.

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Eisen, H.J., Goldfine, I.E., Glinsmann, W.H. Regulation of hepatic glycogen synthesis during fetal development: roles for hydrocortisone, insulin receptors. Proc. Nat. Acad. Sci. (U.S.A.) 70: 759, 1973.

Sherline, P., Eisen, H., Glinsmann, W.H. Acute hormonal regulation of cyclic AMP content and glycogen phosphorylase activity in fetal liver in organ culture. Endocrinology 94: 935, 1974.

Glinsmann, W.H., Eisen, H.J., Lynch, A., Chez, R.A. Glucose regulation by isolated near-term fetal monkey liver. Pediat. Res. 9: 600, 1975.

Eisen, H.J., Glinsmann, W.H. Partial purification of glucocorticoid receptor from rat liver using DNA-cellulose. J. Steroid Biochem. 6: 1171, 1975.

Huang, K. P., Huang, F.F., Glinsmann, W.H., Robinson, J.C. Regulation of glycogen synthetase activity by two kinases. Biochem. Biophys. Res. comm. 65: 1163, 1975.

Huang, F.L., Glinsmann, W.H. Inactivation of rabbit muscle phosphorylase phosphatase by cyclic AMP-dependent kinase. Proc. Nat. Acad. Sci. (U.S.A.) 72: 3004, 1975.

Sparks, J.W., Lynch A., Glinsmann, W.H. Regulation of rat liver glycogen synthesis and activities of glycogen cycle enzymes by glucose and galactose. Metabolism 25: 47, 1976.

Sparks, J.W., Lynch A., Chez, R.A., Glinsmann, W.H. Glycogen regulation in isolated perfused near-term monkey liver. Pediat. Res. 10: 51, 1976.

Huang, F.L., Glinsmann, W.H. A second heat-stable protein inhibitor of phosphorylase phosphatase from rabbit muscle. FEBS Lett. 62: 326, 1976.

Eisen, H.J., Glinsmann, W.H. Partial purification of the glucocorticoid receptor from rat liver: a rapid two-step procedure using DNA-cellulose. Biochem, Biophys, Res. Comm. 70: 367, 1976.

Huang, K. P., Huang, F.L., Glinsmann, W.H., Robinson, J.C. Effect of limited proteolysis on activity and phosphorylation of rabbit muscle glycogen synthetase. Arch. Biochem. Biophys. 173: 6, 1976.

Huang, F.L., Glinsmann, W.H. Separation and characterization of two phosphorylase phosphatase inhibitors from rabbit skeletal muscle. European J. Biochem. 70: 419, 1976.

Nakai, C., Glinsmann, W.H. Effects of polyamines on nucleosidediphosphate kinase activity. Biochem. Biosphys. Res. Comm. 74: 1419, 1977.

Nakai, C., Glinsmann, W.H. Inhibition of rabbit skeletal muscle phosphorylase phosphatase by spermine. Molec. Cellular Biochem. 15: 141, 1977.

Nakai, C., Glinsmann, W.H. Protein inhibitors of phosphorylase phosphatase and cyclic AMP-dependent protein kinase from rabbit muscle. Molec. Cellular Biochem. 15: 133, 1977.

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Glinsmann, W.H., Huang, F.L., Tao, S., Nakai, C. Control of rabbit muscle phosphorylase phosphatase activity. Proc. FEBS Congress, Copenhagen. Elsevier Press, 1977.

Huang, F., Tao, S., Glinsmann, W.H. Multiple forms of protein phosphatase inhibitors in mammalian tissues. Biochem. Biophys. Res. Comm. 78: 615, 1977.

Eisen, H.J., Glinsmann, W.H. Maximizing purification of the activated glucocorticoid receptor by DNA-cellulose chromatography. The Biochem. J., Molecular Aspects, 17: 1977.

Nakai, C., Glinsmann, W.H. Interaction between polyamines and nucleotides. Biochemistry 16: 5636, 1977.

Buffone, G.J., Sparks, J.W., Johnson, J., Iosefsdin, M., Lewis, S.A., Glinsmann, W.H. Evaluation of an immobilized enzyme electrode system for the monitoring of therapeutic galactose concentrations in neonates. Clin. Chem. 23: 1166, 1977.

Tao, S.H., Huang, F.L., Lynch, A., Glinsmann, W.H. Control of rat skeletal muscle phosphorylase activity by adrenalin. Biochem. J. 176: 347, 1978.

Simpkins, R.A., Eisen, H.J., Sparks, J.W., Glinsmann, W.H. Development of gluconeogenesis from galactose by fetal liver explants in organ culture. Devel. Biol. 66: 353, 1978.

Simpkins, R.A., Eisen, H.J., Glinsmann, W.H. Functional integrity of fetal rat liver explants cultured in a chemically defined medium. Devel. Biol. 66: 344, 1978.

Sparks, J.W., Avery, G.B., Fletcher, A.B., Simmons, M.A., Glinsmann, W.H. Parenteral galactose therapy in the glucose-intolerant premature infant. The J. of Pediatrics 100: 255, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Urinary chromium excretion of human subjects; effects of chromium supplementation and glucose loading. Amer. J. Clin. Nutr. 36: 1184, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Mertz, W., and Glinsmann, W.H. Chromium supplementation of human subjects: effects on glucose, insulin, and lipid variables. Metabolism 32: 894, 1983.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters. J. Nutr. 113: 276, 1983.

Yetley, E.A., Glinsmann, W.H. Regulatory issues regarding iron bioavailability. Food Technol. 37: 121, 1983.

Archer, D.L., Glinsmann, W.H. Hypothesis: Intestinal infection and malnutrition initiate acquired immune deficiency syndrome (AIDS). Nutrition Research 5: 9, 1985.

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Archer, D.L., Glinsmann, W.H. Enteric infections and other co-factors in AIDS: Possible intervention points from a historical perspective. Immunology Today 6: 292, 1985.

Glinsmann, W.H., Irausquin, H., Park, Y.K. Evaluation of health aspects of sugars contained in carbohydrate sweeteners; report of task force 1986. J. Nutr. 116 - supplement 11: S1-216, 1986.

Glinsmann, W.H., Tollefson, L.K., Hattan, D.G. Evaluation of adverse reactions reported to be associated with the use of aspartame-containing products. *Proc. International Aspartame Workshop*, Ed. P.B. Dews. Publ. Int'l Life Sci. Inst. - Nutr. Found., Washington, D.C., 1987.

Tollefson, L.K., Barnard, R.J., Glinsmann, W.H. Monitoring of adverse reactions to aspartame. Proc. *First International Meeting on Dietary Phenylalanine and Brain Function*. Ed. R.J. Wurtman and E. Ritter-Walker, p. 347-72, Publ. Ctr. for Brain Sciences and Metabolism Charitable Trust, Cambridge, Massachusetts, 1987.

Glinsmann, W.H., L.K. Tollefson, Park, Y.K. Regulatory status and health aspects of sweeteners. In *Sweeteners: Health Effects*, Ed. G.M. Williams, p. 263-74, Princeton Sci. Publ. Inc., Princeton, New Jersey, 1988.

Glinsmann, W.H., Dennis, D.A. Regulation of nonnutritive sweeteners and other sugar substitutes. In *Sweeteners*, Eds. N. Kretchmer and C. Hollenbeck, p. 257-85, CRC Press, Boca Raton, Florida, 1991.

Glinsmann, W.H. Usefulness of clinical studies in establishing safety of food products. In *ACS Symposium Series, No 484, Food Safety Assessment*, Eds. J.W. Finley, S.F. Robinson, and D.J. Armstrong, p. 105-13, Amer. Chem. Society, 1992.

Vanderveen, J.E., Glinsmann, W.H. Fat substitutes: a regulatory perspective. In Ann. Rev. Nutr., Vol. 12, Eds. R.E. Olsen, D.M. Bier, and D.B. McCormick, p. 473-87, Annual Reviews Inc., Palo Alto, California, 1992.

Workshop on Dietary Fatty Acids and Thrombosis, March 1991, Proceedings. Eds. J.C. Hoak, W.H. Glinsmann, J.T. Judd. Amer. J. Clin. Nutr. 56 - supplement 4: 7835-8265, 1992.

Hyman, F.N., Sempos, E., Saltsman, J., Glinsmann, W.H. Evidence for success of caloric restriction in weight loss and control: summary of data from industry. *NIH Technology Assessment Conference on Methods for Voluntary Weight Loss and Control*. Ann. Int. Med. 119: 681-87, 1993.

Glinsmann, W.H., Bowman, B. Public health significance of dietary fructose. In *Health Effects of Dietary Fructose*, Eds. A.L. Forbes and B.A. Bowman. Amer. J. Clin. Nutr. 58 - Supplement 5:820-23, 1993.

Glinsmann, W.H., Park, Y.K. Perspective on the 1986 FDA assessment of the safety of carbohydrate sweeteners; uniform definitions and recommendations for future assessments. Amer. J. Clin. Nutr. 62 (suppl): 161S-9S, 1995.

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Shank, F.R., Carson, K., Glinsmann, W.H. Putting things in perspective: building on our experience. (1995 Ceres Forum: *Fortifying Policy with Science - The Case for Folate*) J. Nutrition 126 (suppl): 781-87S, 1996.

Glinsmann, W. Focus on substitutes that alter gastrointestinal physiology. (*Proceedings of the Workshop on Safety and Regulatory Aspects of Macronutrient Substitutes,* Nov. 1994, Washington, D.C.) Regulatory Toxicol. and Phamacol. 23(suppl): S27-30, 1996.

Glinsmann, W. H., Bartholmay, S.J., Coletta, F. Dietary guidelines for infants: a timely reminder. Nutrition Reviews 54:50-57, 1996.

Glinsmann, W.H. Functional foods in North America. In *Proceedings of First International Conference on Functional Foods*, Singapore, September 1995. Eds. F.M. Clydesdale and S.H. Chan. Nutrition Reviews, Vol. 54, No. 11, Part II, S33-37, 1996.

Glinsmann, W.H. Perspective on functional food development and commercialization. J. Nutraceuticals, Functional & Medical Foods, 1:89-93, 1997.

Glinsmann, W.H. Functional foods: an overview of regulatory status. Nutrition Today, 34:1-4, 1999.

Glinsmann, W. Functional Foods: Special Considerations in the Pediatric Diet. Pediatric Basics, 92:2-15, 2000.

Flamm, G., Glinsmann, W., Kritchevsky, D., Prosky, L., Roberfroid, M. Inulin and oligofructose as dietary fiber: A review of the evidence. Critical Reviews in Food Science Nutrition, 41:353-62, 2001.

Campbell, E., Glinsmann, W., Rheinhardt, W., Claims regarding the health benefits of foods. Nutrition and the M.D., 28:1-5, 2002.

Borzelleca, J.F., Glinsmann, W., Kennepohl, K. Safety aspects of diglyceride oil. In *Diacylglycerol Oil*, Eds. Y Katsuragi, T. Yasukawa, N. Matsuo, B. Flickinger, I. Tokimitsu, and M. G. Matlock, p. 165-81, AOCS Press, Champaign, Illinois, 2004.

Yasunaga, K, Glinsmann, W. H., Seo, Y., Katsuragi, K., Kobayashi, S., Flickinger, B., Kennepohl, K., Yasukawa,T., Borzelleca, J. F., Safety aspects regarding the consumption of high-dose dietary diacylglycerol oil in men and women in a double-blind controlled trial in comparison with consumption of a triacylglycerol control oil. Food and Chemical Toxicology 42: 1419-1429, 2004.

Forshee, R. A., Storey, M.L., Allison, D.B., Glinsmann, W.H., Hein, G.L., Lineback, D.R., Miller, S.A., Nicklas, T.A., Weaver, G.A., White, J.S. A critical examination of the evidence relating high fructose corn syrup and weight gain. Critical Reviews in Food Science and Nutrition, (in press).

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CURRICULUM VITAE

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Tufts University School of Medicine
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Scientist,
Jean Mayer USDA Human Nutrition Research
Center on Aging at Tufts University

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E-mail: norman.krinsky@tufts.edu

Born:
Married:
Children:

EDUCATION

1948 B.S.	University of Southern California, Los Angeles, CA
1950 M.S.	University of Southern California, Los Angeles, CA (Biochemistry and Nutrition)
1953 Ph.D.	University of Southern California, Los Angeles, CA (Biochemistry, with Harry J. Deuel, Jr.)

PROFESSIONAL EXPERIENCE

1953-55	U.S. Public Health Service Post-doctoral Fellow; Harvard University (with George Wald)
1955-56	National Council to Combat Blindness Post-doc. Fellow; Harvard University (with George Wald)
1956-60	Instructor, Lecturer, Department of Biology, Harvard University
1960-64	Assistant Professor, Department of Pharmacology, Tufts University School of Medicine (TUSM)
1964-67	Associate Professor, Department of Pharmacology, TUSM
1967-69	Associate Professor, Department of Biochemistry, TUSM
1969-70	Professor, Department of Biochemistry, TUSM
1970-87	Professor, Department of Biochemistry and Pharmacology, TUSM
1973	Visiting Professor, Department of Physiology/Anatomy, University of California, Berkeley, CA
1981-82	Research Associate, Boston Veterans Administration Medical Center
1987-2000	Professor, Department of Biochemistry, Tufts University School of Medicine
1993-present	**Scientist, USDA Human Nutrition Research Center on Aging, Tufts University**
2000-present	**Professor Emeritus, Department of Biochemistry, Tufts Univ. School of Medicine**

RESEARCH INTERESTS

Function and metabolism of carotenoids, including antioxidant and anticarcinogenic actions and metabolism to retinoic acid and apocarotenoids. Role of carotenoids in primate macula. Analysis of tissue carotenoids. Biological oxidant damage, and mechanisms of lipophilic and hydrophilic protection.

EDITORIAL BOARDS

1984-1986	Journal of Free Radicals in Biology and Medicine
1984-1986	Advances in Free Radical Biology and Medicine
1987-1994	Free Radical Biology and Medicine
1993-2003	Archives of Biochemistry and Biophysics

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1994-2002	Free Radical Research
1997-present	Environmental & Nutritional Interactions
2002-present	Nutrition Reviews

PUBLICATIONS (see attached listing)

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PROFESSIONAL SOCIETIES

1948	American Association for the Advancement of Science (Fellow, 1966)
1949	Society of the Sigma Xi
1951	American Chemical Society
1951	New York Academy of Sciences
1959	American Society for Biochemistry and Molecular Biology
1972	American Society for Photobiology
1982	Society for Free Radical Research
1988	The Oxygen Society (2003: Society for Free Radical Biology and Medicine)
1988	International Society for Nutrition and Cancer
1993	European Retinoid Research Group
1994	International Carotenoid Society
1998	American College of Nutrition (Fellow, 1998)
1999	International Society for Coenzyme Q Research

PROFESSIONAL ACTIVITIES/HONORS

1950	Phi Sigma Award in the Biological Sciences, University of Southern California
1952	Phi Lambda Upsilon
1966	Fellow, American Association for the Advancement of Science
1967-1968	President, Tufts University Chapter, Society of the Sigma Xi
1975-1981	Secretary-Treasurer, American Society for Photobiology
1978	Organizing Committee, Fifth International Symp. on Carotenoids and Vitamin A, Madison, WI
1980	Co-Chairman, Workshop on Biological Chemiluminescence, American Society for Photobiology, Colorado Springs, CO
1981	Chairman, 1st Gordon Research Conference on "Oxygen Radicals in Biology and Medicine" Ventura, CA
1981-1984	Teaching Award, Tufts University School of Medicine
1982-1983	President, American Society for Photobiology
1984	Treasurer, Ninth International Congress on Photobiology, Philadelphia, PA
1987	Organizing Committee, Fourth International Congress on Oxygen Radicals, La Jolla, CA
1987	Chairman, Eighth International Symposium on Carotenoids, Boston, MA
1988-1991	Council, The Oxygen Society
1989-2000	Executive Committee, International Society for Nutrition and Cancer
1990	Lottie Arnrich Lecturer, Dept of Food & Nutrition, Iowa State University, Ames, IA May 1. 1990
1992	Chairman, 1st Gordon Research Conf. on "Chemistry and Biology of Carotenoids", Oxnard, CA
1993	Co-Chair, New York Academy of Sciences Conference on "Carotenoids in Human Health ", San Diego, CA
1993	Honorary Member, The Vitamin Society of Japan
1993	Distinguished Faculty Award, Tufts University School of Medicine
1994	Fellow, The Oxygen Society
1994	Co-Chair, Second International Conference on "Antioxidant Vitamins and ß-Carotene in Disease Prevention", October 10-12, Berlin, Germany
1994-1999	President, New England Free Radical/Oxygen Society
1995	Co-Chair, FASEB Summer Research Conference on "Antioxidant Nutrients in the Cellular Biology of Health and Disease", Saxtons River, VT
1995-1996	Secretary-General, The Oxygen Society
1996-1998	Advisory Committee, International Antioxidant Research Centre, King's College, London
1997	Mordechai Avron Memorial Lecturer, Nikken Sohonsha Corp., Gifu and Tokyo, Japan, 2/21/97
1997	Award Lecturer, American College of Nutrition, New York, NY September 27, 1997
1997-1999	Chair, Panel on Antioxidants and Related Nutrients, Food & Nutrition Board, Inst. of Med./NAS

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1998	Fellow, American College of Nutrition
1998	Dozor Visiting Professor, Ben-Gurion University of the Negev, Beer-Sheva, Israel
1999	Visiting Scholar, Linus Pauling Institute, Oregon State University, Corvallis, OR
1999	Honorary Member, Oxygen Club of California
1999	Lars Ernster Lecture, Oxygen Club of California 1999 World Congress, Santa Barbara, CA
2000	Robert S. Harris Lecture, Massachusetts Institute of Technology, Cambridge, MA
2001	National Associate, National Academy of Science/National Research Council
2002	Chair, Committee on the Examination of the Evolving Science for Dietary Supplements, Food & Nutrition Board, IOM/NAS
2003-2007	Member, Food Advisory Committee, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety, FDA
2003-2007	Chair, Nutrition Subcommittee, Food Advisory Committee, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety, FDA

RESEARCH TRAINEES: PRE-DOCTORAL		PRESENT POSITION
1964-1967	"Chemical and Biochemical Reduction of Carotenoid Epoxides"	Professor, Banting & Best Dept. of Medical Research University of Toronto, Toronto, Canada
1967-1974	"The Concentration, Turnover, Exchange & Enrichment of Cholesterol in Mitochondria and Mitochondrial Fractions"	Private Practice of Medicine New York, New York
1968-1974	"Mechanism of Photodynamic Oxidation and Lysis of a Model Membrane System (Liposomes)"	Associate Professor Department of Medicine Univ. of Texas, San Antonio, TX
1973-1980	"Kinetic and Structure-Function Studies Concerning Human Myeloperoxidase	Senior Scientist Seradyne.1200 S. Madison Avenue Indianapolis, IN
1987-1991	"Characterization of Tissue Carotenoids, Their Breakdown Products, and Relationship to Biological Metabolites"	Assistant Professor University of Massachusetts Lowell, MA

RESEARCH TRAINEES: POST-DOCTORAL	PRESENT POSITION
1963-1965	Associate Director (Retired), National Institute of Nutrition Hyderabad, India
1964-1968	Assoc. Professor (Med), Channing Laboratory Harvard Medical School, Boston, MA
1966-1967	Consultant, New York, NY
1971	Chairman, Environmental Sciences Program

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	University of Massachusetts, Boston, MA
1972	Director, Dermal & Ocular Branch Division of Toxicology, Food & Drug Administration, Washington, DC
1977	Research Associate, Sylvius Laboratoria, Univ. of Leiden, Leiden, The Netherlands
1979-1989	Scientist, Duracell Technology Center, Needham, MA
1988	Professor, Nutrition Physiology Institute für Physiologie, Veterinary Faculty University of Leipzig. D-7010, Leipzig, FRG
1990-1992	Institute of General Pathology Catholic University, Rome. Italy
1996-1999	USDA HNRCA, Boston, MA
1999-2003	University of Milan, Milan, Italy

RESEARCH TRAINEES - UNDERGRADUATES/MEDICAL STUDENTS

1964-1966	[redacted], TUSM, 1968
1966-1967	[redacted], TUSM, 1968
1973-1974	[redacted], Tufts University, 1973
1974	[redacted], Tufts University, 1974
1974	[redacted], Tufts University, 1974
1974	[redacted], Tufts University, 1974
1974	[redacted], Tufts University, 1974
1974	[redacted], TUSM, 1977
1974	[redacted], Hampshire College, 1975
1974-1975	[redacted], Tufts University, 1975
1975-1976	[redacted], Tufts University, 1979
1977-1978	[redacted], Tufts University, 1979
1979-1980	[redacted], Tufts University, 1981
1980	[redacted], Tufts University, 1980
1980	[redacted], Oberlin College, 1981
1980	[redacted], Tufts University, 1981
1983-1984	[redacted], Tufts University, 1984
1983-1984	[redacted], TUSM, 1987
1984-1985	[redacted], Tufts University, 1985
1988-1989	[redacted], Tufts University 1990
1991	[redacted], Wellesley College 1992

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FACULTY ACTIVITIES

TUFTS UNIVERSITY SCHOOL OF MEDICINE

1963-1966	Pre-Clinical Curriculum Study (Director)
1963-1967	Curriculum Committee
1967-1969	Faculty Medical Education Group
1968-1971	Committee on Extended Educational Opportunity (Chairman)
1968-1969	Health Information Sciences Committee
1969-1970	Advisory Committee on Medical Education
1970-1972	Committee on Faculty Affairs
1973-1978	Committee on Educational Affairs
1974-1975	Fringe Benefits Subcommittee, Faculty Affairs Committee
1974-1975	Admissions Committee
1977	Medical Bylaws Committee
1978-1979	Faculty Affairs Committee (Chairman)
1979-1981	Budgetary Advisory Subcommittee, Faculty Affairs Committee
1979-1981	Boston Tuition Scholarship Benefits Committee
1980-1983	Curriculum Coordinator, Year I
1980-1983	Student Promotions Committee
1981-1982	Ad Hoc Committee on Student Performance Evaluation
1981	Special Program Development Committee
1981-1983	Library and Educational Spaces Planning Subcommittee
1981-1986	Curriculum Committee
1982-1983	Committee on the Teaching of Nutrition at TUSM (Co-Chairman)
1982-1985	Ad Hoc Grievance Committee
1982-1983	Basic Science Appointment, Promotion and Tenure Committee
1983-1985	Task Force on Curriculum Planning
1983-1985	Faculty Advisor
1984-1987	Course Director, Biochemistry
1984-1987	Faculty Affairs Committee
1985-1987	Curriculum Committee Sub-Committee on Curriculum Planning and Implementation
1985-1990	Problem-Based Learning Committee
1988-1989	Curriculum Committee
1989-1992	Faculty Affairs Committee (Chairman, 1990-1992)
1991-1992	Self-Study Sub-Committee on Governance and Administration, LCME, (Chairman)
1992-1993	Steering Committee, RWJ Foundation Generalist Physician Initiative Program
1993-1994	Member, Faculty Senate
1994-1995	Member, Core Curriculum Collaborators Group
1994-1996	Member, Faculty Prizes/Awards Committee
1996-1998	Self-Study Sub-Committee on Governance and Administration, LCME

TUFTS-NEW ENGLAND MEDICAL CENTER

1963	Committee on the Role of the Basic Scientist in the Medical Center, (Chairman)
1968-1969	Audio-visual Task Force
1970-1971	Advisory Committee on Minority Opportunity and Planning
1982-1984	Board of Directors, Women's Resource Center

TUFTS UNIVERSITY

1966-1968	Policy and Program Committee, Graduate School of Arts and Sciences
1967-1973	Molecular Basis of Biological Phenomena Program (Chairman)
1968-1971	Committee on Equal Educational Opportunity, Faculty of Arts and Sciences

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1968-1970	Faculty Representative, Trustees Committee on Honorary Degrees
1970-1971	University-wide Committee on Equal Employment Advancement
1970-1971	Committee on Educational Planning
1978-1979	Advisory Committee on University Investments
1986-1987	Faculty Representative, Trustees Academic Affairs Committee
1993-1999	University-wide Benefits Advisory Committee

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SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

1983-1984 Faculty Secretary
1983-1987 Nominating Committee (Chairman)

TUFTS UNIVERSITY SCHOOL OF DENTAL MEDICINE

1964-1965 Curriculum Committee

JEAN MAYER HUMAN NUTRITION RESEARCH CENTER ON AGING AT TUFTS UNIVERSITY

1995-2000 Promotions Committee

TEACHING EXPERIENCE

HARVARD UNIVERSITY

1956-1960 Biology 191 (Experimental Biochemistry)
1956-1960 Undergraduate Advisor, Department of Biology
1958 Biology 190 (General Biochemistry, with George Wald)

TUFTS UNIVERSITY SCHOOL OF MEDICINE

1960-1967 Pharmacology
1967-1999 Biochemistry (Course Director, 1984-1987, 1994)
1968-1986 Neuropharmacology
1974-1979 Biochemistry of Disease
1980-1985 Principles of Pharmacology
1985-1991 Problem-Based Learning Facilitator
1990 Nutrition and Medicine Facilitator

TUFTS UNIVERSITY SCHOOL OF DENTAL MEDICINE

1960-1966 Pharmacology
1966-1968 Basic Health Sciences
1968-1988 Pharmacology
1984-1993 Biochemistry

TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE

1979-1985 Biochemistry
1980-1985 Neuropharmacology
1980-1985 Pharmacology

TUFTS UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

1960-1967 Graduate Pharmacology
1970 Mitochondrial Membranes and Bacterial Envelopes (BCM 294)
1972 Energy Flow in Biological Systems (BCM 214)
1974, 1978 Metabolic Pathways (BCM 213)
1978, 1982 Membranes (BCM 211)
1981- 1982 Advanced Biochemistry (BCM 223)

TUFTS UNIVERSITY SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

1984 Membranes (BCM 221)
1984-1999 Graduate Biochemistry (BCM 223)

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1985 Recent Advances in Neurochem. and Neuropharm. (BCM 220)
1995 Free Radicals in Biology & Medicine (BCM 293)

TUFTS UNIVERSITY SCHOOL OF NUTRITION

1991, '93, '99 Dietary Antioxidants and Degenerative Diseases (Nutrition 291-DA)

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SCIENTIFIC CONFERENCES AND MEETINGS: INVITED PARTICIPATION

1. Invited Speaker: The Lipoprotein Nature of Rhodopsin Symposium on "Visual Mechanisms" (Sponsored by National Institutes of Health) Bethesda, Maryland, September 11-12, 1957.

2. Invited Speaker: The Role of Carotenoid Pigments as Protective Agents against Photosensitized Oxidations in Chloroplasts. Symposium on "Biochemistry of Chloroplasts" NATO Advanced Study Institute, Aberystwyth, Wales, U.K., August 5-9, 1965.

3. Invited Speaker: A Biochemical Basis for Carotenoid Function in Green Plants and Algae. Joint Japan-U.S. Seminar on "Carotenoid Biosynthesis and Related Topics" National Science Foundation/Japan Society for the Promotion of Science, Kyoto, Japan, November 29 - December 1, 1965.

4. Invited Speaker: Carotenoid De-epoxidation Reactions. Conference on "Photosynthetic Pigments" in honor of Harold H. Strain, Argonne National Laboratory, Argonne, Illinois, November 7-8,1968.

5. Invited Speaker: Minority Programs at Tufts University School of Medicine. Conference on "Minority Groups in Professional Schools" American Personnel and Guidance Association, Las Vegas, Nevada, March 30 - April 2, 1969.

6. Invited Participant: Minority Enrollment at Tufts University School of Medicine. Conference on "The Impact of Cultural and Economic Background on Programs to Recruit Negroes for Medicine" Macy Foundation, Princeton, NJ, April 13-16, 1969.

7. Invited Speaker: Evolution of Photosensitive Pigments in Microbes. Colloquium on "Photosynthetic Organisms: Origin and Evolution on Early Earth" 123rd meeting of the American Association for the Advancement of Science, Boston, MA, December 26, 1969.

8. Invited Speaker: The Protective Function of Carotenoid Pigments against Aerobic Photosensitivity. Colloquium on "Molecular Mechanisms of Photodynamic Action with and without Molecular Oxygen" VIth International Congress on Photobiology, Bochum, W. Germany, Aug. 21-25, 1972.

9. Sigma Xi Lecturer: Function of Carotenoids. University of Rhode Island, Kingston, RI, October 10, 1973.

10. Invited Speaker: Photosensitization and Protection of Biomembranes and Model Systems. Colloquium on "Photochemistry of Biomembranes" at the 2nd Meeting of the American Society for Photobiology, Vancouver, British Columbia, Canada, July 24, 1974.

11. Theme Speaker: Light and Life: Biochemical Responses to Light. New England Association of Chemistry Teachers 36th Summer Conference, St. Anselem's College, Manchester, New Hampshire, Aug. 20-24, 1974.

12. Invited Speaker: Singlet Oxygen Production in Biological Systems, Workshop on "The Role of Oxygen in the Production of Excited States in Biological Systems" Photobiology Group, Biophysical Society, Philadelphia, PA, February 18, 1975.

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13. Invited Speaker: Damage and Protection against Singlet Oxygen. Workshop on "Free Radical Damage and Protection" Bioenergetics Group, Biophysical Society Seattle, WA, February 24, 1976.

14. Invited Speaker: Cellular Damage Initiated by Visible Light. Symposium on "The Survival of

Vegetative Microbes" Society for General Microbiology, Cambridge, England, April 5-8, 1976.

15. Invited Speaker: Non-Photosynthetic Functions of Carotenoids. Discussion. Meeting on "The Biochemical Functions of Terpenoids in Plants" The Royal Society, London, England, January 26-27, 1978.

16. Invited Speaker: Carotenoid Protection against Oxidation. Fifth International Symposium on "Caroten and Vitamin A" Madison, WI, July 24-28, 1978.

17. Invited Participant: Joint Seminar on "Chemi- and Bio-energized Processes" Universidade de Sáo Paulo, Sáo Paulo, Brazil, August 5-7, 1978.

18. Invited Speaker: Cholesterol Oxidation by Either Polymorphonuclear Leukocyte or by Isolated Myeloperoxidase. International Conference on "Chemi- and Bio-energized Processes" Guaruja, Estado de Sáo Paulo, Brazil, August 8-10, 1978.

19. Invited Speaker: Carotenoid Pigments: Multiple Mechanisms for Coping with the Stress of Photosensitized Oxidations. Conference on "Strategies of Microbial Life in Extreme Environments" Dahlem Konferenzen, Berlin, Fed. Rep. Germany, November 20-24, 1978.

20. Invited Speaker: Is Singlet Oxygen Involved in Biological Chemiluminescence? Symposium on "Biological Basis of Chemiluminescence" American Society for Photobiology, Colorado Springs, CO, February 21, 1980.

21. Invited Speaker: Photosensitized Damage. Round Table on "Sensitized Photooxidation of Biomolecules" International Conference in Oxygen and Oxy-Radicals in Chemistry and Biology, Austin, TX, May 25-29, 1980.

22. Invited Speaker: Molecular Bases for Cellular Damage Initiated by Photosensitized Oxidations. Round Table on "Endogenous and Exogenous Inhibitors and Sensitizers. Fundamental Aspects" 8th International Congress on Photobiology, Strasbourg, France, July 20-25, 1980.

23. Invited Speaker: Interaction of Oxygen and Oxyradicals with Carotenoids Symposium on "Photochemical Toxicity" Food and Drug Administration, Bethesda, MD, March 16-17, 1981.

24. Invited Speaker: Possible Participation of Singlet Oxygen in Biological Systems. Symposium on "Radicals and Excited States in Biological Systems" Seventh International Biophysics Congress and Third Pan-American Biochemistry Congress, Mexico City, Mexico, August 24-28, 1981.

25. Invited Speaker: In vivo Analysis of UV-B Formation of 5.6-a-Epoxy- cholesterol. 2nd NCI/EPA/NIOSH Collaborative Workshop on "Progress on Joint Environmental and Occupational Cancer Studies" Rockville, MD, September 9-11, 1981.

26. Invited Speaker: The Biological Implications of Singlet Oxygen Production. Table Ronde Roussel Uclaf on "New Concepts of Free Radicals in Chemistry and Biology" Paris, France, October 22-23, 1981.

27. Invited Speaker: Photosensitization. Singlet Oxygen Damage and Cancer. "International Workshop on Photobiology" Cheju, Korea, May 25-June 1, 1982.

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28. Invited Speaker: Introduction to Photobiology and Photosensitization. Symposium on "Photobiology" Chosun University, Gwang Ju, Korea, June 2, 1982.

29. Invited Speaker: Free Radicals as Possible Mutagens and Carcinogens. Symposium on "Free Radicals

and Cancer" Council for Tobacco Research, New York, NY, June 21, 1982.

30. Invited Speaker: Mutagenic and Carcinogenic Effects of Oxygen Radicals Symposium on "Possible Roles of Free Radicals in Aging" Gerontological Society of America, Boston, MA, Nov. 21, 1982.

31. Invited Speaker: Biology and Photobiology of Singlet Oxygen 3rd International Conference on Oxygen Radicals, Munich, FRG, July 10-15, 1983.

32. Invited Speaker: Comparison of the Oxidant Mechanisms of Myeloperoxidase and UV-B Irradiation EMBO Workshop on "Oxidative Enzymes-Damage and Consequences" Grottoferrata, Italy, October 2-7, 1983.

33. Public Lecture: New Findings on the Role of Provitamin A in Health and Disease. Institute for Research on Aging, University of California, San Diego, CA, September 13, 1984.

34. Invited Speaker: The Action of Carotenoids In vitro as Compared to their Function In vivo. Symposium on "Nutrition and Disease: Cancer" Helicon Foundation, San Diego, CA, September 15, 1984.

35. Invited Speaker: Detection and Biological Function of Active Oxygen Species School Lecture, American Society for Photobiology, New Orleans, and LA, June 27, 1985.

36. Invited Speaker: The Unique Singlet Oxygen Quenching Properties of Carotenoids. FASEB Summer Research Conference on "Micronutrients Retinoids" Saxtons River, VT, June 22-27, 1986.

37. Invited Speaker: Mechanisms of Inactivation of Oxygen Species by Carotenoids. 2nd International Conference on Anticarcinogenesis and Radiation Protection, National Bureau of Standards, Gaithersburg, MD, March 9-12, 1987.

38 Invited Speaker: Beta-carotene and Cancer: Overview and Rationale. VNIS Health Communications Conference: Beta-Carotene, Boca Raton, FL, April 11-12, 1987.

39. Invited Speaker: Overview of Carotenoids in Medicine. Eighth International Symposium on Carotenoids, Boston, MA, July 26-31, 1987.

40. Invited Speaker: Enzymic and Pigment Protection from Photodynamic Damage. FEMS/Society for Applied Bacteriology Symposium on "Homeostatic Mechanisms in Micro-organisms." Warwick University, Coventry, UK, September 14-18, 1987.

41. Invited Speaker: The Evidence for the Role of Carotenes in Preventive Health Symposium on "Carotenes in Food and Health" Department of Food Science and Office of Continuing Professional Education, Rutgers, The State University of New Jersey, Iselin, NJ, December 3, 1987.

42. Invited Speaker: Carotenoids as Chemopreventive Agents. Third International Conference on "The Prevention of Human Cancer: Chemoprevention" Arizona Cancer Center, Tucson, AZ, January 12-15, 1988.

43. Invited Speaker: Theoretic and Experimental Basis for Anti-carcinogenic Effects of Retinoids. Workshop on "Emerging Role of Retinoids in the Treatment of Aging and Skin Cancer" Miami, FL, March 11-13, 1988.

44. Invited Speaker: Experimental Studies on Carotenoids and Cancer in Animal Models. Symposium on "The Biological Actions of Carotenoids" American Institute of Nutrition, Las Vegas, NV, May 1-6,

1988.

45. Invited Speaker: Biological Functions of Carotenoids and Retinoids. Symposium on "Biology of Human Skin Aging" American Academy of Dermatology, Philadelphia, PA, May 18-20, 1988.

46. Invited Speaker: Membrane Antioxidants. Conference on Biological Membranes in Cancer Cells, New York Academy of Sciences, Torgiano, Italy, June 13-18, 1988.

47. Invited Speaker: Pigment and Enzymic Protection Against Photodynamic Damage. Tenth International Congress of Photobiology. Jerusalem, Israel, October 31 1988.

48. Invited Speaker: Cancer Prevention: Animal and In vitro Studies. International Conference on "Anti-Oxidant Vitamins and Beta-Carotene in Disease Prevention" British Nutrition Foundation, London, U.K. October 2-4, 1989.

49. Invited Speaker: Carotenoid Metabolism. Workshop on "Carotenoids" FASEB Annual Meeting, Washington, DC, April 1, 1990.

50. Invited Speaker: Carotenoids and Cancer. Symposium on "Nutrition Related Cancer Research: An Interdisciplinary Update" Nutrition Council at Tufts, Boston, MA, April 25, 1990.

51. Invited Speaker: Carotenoid Function. Workshop on "Carotenoids" FASEB Annual Meeting, Atlanta, April 20, 1991.

52. Invited Speaker: Role of Carotenoids. Seminar on "Recipe for Cancer Prevention: Food Issues for the 1990s" American Cancer Society and Nestlé Beverage Company, New York, NY, June 12, 1991.

53. Invited Speaker: Mechanisms of Action of Antioxidants. Conference on Molecular and Comparative Nutrition, US-Japan Malnutrition Panel, Bethesda, MD, July 22-24, 1991.

54. Invited Participant: National Heart, Lung and Blood Institute Workshop on "Antioxidants in the Prevention of Human Atherosclerosis" Bethesda, MD, September 5-6, 1991.

55. Invited Speaker: Carotenoids in Cellular and Animal Systems: Effects on Mutagenesis, Carcinogenesis and Age-related Diseases. Symposium on "Free Radicals and Aging" Society for Free Radical Research (Europe), Paris, France, September 26-28, 1991.

56. Invited Speaker: Conversion of Carotenoids to Retinoids. Symposium on "Retinoids: New Trends in Research and Clinical Applications" Palermo, Italy, October 21-24, 1991.

57. Invited Speaker: Beta-Carotene - Animal Data. Symposium on "Vitamins and Cancer Prevention" Pennington Biomedical Research Center, Baton Rouge, LA, October 30 November 1, 1991.

58. Invited Speaker: Carotenoids as Biological Antioxidants. Symposium on "Active Oxygens, Lipid Peroxides and Antioxidants" 5th International Congress on Oxygen Radicals, Kyoto, Japan, November 17-21, 1991.

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59. Invited Speaker: Excentric Cleavage Mechanism(s) for Carotenoid Metabolism. Gordon Research Conference on "Chemistry and Biology of Carotenoids" Oxnard, CA, March 9-13, 1992

60. Invited Speaker: Nutritional Factors an Their Influence on Mutagenicity and Malignant Transformation. Tobacco and Health Research Institute, University of Kentucky Symposium on "Tobacco Smoking and Nutrition: Influence of Nutrition on Tobacco Associated Health Risks" Lexington, KY,

September 14-16, 1992

61. Invited Speaker: Excentric Cleavage of Carotenoids. New York Academy of Sciences Conference on "Carotenoids in Human Health" San Diego, CA, February 6-9, 1993.

62. Invited Speaker: Antioxidant Effects of Carotenoids. International Conference on "Critical Aspects of Free Radicals in Chemistry, Biochemistry and Medicine" Vienna, Austria, February 14-17, 1993.

63. Invited Speaker: Antioxidant Properties of Carotenoids. The Kurashiki Symposium for Medical Science, Kurashiki, Japan, May 21-22, 1993.

64. Invited Speaker: ß-Carotene: Disease Prevention and Its Health Impact. Japan Vitamin Society, Gifu City, Japan, May 25-27, 1993.

65. Invited Speaker: Function, Actions, and Associations of Carotenoids. Tenth International Symposium on Carotenoids, Trondheim, Norway, June 20-25, 1993.

66. Invited Speaker: Antioxidants: Classification and Mode of Action. Symposium on "Antioxidants and Disease Prevention: Biochemical, Nutritional, and Pharmacological Aspects" Stockholm. Sweden, June 30-July 3, 1993.

67. Invited Speaker: Carotenoid Metabolism. Symposium on "Retinoids: New Trends in Research and Cl Applications" Genoa, Italy, October 4-7, 1993.

68. Invited Speaker: The Effects of Carotenoids on Cells. Workshop on "Cell Proliferation and Differentiation: Modulation by Free" Rome, Italy, October 8, 1993.

69. Invited Discussant: Antioxidant Nutrients. Symposium on "Nutritional Assessment of Elderly Populatior Measure and Function" Boston, MA, October 11-13, 1993.

70. Invited Speaker: Clinical and Experimental Studies of ß-Carotene and Cancer. FDA Public Conference on Antioxidant Nutrients and Cancer and Cardiovascular Disease. Washington, DC, November 1-3, 1993.

71. Invited Speaker: Recent Research Findings on Beta-Carotene. Henkel Symposium on Vitamin E Palm Beach, FL, June 7-8, 1994.

72. Invited Speaker: Comments on Antioxidant Vitamins and ß-Carotene. "Second International Conference on Antioxidant Vitamins and Beta Carotene in Disease Prevention" Berlin, Germany, October 10-12, 1994.

73. Invited Speaker: Plant Carotenoids and Related Molecules - Important Dietary Antioxidants. Symposium on "Free Radicals and Oxidative Stress - Environment, Drugs and Food Additives" Biochemical Society, Brighton, U.K., December 14-16, 1994

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74. Invited Speaker: Antioxidants and Their Role in Human Health. 22nd Annual Texas Human Nutrition Conference, "Health Claims for Foods and Nutrients" Texas A & M Univ., Tyler, TX, February 3, 1995.

75. Plenary Lecture: An Overview of the Functions and Actions of Carotenoids: A Personal Perspective. 2nd Gordon Research Conference on Carotenoids, Ventura, CA February 5-9, 1995.

76. Invited Speaker: Carotenoids as Biological Antioxidants. 2nd Symposium on Vitamins and

Biofactors, San Diego, CA February 15-19, 1995.

77. Invited Speaker: Overview of Carotenoids. USAID Workshop on the Bioavailability and Bioconversion of Carotenoids. Washington, DC April 4-5, 1995

78. Invited Speaker: Functions of Carotenoids. FASEB Summer Conference on Antioxidant Nutrients in the Cellular Biology of Health and Disease, Saxtons River, VT August 17-21, 1995

79. Invited Speaker: Biological Effects of Radicals on Carotenoids, 6th European Society for Photobiology, Cambridge, UK September 2-9, 1995.

80. Invited Speaker: Low Molecular Weight Antioxidants; You are What You Eat, Oxygen '95 Free Radical School, Annual Meeting of the Oxygen Society, Pasadena, CA November 17, 1995

81. Invited Speaker Carotenoids: Structure and Function, Workshop on "Potential Effects of Reducing Carotenoid Levels on Human Health" Department of Nutrition, Harvard School of Public Health, Boston, MA January 17th, 1996

82. Invited Speaker Metabolism and Mechanism of Action of Antioxidants, The Toxicology Forum, Givens Institute, Aspen, CO, July 9, 1996.

83. Invited Speaker Are the Oxidative Breakdown Products of Carotenoids Evidence of Antioxidant Action or the Generation of Biologically Active Molecules? VIII Biennial Meeting, International Society for Free Radical Research, Barcelona, Spain October 4, 1996

84. Invited Speaker ß-Carotene and Disease: A Causal Relationship? Oxygen '96, Annual Meeting of the Oxygen Society, Miami □Beach. FL November 22, 1996

85. Invited Lecturer: Natural and Synthetic Carotenoids: Their Actions in Biology. 5th Mordechai Avron Memorial Lecture, Gifu and Tokyo, Japan, Nikken Sohonsha Corp., February 21 and 23, 1997

86. Invited Speaker: Overview of Lycopene, Carotenoids and Disease Prevention, International Symposium on the Role of Lycopene and Tomato Products in Disease Prevention, American Health Foundation/Tomato Research Council, New York, NY, March 3, 1997

87. Invited Speaker: Hypothetical Health Benefits Of ß-Carotene And Other Carotenoids, Society of Toxicology, Cincinnati, OH, March 11, 1997

88. Invited Lecturer: The Properties of Carotenoids that Define Their Actions (June 1) and The Actions of Carotenoids in Biology and Medicine (June 3), NATO Advanced Study Institute on Free Radicals, Oxidative Stress and Antioxidants. Pathological and Physiological Significance, Antalya, Turkey, May 24-June 4, 1997

89. Invited Speaker: Carotenoids and Chronic Degenerative Diseases, International Conference on Nutrition and Cancer, Irvine, CA July 16-July 19, 1997

90. Invited Speaker: The Antioxidant and Biological Properties of the Carotenoids, 7th Congress of the International Association of Biomedical Gerontology, Adelaide, Australia, August 15-August 18, 1997

91. Invited Speaker: Biochemistry of Carotenoids: Actions and Functions. American College of Nutrition Award Lecture, American College of Nutrition Annual Meeting, New York, NY, September 26-28, 1997

92. Invited Speaker: Measurement of Carotenoids, WORKSHOP on Quantitative Methods for Determination of Hydroxyl Radicals, Oxidation of Biological Molecules and Antioxidants, The Oxygen Society, San Francisco, CA, November 20-24, 1997.

93. Invited Speaker: Actions of Carotenoids, Oxygen Club of California, Santa Barbara, CA, February 7, 1998

94. Plenary Lecture: Carotenoids in Health and Disease, Gordon Research Conference on Oxygen Radicals in Biology, Ventura, CA, February 12, 1998

95. Invited Speaker: Role of Carotenoids in Health and Disease, The First Regional Meeting on Medical Sciences: "The Roles of Free Radicals in Health and Disease" Jerusalem and Amman, March 22-27, 1998

96. Invited Speaker: Activity of ß-Carotene Oxidation Products, European Conference on Biomedical Research and Peace, Paralimni, Cyprus, October 17-21, 1999

97. Invited Speaker: What is the Scientific Evidence for Establishing Carotenoids as Recommended Nutrients? Symposium on Dietary Antioxidants: the New Dietary Reference Indices; The Oxygen Society, New Orleans, LA, November 21, 1999

99. Invited Speaker: The Relationship Between Antioxidant and Chronic Disease Symposium on Dietary Reference Intakes, Experimental Biology '00, San Diego, CA April 17, 2000

100. Invited Speaker Carotenoids, Smoking and Cancer, 3rd International Conference on Antioxidants and Free Radicals in Health and Disease, Vancouver, BC, Canada July 23, 2000

101. Invited Speaker: Antioxidants and Chronic Diseases: How Much Science is Enough? Symposium on Dietary Reference Intakes, American Dietetic Association, Denver, CO October 18, 2000

102. Invited Speaker: Antioxidants and Chronic Diseases, Symposium on Dietary Reference Intakes, American Public Health Association, Boston, MA Nov. 13, 2000

103. Invited Speaker: Carotenoids in Health and Disease, Robert S. Harris Lecture, Massachusetts Institute of Technology, Cambridge, MA March 15, 2001

104. Invited Speaker Possible Biologic Mechanism for the Protective Role of Xanthophylls, Symposium on Lutein and Macular Degeneration, FASEB Meeting, Orlando, FL, April 1, 2001

105. Invited Speaker: Carotenoid Research in the Past and Present Millennia, CARIG Lecturer, EB'01 Conference, Orlando, FL, April 2, 2001

106. Invited Speaker: Possible Biologic Mechanism for the Protective Role of Xanthophylls in Age-Related Macular Degeneration, American Society of Nutritional Sciences (EB'01), Orlando, FL, April 1, 2001

107. Invited Speaker: Dietary Carotenoids: What do They Do? PAX Mechanisms Conference, Cambridge, MA, September 30, 2001

108. Invited Plenary Lecturer Historical Critical Evaluaiton of free Radical and Antioxidant Research Oxygen Club of California, Santa Barbara, CA, March 8, 2002

109. Invited Speaker: Health Benefits of Carotenoids, Helmut Sies Festschrift, L'Abbaye de Royamount,

Royamount, France, July 15, 2002

110. Invited Speaker: Dietary Carotenoids Modify Human Plasma Lipid Oxidizability, International Society for Free Radical Research Meeting, Paris France, July 16-20, 2002

111. Invited Plenary Lecturer Human Requirements for Fat-Soluble Vitamins, XIIth European Meeting on Fat-Soluble Vitamins, Rieti, Italy March 13-15, 2003

112. Invited Speaker: Overview of Lutein and Zeaxanthin, Advisory Committee, National Eye Institute, May 17, 2004

A. Peer Reviewed Journal Articles (99)

1. Ganguly, J, Krinsky, NI, Mehl, JW and Deuel, HJ Jr, Studies of the Distribution of Vitamin A as Ester and Alcohol and of Carotenoids in Plasma Proteins of Several Species. Arch. Biochem. Biophys. 38:275-282 (1952).

2. Krinsky, NI and Ganguly, J, Intracellular Distribution of Vitamin A Ester and Vitamin A Alcohol in Rat Liver. J. Biol. Chem. 202:227-232 (1953).

3. Ganguly, J and Krinsky, NI, Absence of Relationship between Vitamin A Alcohol Levels in Plasma and Liver of Rats. Biochem. J. 54:177-181 (1953).

4. Ganguly, J, Krinsky, NI, Pinckard, JH and Deuel, HJ, Jr., Untersuchungen über den Carotinoid-Stoffwechsel, XIV. Biologische Wirksamkeit von Echinenon. Z. Physiol. Chem. 295:61-66 (1953).

5. Ganguly, J, Krinsky, NI and Pinckard, JH, Isolation and Nature of Echinenone, a Provitamin A. Arch. Biochem. Biophys. 60:345-351 (1956).

6. Stefanini, M, Krinsky, NI and Magalini, SI, Studies on Platelets, XIX. Carotenoid Pigments in Human Platelets. J. Lab. Clin. Med. 50:225-228 (1957).

7. Krinsky, NI, Cornwell, DG and Oncley, JL, The Transport of Vitamin A and Carotenoids in Human Plasma. Arch. Biochem. Biophys. 73:233-246 (1958).

8. Krinsky, NI, Enzymatic Esterification of Vitamin A. J. Biol. Chem. 232:881-894 (1958).

9. Krinsky, NI, The Lipoprotein Nature of Rhodopsin. Arch. Ophthal. 60:688-694 (1958).

10. Goldsmith, TH and Krinsky, NI, The Epoxide Nature of the Carotenoid Neoxanthin. Nature (London) 188:491-493 (1960).

11. Krinsky, NI and Goldsmith, TH, The Carotenoids of the Flagellated Alga, Euglena gracilis. Arch. Biochem. Biophys. 91:271-279 (1960).

12. Krinsky, NI, A Relationship between Partition Coefficients of Carotenoids and their Functional Groups. Anal. Biochem. 6:293-302 (1963).

13. Krinsky, NI, Gordon, A and Stern, AI, The Appearance of Neoxanthin During the Re-greening of Dark-grown Euglena. Plant Physiol. 39:441-445 (1964).

14. Krinsky, NI and Levine, RP, Carotenoids of Wild Type and Mutant Strains of the Green Alga, Chlamydomonas reinhardi. Plant Physiol. 39:680-687 (1964).

15. Krinsky, NI, Carotenoid De-epoxidations in Algae. I. Photochemical Transformation of Antheraxanthin to Zeaxanthin. Biochim. Biophys. Acta 88:487-491 (1964).

16. Bamji, MS and Krinsky, NI, Carotenoid De-epoxidations in Algae. II. Enzymatic Conversion of Antheraxanthin to Zeaxanthin. J. Biol. Chem. 240:467-470 (1965).

17. Mathews, MM and Krinsky, NI, The Relationship between Carotenoid Pigments and Resistance to Radiation in Non-photosynthetic Bacteria. Photochem. Photobiol. 4:813-817 (1965).

18. Krinsky, NI, The Carotenoids of the Brine Shrimp, Artemia salina. Comp. Biochem. Physiol. 16:181-187 (1965).

19. Krinsky, NI and Lenhoff, HM, Some Carotenoids in Hydra. Comp. Biochem. Physiol. 16:189-198 (1965).

20. Bamji, MS and Krinsky, NI, The Carotenoid Pigments of a Radiation-resistant Micrococcus sp. Biochim. Biophys. Acta 115:276-284 (1966).

21. Schimmer, BP and Krinsky, NI, The Structure of Neoxanthin and the Trollein-like Carotenoid from Euglena gracilis. Biochemistry 5:1814-1820 (1966).

22. Schimmer, BP and Krinsky, NI, Reduction of Carotenoid Epoxides with Lithium Aluminum Hydride. Biochemistry 5:3649-3657 (1966).

25. Mathews-Roth, MM and Krinsky, NI, Carotenoid Pigments and the Stability of the Cell Membrane of Sarcina lutea. Biochim. Biophys. Acta 203:357-359 (1970).

26. Mathews-Roth, MM and Krinsky, NI, Studies on the Protective Function of the Carotenoid Pigments of *Sarcina lutea*. Photochem. Photobiol. 11:419-428 (1970).

27. Mathews-Roth, MM and Krinsky, NI, Failure of Conjugated Octaene Carotenoids to Protect a Mutant of Sarcina lutea Against Lethal Photosensitization. Photochem. Photobiol. 11:555-557 (1970).

28. Cooney, JJ and Krinsky, NI, Photodynamic Killing of Acholeplasma laidlawii. Photochem. Photobiol. 16:523-526 (1972).

29. Kornhauser, A, Krinsky, NI, Huang, P-KC and Clagett, DC, A Comparative Study of Photodynamic Oxidation and Radiofrequency Discharge Generated $^1O_2$ Oxidation of Guanosine. Photochem. Photobiol. 18:63-69 (1973).

30. Anderson, SM and Krinsky, NI, Protective Action of Carotenoid Pigments against Photodynamic Damage to Liposomes. Photochem. Photobiol. 18:403-408 (1973).

31. Krinsky, NI, Bymun, EN and Packer, L, Retention of K^+ Gradients in Imidoester Cross-Linked Erythrocyte Membranes. Arch. Biochem. Biophys. 160:350-352 (1974).

32. Mathews-Roth, MM, Wilson, T, Fujimori, E and Krinsky, NI, Carotenoid Chromophore Length and Protection against Photosensitization. Photochem. Photobiol. 19:217-222 (1974).

33. Anderson, SM, Krinsky, NI, Stone, MJ and Clagett, DC, Effect of Singlet Oxygen Quenchers on Oxidative Damage to Liposomes Initiated by Photosensitization or by Radiofrequency Discharge. Photochem. Photobiol. 20:65-69 (1974).

34. Krinsky, NI, Singlet Excited Oxygen as a Mediator of the Antibacterial Action of Leukocytes. Science 186:363-365 (1974).

35. Levine, PH, Weinger, RS, Simon, J, Scoon, KL and Krinsky, NI, Leukocyte-Platelet Interaction. Release of Hydrogen Peroxide by Granulocytes as a Modulator of Platelet Reactions. J. Clin. Investigation 57:955-963 (1976).

36. Deneke, CF and Krinsky, NI, Enhanced Dimol Emission of Singlet Oxygen by Cyclic Tertiary Amines. J. Am. Chem. Soc. 98:3041-3042 (1976).

37. Deneke, CF and Krinsky, NI, Inhibition and Enhancement of Singlet Oxygen ($^1\Delta_g$) Dimol Chemiluminescence. Photochem. Photobiol. 25:299-304 (1977).

38. Deneke, CF and Krinsky, NI, A Cheap and Durable Cuvet Washer. J. Chem. Educ. 54:257 (1977).

39. Krinsky, NI, Scoon, KL, Hardin, JC and Levine, PH, The Source of Hydrogen Peroxide and of Chemiluminescence Observed in Activated Human Platelet Preparations. Blood 50:597-602 (1977).

40. Lederman, DM, Cumming, RD, Petschek, HE, Levine, PH and Krinsky, NI, The Effect of Temperature on the Interaction of Platelets and Leukocytes with Materials Exposed to Flowing Blood. Trans. Am. Soc. Artif. Intern. Organs. 24:557-560 (1978).

41. Levine, PH, Hardin, JC, Scoon, KL and Krinsky, NI, Effect of Corticosteroids on the Production of Superoxide and Hydrogen Peroxide and the Appearance of Chemiluminescence by Phagocytosing Polymorphonuclear Leukocytes. Inflammation 5:19-27 (1981).

42. Andrews, PC and Krinsky, NI, The Reductive Cleavage of Myeloperoxidase in Half, Producing Enzymically Active Hemi-Myeloperoxidase. J. Biol. Chem. 256:4211-4218 (1981).

43. Krinsky, NI, Sladdin, DG, Levine, PH, Taub, IA and Simic, MG, Modification of Platelet Function by Radical Species Produced During Irradiation of Oxygenated Water. Thromb. Haemostasis 45:116-120 (1981).

44. Levine, PH, Sladdin, DG and Krinsky, NI, Superoxide, Xanthine Oxidase and Platelet Reactions. Further Studies on Mechanisms by which Oxidants Influence Platelets. Thromb. Haemostasis 45:290-293 (1981).

45. Krinsky, NI and Deneke, SM, The Interaction of Oxygen and Oxy-Radicals with Carotenoids. JNCI 69:205-210 (1982).

46. Andrews, PC and Krinsky, NI, A Kinetic Analysis of the Interaction of Human Myeloperoxidase with Hydrogen Peroxide, Chloride Ions and Protons. J. Biol. Chem. 257:13240-13245 (1982).

47. Andrews, PC and Krinsky, NI, Quantitative Determination of Myeloperoxidase Using Tetramethylbenzidine as Substrate. Anal. Biochem. 127:346-350 (1982).

48. Andrews, PC, Parnes, C and Krinsky, NI, Comparison of Myeloperoxidase and Hemi-Myeloperoxidase with Respect to Catalysis, Regulation and Bactericidal Activity. Arch. Biochem. Biophys. 228:439-442 (1984).

49. Peak, MJ, Foote, CS, Krinsky, NI and Peak, JG, Oxygen-Independent Direct DNA Backbone Breakage Caused by Rose Bengal and Visible Light. J. Photochem. 25:309-315 (1984).

50. Mathews-Roth, MM and Krinsky, NI, Effect of Dietary Fat Level on UV-B Induced Skin Tumors, and Anti-Tumor Action of Beta-Carotene. Photochem. Photobiol. 40:671-673 (1984).

51. Mathews-Roth, MM and Krinsky, NI, Carotenoid Dose Level and Protection Against UV-B Induced Skin Tumors. Photochem. Photobiol. 42:35-38 (1985).

52. Cunningham, ML, Krinsky, NI, Gioranazzi, SM and Peak, MJ, Superoxide Anion is Generated from Cellular Metabolites by Solar Radiation and its Components. J. Free Radic. Biol. Med. 1:381-385 (1985).

53. Ito, A, Krinsky, NI, Cunningham, ML and Peak, MJ, Comparison of the Inactivation of *Bacillus subtilis* Transforming DNA by the Potassium Superoxide and Xanthine-Xanthine Oxidase Systems for Generating Superoxide. Free Radical Biol. Med. 3:111-118 (1987).

54. Mathews-Roth, MM and Krinsky, NI, Carotenoids Affect Development of UV-B Induced Skin Cancer. Photochem. Photobiol. 46:507-509 (1987).

55. Krinsky, NI, Mathews-Roth, MM, Welankiwar, S, Sehgal, PK, Lausen, NCG and Russett, M, The Metabolism of [14C]-ß-Carotene and the Presence of Other Carotenoids in Rats and Monkeys. J. Nutr. 120:81-87 (1990).

56. Mathews-Roth, MM, Welankiwar, S, Sehgal, PK, Lausen, NCG, Russett, M and Krinsky, NI, Distribution of [^{14}C]Canthaxanthin and [^{14}C]Lycopene in Rats and Monkeys. J. Nutr. 120:1205-1213 (1990).

57. Krinsky, NI, Russett, MD, Handelman, GJ and Snodderly, DM, Structural and Geometrical Isomers of Carotenoids in Human Plasma. J. Nutr. 120:1654-1661 (1990).

58. Snodderly, DM, Russett, MD, Land, RI and Krinsky, NI, Plasma Carotenoids of Monkeys (*Macaca Fascicularis and Saimiri Sciureus*) Fed a Nonpurified Diet. J. Nutr. 120:1663-1671 (1990).

59. Handelman, GJ, Snodderly, DM, Krinsky, NI, Russett, MD and Adler, AJ, Biological Control of Primate Macular Pigment. Biochemical and Densitometric Studies. Invest. Ophthalmol. Vis. Sci 32:257-267 (1991).

60. Wang, X-D, Tang, G-W, Fox, JG, Krinsky, NI and Russell, RM, Enzymatic Conversion of ß-Carotene into ß-Apo-Carotenals and Retinoids by Human, Monkey, Ferret, and Rat Tissues. Arch. Biochem. Biophys. 285:8-16 (1991).

61. Mathews-Roth, MM, Lausen, N, Drouin, G, Richter, A and Krinsky, NI, Effects of Carotenoid Administration on Bladder Cancer Prevention. Oncology 48:177-179 (1991).

62. Handelman, GJ, van Kuijk, FJGM, Chatterjee, A and Krinsky, NI, Characterization of Products Formed During the Autoxidation of ß-Carotene. Free Radical Biol. Med. 10:427-437 (1991).

63. Palozza, P and Krinsky, NI, The Inhibition of Radical-Initiated Peroxidation of Microsomal Lipids by both α-Tocopherol and ß-Carotene. Free Radical Biol. Med. 11:407-414 (1991).

64. Tang, G, Wang, X-D, Russell, RM and Krinsky, NI, Characterization of ß-Apo-13-Carotenone and ß-apo-14'-Carotenal as Enzymatic Products of the Excentric Cleavage of ß-Carotene. Biochemistry 30:9829-9834 (1991).

65. Wang, X-D, Krinsky, NI, Tang, G and Russell, RM, Retinoic Acid can be Produced from Excentric Cleavage of ß-Carotene in Human Intestinal Mucosa. Arch. Biochem. Biophys. 293:293-304 (1992).

66. Palozza, P and Krinsky, NI, ß-Carotene and α-Tocopherol are Synergistic Antioxidants. Arch. Biochem. Biophys. 297:184-187 (1992).

67. Palozza, P, Moualla, S and Krinsky, NI, Effects of ß-Carotene and α-Tocopherol on Radical-Initiated Peroxidation of Microsomes. Free Radical Biol. Med. 13:127-136 (1992).

68. Palozza, P and Krinsky, NI, Astaxanthin and Canthaxanthin are Potent Antioxidants in a Membrane Model. Arch. Biochem. Biophys. 297:291-295 (1992).

69. Wang, XD, Krinsky, NI, Marini, R, Tang, G, Yu, J, Fox, JG and Russell, RM, Intestinal Uptake and Lymphatic Absorption of ß-Carotene in Ferrets: A Model for Human ß-Carotene Metabolism. Am. J. Physiol. 263:G480-G486 (1992).

70. Wang, X-D, Russell, RM, Marini, R, Tang, G, Dolnikowski, G, Fox, JG and Krinsky, NI, Intestinal Perfusion of ß-Carotene in the Ferret Raises Retinoic Acid Levels in Portal Blood. Biochim. Biophys. Acta 1167:159-164 (1993).

71. Wang, X-D, Krinsky, NI and Russell, RM, Retinoic Acid Regulates Retinol Metabolism via Feedback Inhibition of Retinol Oxidation and Stimulation of Retinol Esterification in Ferret Liver. J. Nutr. 123:1277-1286 (1993).

72. Palozza, P and Krinsky, NI, Antioxidant Effects of Carotenoids on Biological Membranes. Acta Medica Romano 31:131-140 (1993).

73. Wang, X-D, Krinsky, NI, Benotti, PN and Russell, RM, Biosynthesis of 9-*cis*-retinoic acid from 9-*cis*-ß-carotene in human intestinal mucosa in vitro. Arch. Biochem. Biophys. 313:150-155 (1994).

74. Kennedy, AR and Krinsky, NI, Effects of retinoids, ß-carotene and canthaxanthin on UV and X-ray-induced transformation of C3H10T1/2 cells *in vitro*. Nutr. Cancer 22:219-232 (1994).

75. Gaziano, JM, Hatta, A, Flynn, M, Johnson, EJ, Krinsky, NI, Ridker, PR, Hennekens, CH and Frei, B, Supplementation with ß-carotene in vivo and in vitro does not inhibit low density lipoprotein (LDL) oxidation. Atherosclerosis 112:187-195 (1995).

76. Wang, X-D, Marini, RP, Hebuterne, X, Fox, JG, Krinsky, NI and Russell, RM, Vitamin E enhances the lymphatic transport of ß-carotene and is conversion into vitamin A in the ferret. Gastroent. 108:719-726 (1995).

77. Gaziano, JM, Johnson, EJ, Russell, RM, Frei, B, Manson, JE, Stampfer, M, Ridker, PR, Hennekens, CH and Krinsky, NI, Discrimination in absorption or transport of ß-carotene isomers following oral supplementation with either all-*trans*- or 9-*cis*-ß-carotene. Am. J. Clin. Nutr. 61:1248-1252 (1995).

78. Hébuterne, X, Wang, X-D, Johnson, EJ, Krinsky, NI and Russell, RM, Intestinal absorption and metabolism of 9-*cis*-ß-carotene *in vivo*: biosynthesis of 9-*cis*-retinoic acid. J. Lip. Res. 36: 1264-1273 (1995).

79. Yeum, K-J, Lee-Kim, YC, Yoon, S, Lee, KY, Park, IS, Lee, KS, Kim, BS, Tang, G, Russell, RM and Krinsky, NI, Similar metabolites formed from ß-carotene by either human gastric mucosal homogenates, lipoxygenase or linoleic acid hydroperoxide. Arch. Biochem. Biophys. 321: 167-174 (1995).

80. Hammond, BR, Jr., Curran-Celentano, J, Judd, S, Fuld, K, Krinsky, NI, Wooten, BR and Snodderly, DM, Sex Differences in Macular Pigment Density: Relation to Plasma Carotenoid Concentrations and Dietary Patterns. Vision Research 36: 2001-2012 (1995).

81. Yeum, K-J, Booth, S, Sadowski, J, Lin, C, Tang, G, Krinsky, NI and Russell, RM
Human Plasma Carotenoid Response to the Ingestion of Controlled Diets High in Fruits and Vegetables
Am. J. Clin. Nutr., 64: 594-602 (1996)

82. Wang, X-D, Russell, RM, Stickel, F, Smith, D and Krinsky, NI ß-Oxidation in Rabbit Liver *in vitro* and in the Perfused Ferret Liver Contributes to Retinoic Acid Biosynthesis from ß-Apo-Carotenoic Acids. J. Biol. Chem., 271: 26490-26498 (1996)

83. Snodderly, DM, Shen, B, Land, RI, and Krinsky, NI, Dietary Manipulation of Plasma Carotenoid Concentrations of Squirrel Monkeys (*Saimiri sciureus)* J. Nutr. 127: 122-129 (1997)

84. Johnson, EJ, Krinsky, NI and Russell, RM, Bioavailability of all-*trans* and 9-*cis* isomers of ß-carotene in humans. J. Am. Coll. Nutr. 15: 620-624 (1997).

85. Hammond, BR, Jr., Johnson, EJ, Russell, RM, Krinsky, NI, Yeum, K-J, Edwards, R B and Snodderly, DM, Dietary Modification of Human Macular Pigment Density Invest. Ophthalmol. Vis. Sci. 38: 1795-1801 (1997)

86. Johnson, EJ, Qin, J, Krinsky, NI and Russell, RM, Ingestion by Men of a Combined Dose of ß-Carotene and Lycopene does not effect the Absorption of ß-Carotene but improves that of Lycopene. J. Nutr. 127: 1833-1837 (1997).

87. Johnson, EJ, Qin, J, Krinsky, NI and Russell, RM, ß-Carotene Isomers in Human Serum, Breast Milk and Buccal after Continuous Oral Doses of all-*trans* and 9-*cis* ß-Carotene J. Nutr. 127: 1993-1999 (1997).

88. Yeum, K-J, Ahn, S-H, de Paiva, SAR, Lee-Kim, YC, Krinsky, NI and Russell, RM, Correlations between Carotenoid Concentrations in Serum and Breast Adipose Tissue of Women with Benign Breast Tumor or Breast Cancer. J. Nutrition, 128: 1920-1926 (1998)

89. Wang, X-D, Liu, C, Bronson, RT, Smith, DE, Krinsky, NI and Russell, RM Altered Retinoid Signaling and AP-1 Expression by ß-Carotene and Smoking Leads to Lung Metaplasia. J. Natl. Cancer Inst., 91: 60-66 (1999)

90. Ferreira, A.L.A., Yeum, K.-Y., Liu, C., Smith, D., Krinsky, N.I., Wang, X.-D. and Russell, R.M. Tissue distribution of lycopene in ferrets and rats after lycopene supplementation J. Nutr., 130:1256-1260 (2000)

91. Yeum, K.-Y., Ferreira, A.L.A., Smith, D., Krinsky, N.I. and Russell, R.M. The Effect of α-Tocopherol on The Mechanisms of ß-Carotene Cleavage. Free Radic. Biol. Med. 29:105-114 (2000)

92. Liu, C., Wang, X.-D., Bronson, R.T., Smith, D.E., Krinsky, N.I. and Russell, R.M. Effects of Physiological versus Pharmacological ß-Carotene Supplementation on Cell Proliferation and Histopathological Changes in the Lungs of Cigarette Smoke-exposed Ferrets. Carcinogenesis 21:101-110 (2000)

93. Prakash, P., Russell, R.M. and Krinsky, N.I. *In vitro* Inhibition of Proliferation of Estrogen-dependent and Estrogen-independent Human Breast Cancer Cells Treated with Carotenoids or Retinoids. J. Nutr. 131:1574-1580 (2001)

94. Aldini, G, Yeum, K-J, Russell, RM and Krinsky, NI, A selective Method to Measure the Oxidizability of the Aqueous and Lipid Compartments of Plasma. Free Radic. Biol. Med. 31:1043-1050 (2001)

95. Krinsky, NI, Possible Biological Mechanisms for a Protective role of Xanthophylls. J. Nutrition 132:540S-542S (2002)

96. Tibaduiza, EC, Fleet, JC, Russell, RM and Krinsky, NI, Excentric Cleavage Products of ß-Carotene Inhibit Estrogen Receptor Positive and Negative Breast Tumor Cell Growth in Vitro and Inhibit Activator Protein-1-Mediated Transcriptional Activation. J. Nutrition 132:1368-1375 (2002)

97. Aldini, G., Yeum, KJ., Carini, M., Krinsky, N.I. and Russell, RM, (-)-Epigallocatechin-(3)-gallate Spares Carotenoids, Recycles α-Tocopherol and Prevents Oxidative Damage in Both the Aqueous and Lipid Compartments of Human Plasma. Biochem Biophys Res Commun 302:413-418 (2003)

98. Yeum, K.-J., Aldini, G., Chung, H.-Y., Krinsky, N.I. and Russell, R.M., J Nutrition 133:2688-2691 (2003) The Activities of Antioxidant Nutrients Human Plasma Depend on the Localization of Attacking Radical Species

99. Ferreira, A.L.A., Yeum, K.-Y., Russell, R.M., Krinsky, N,I, and Tang, G., J. Nutr. Biochem. 14:531-540 (2003) Enzymatic and Oxidative Metabolites of Lycopene

100. Prakash, P., Liu, C., Hu, K.-Q., Krinsky, N.I., Russell, R.M. and Wang, X.-D. Effects of ß-Carotene, ß-Apo-14'-carotenoic Acid and Benzo[a]pyrene on Retinoic Acid Receptor ß Expression and Growth of Normal Human Bronchial Epithelial Cells. J. Nutr. 134:667-673 (2004)

101. Yeum, K.-Y., Russell, R.M., Krinsky, N.I. and Aldini, G. Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma. Arch. Biochem. Biophys. in press (2004)

C. Book Chapters and Invited Reviews (66)

1. Krinsky, NI, The Role of Carotenoid Pigments as Protective Agents against Photosensitized Oxidations in Chloroplasts **in:** Biochemistry of Chloroplasts (Goodwin, TW, Eds.) pp. 423-430, Academic Press, New York (1966), vol. 1,

2. Krinsky, NI, The Protective Function of Carotenoid Pigments **in:** Photophysiology (Giese, AC, Eds.) pp. 123-195, Academic Press, New York (1968), vol. 2,

3. Krinsky, NI, Function of Carotenoids **in:** Carotenoids (Isler, O, Eds.) pp. 669-716, Birkhäuser, Basel/Stuttgart (1971)

4. Krinsky, NI, Cellular Damage Initiated by Visible Light **in:** The Survival of Vegetative Organisms (Gray, TGR and Postgate, JR, Eds.) pp. 209-239, Cambridge Univ. Press, Cambridge (1976), vol. 26,

5. Krinsky, NI, Singlet Oxygen in Biological Systems. Trends in Biochemical Science 2:35-38 (1977).

6. Krinsky, NI, Non-photosynthetic Functions of Carotenoids. Phil. Trans. Roy. Soc. London B. 284:581-590 (1978).

7. Krinsky, NI, Carotenoid Protection against Oxidation. Pure & Appl. Chem. 51:649-660 (1979).

8. Krinsky, NI, Biological Roles of Singlet Oxygen **in:** Singlet Oxygen (Wasserman, HH and Murray, RW, Eds.) pp. 597-641, Academic Press, New York (1979)

9. Kuenen, JG, Hassan, HM, Krinsky, NI, Morris, JG, Pfenning, N, Schlegel, H, Shilo, M, Vogels, GS, Weser, U and Wolfe, R, Oxygen Toxicity: Group Report. **in:** Strategies of Microbial Life in Extreme Environments (Shilo, M, Eds.) pp. 223-241, Dahlem Konferenzen, Berlin (1979)

10. Krinsky, NI, The Biological Implications of Singlet Oxygen Production **in:** New Concepts of Free Radicals in Chemistry and Biology, pp. 30-31, Table Ronde Roussel UCLAF, France (1981), vol. 41,

11. Krinsky, NI, Sladdin, DG and Levine, PH, Effects of Oxygen Radicals on Platelet Functions **in:** Oxygen and Oxy-Radicals in Chemistry and Biology (Rodgers, MAJ and Powers, EL, Eds.) pp. 153-160, Academic Press, New York (1981)

12. Krinsky, NI, Photobiology of Carotenoid Protection **in:** The Science of Photomedicine (Regan, JD and Parrish, JA, Eds.) pp. 397-403, Plenum Press, New York (1982)

13. Krinsky, NI, Photosensitization and Singlet Oxygen Damage **in:** Topics In Photobiology (Kim, H-O and Song, PS, Eds.) pp. 67-71, Jeju National University, Jeju, Korea (1983)

14. Krinsky, NI and Welankiwar, S, Assay of Carotenoids. Meth. Enzymol. 105:155-162 (1984).

15. Krinsky, NI, Biology and Photobiology of Singlet Oxygen **in:** Oxygen Radicals In Chemistry And Biology (Bors, W, Saran, M and Tait, D, Eds.) pp. 453-464, Walter de Gruyter & Co., Berlin (1984)

16. Andrews, PC and Krinsky, NI, Myeloperoxidase Activity **in:** Handbook of Methods for Oxygen Radical Research (Greenwald, RA, Eds.) pp. 297-302, CRC Press, Boca Raton, FL (1985)

17. Andrews, PC and Krinsky, NI, Human Myeloperoxidase and Hemi-myeloperoxidase **in:** Immunochemical Techniques, Part J. Phagocytosis and Cell-Mediated Cytotoxicity. (Di Sabato, G and Everse, J, Eds.) pp. 369-378, Academic Press, New York (1986), vol. 132,

18. Krinsky, NI, Mechanisms of Inactivation of Oxygen Species by Carotenoids **in:** Anticarcinogenesis and Radiation Protection (Cerutti, PA, Nygaard, O and Simic, MG, Eds.) pp. 41-46, Plenum Press, New York (1987)

19. Krinsky, NI, The Evidence for the Role of Carotenes in Preventive Health. Clin. Nutr. 7:107-114 (1988).

20. Krinsky, NI, Theoretical Basis for Anticarcinogenic Effects of Retinoids. J. Cutan. Aging Cosm. Derm. 1:53-58 (1988).

21. Krinsky, NI, Membrane Antioxidants. Ann. N.Y. Acad. Sci. 551:17-33 (1988).

22. Krinsky, NI, Carotenoids and Cancer in Animal Models. J. Nutr. 119:123-126 (1989).

23. Krinsky, NI, Beta-Carotene: Functions **in:** New Protective Roles for Selected Nutrients (Spiller, GA and Scala, J, Eds.) pp. 1-15, Alan R. Liss, New York (1989)

24. Krinsky, NI, Carotenoids as Chemopreventive Agents. Prev. Medicine 18:592-602 (1989).

25. Krinsky, NI, Antioxidant Functions of Carotenoids. Free Radical Biol. Med. 7:617-635 (1989).

26. Krinsky, NI, Carotenoids in Medicine **in:** Carotenoids: Chemistry and Biology (Krinsky, NI, Mathews-Roth, MM and Taylor, RF, Eds.) pp. 279-292, Plenum Press, New York and London (1989)

27. Krinsky, NI, Effects of Carotenoids in Cellular and Animal Systems. Am. J. Clin. Nutr. 53:238S-246S (1991).

28. Krinsky, NI, Photooxidative Stress and Photodynamic Therapy: An Overview **in:** Oxidative Damage & Repair. Chemical, Biological and Medical Aspects (Davies, KJA, Eds.) pp. 298-299, Pergamon Press, Oxford (1991)

000294

29. Krinsky, NI, Mechanism of Action of Biological Antioxidants. Proc. Soc. Exp. Biol. Med. 200:248-254 (1992).

30. Steinberg, D, et al., Antioxidants in the Prevention of Human Atherosclerosis. Circulation 85:2337-2344 (1992).

31. Krinsky, NI, Anticarcinogenic Activities of Carotenoids in Animals and Cellular Systems **in:** Free Radicals and Aging (Emerit, I and Chance, B, Eds.) pp. 227-234, Birkhäuser, Basel (1992)

32. Mathews-Roth, MM and Krinsky, NI, Mammalian Metabolism of Carotenoids Other than Vitamin A. Meth. Enzymol. 213:265-272 (1992).

33. Handelman, GJ, Shen, B and Krinsky, NI, High-Resolution HPLC Analysis of Carotenoids in Human Plasma. Meth. Enzymol. 213:336-346 (1992).

34. Palozza, P and Krinsky, NI, Antioxidant Effects of Carotenoids *in Vitro* and *in Vivo*: An Overview. Meth. Enzymol. 213:403-420 (1992).

35. Krinsky, NI, Actions of Carotenoids in Cells and Animals **in:** Vitamins and Cancer Prevention (Bray, GA and Ryan, DH, Eds.) pp. 260-270, Louisiana State Univ. Press, Baton Rouge (1993)

36. Krinsky, NI, Wang, X-D, Tang, G and Russell, RM, Conversion of Carotenoids to Retinoids **in:** Retinoids: Progress in Research and Clinical Applications (Livrea, MA and Packer, L, Eds.) pp. 1-16, Marcel Dekker, New York (1993)

37. Tang, G and Krinsky, NI, Differentiation between Central and Excentric Cleavage of ß-Carotene. Meth. Enzymol. 214:69-74 (1993).

38. Krinsky, NI, Micronutrients and Their Influence on Mutagenicity and Malignant Transformation. Ann. N. Y. Acad. Sci. 686:229-242 (1993).

39. Krinsky, NI, Actions of Carotenoids in Biological Systems. Annu. Rev. Nutr. 13:561-587 (1993).

40. Krinsky, NI, Effects of Carotenoids on Cells. Mol. Aspects Med. 14:241-246 (1993).

41. Krinsky, NI, Wang, X-D, Tang, G and Russell, RM, Mechanism of Carotenoid Cleavage to Retinoids **in:** Carotenoids in Human Health (Canfield, LM, Krinsky, NI and Olson, JA, Eds.) pp. 156-166, New York Acad. Sci., New York (1993), vol. 691,

42. Krinsky, NI, The biological properties of carotenoids. Pure & Appl. Chem. 66:1003-1010 (1994).

43. Krinsky, NI, Wang, X-D, Tang, G and Russell, RM, Cleavage of ß-carotene to retinoids **in:** Retinoids: From Basic Science to Clinical Applications (Livrea, MA and Vidali, G, Eds.) pp. 21-28, Birkhaüser, Basel (1994)

44. Palozza, P and Krinsky, NI, Antioxidant properties of carotenoids **in:** Retinoids: From Basic Science to Clinical Applications (Livrea, MA and Vidali, G, Eds.) pp. 35-41, Birkhaüser, Basel (1994)

45. Krinsky, NI, Carotenoids and Cancer: Basic Research Studies **in:** Natural Antioxidants in Human Health and Disease (Frei, B, ed.) pp. 239-261, Academic Press, San Diego (1994)

46. Krinsky, NI, Selected actions of micronutrient antioxidants **in:** Nutritional Assessment of Elderly Populations: Measure and Function (Rosenberg, IH, ed.) pp. 205-211, Raven Press, New York (1994)

47. Krinsky, NI, Plant Carotenoids and Related Molecules: Important Dietary Antioxidants **in**: Free Radicals and Oxidative Stress: Environment, Drugs and Food Additives (Rice-Evans, C., Halliwell, B. and Lunt, G.G., Eds.) Biochem. Soc. Symp. 61: 117-126, Portland Press, London (1995).

48. Krinsky, NI and Sies, H, The present status of antioxidant vitamins and beta-carotene. Am. J. Clin. Nutr. 62 (Suppl): 1299S-1300S (1995).

49. Olson, J.A. and Krinsky, N.I., The Colorful Fascinating World of the Carotenoids. FASEB J., 9: 1547-1550 (1995)

50. Krinsky, NI, Cellular aspects of carotenoids **in:** Handbook of Antioxidants (Cadenas, E and Packer, L, Eds.) pp. 315-336, Marcel Dekker, New York (1996)

51. Wang, X-D and Krinsky, NI, Identification and Quantification of Retinoic Acid and other Metabolites from ß-Carotene Excentric Cleavage in Human Intestine *in vitro* and Ferret Intestine *in vivo.* **in** METHODS IN ENZYMOLOGY (Suttie, JM and McCormack, D, eds.) 282: 117-130 (1997)

52. Omaye, ST, Krinsky, NI, Kagan, VE, Mayne, ST, Liebler, DC and Bidlack, WR, ß-Carotene: Friend or Foe? Fundam. Appl. Toxicol. 40: 163-174 (1997)

53. Krinsky, NI, Carotenoid Properties Define Primary Biological Actions And Metabolism Defines Secondary Biological Actions, **in** FREE RADICALS, OXIDATIVE STRESS, AND ANTIOXIDANTS: PATHOLOGICAL AND PHYSIOLOGICAL SIGNIFICANCE (Õzben, T, ed.) pp. 323-332, NATO Advanced Study Institute (1998).

54. Wang, X-D and Krinsky, NI, The Bioconversion of ß-Carotene into Retinoids **in** SUBCELLULAR BIOCHEMISTRY, VOL. 30: FAT-SOLUBLE VITAMINS (Quinn, PJ and Kagan, V, eds.) pp. 159-180, Plenum/London (1998)

55. Krinsky, NI, Overview of Lycopene, Carotenoids, and Disease Prevention. Proc. Soc. Exp. Biol. Med. 218: 95-97 (1998)

56. Krinsky, NI, The Antioxidant and Biological Properties of the Carotenoids. Annals, New York Academy of Sciences 854: 443-447 (1998)

57. Krinsky, NI and Rock. C L, Carotenoids (a) Chemistry, sources and physiology **in** ENCYCLOPEDIA OF HUMAN NUTRITION (Sadler, M, Strain, S and Caballero, B eds.) pp. 304-314, Academic Press, London (1998)

58. Krinsky, NI and Mayne, ST, Current Views on Carotenoids: Biology, Epidemiology and Trials **in** VITAMIN A AND RETINOIDS: AN UPDATE OF BIOLOGICAL ASPECTS AND CLINICAL APPLICATIONS, (Livrea, MA, ed.) pp. 45-57, Birkhäuser, Basel (2000)

59. Prakash, P, Krinsky, NI. and Russell, RM, Retinoids, Carotenoids, and Human Breast Cancer Cultures: A Review of Differential Effects. Nutrition Reviews 58:170-176 (2000)

60. Krinsky, NI, Carotenoids as Antioxidants. Nutrition 17:815-817 (2001)

61. Krinsky, NI, Carotenoids and Oxidative Stress **in** CRITICAL REVIEWS OF OXIDATIVE STRESS AND AGING: ADVANCES IN BASIC SCIENCE, DIAGNOSTICS AND INTERVENTION, (Cutler, RG and Rodriguez, H, eds.) 598-611, World Scientific Publishing Co., New York (2003)

62. Krinsky, NI, Landrum, JT and Bone, RA, Biologic Mechanism of the Protective Role of Lutein and Zeaxanthin in the Eye, Annual Review of Nutrition 23:000-000 (2003)

63. Krinsky, NI and Yeum, K-J., Biochem Biophys Res Commun 305:754-60 (2003) Carotenoid-Radical Interactions

64. Aldini, G., Yeum' KJ., Russell, R.M. and Krinsky, N.I., Nutritional Sciences 6:12-19 (2003) A Selective Assay to Measure Antioxidant Capacity in both the Aqueous and Lipid Compartments of Plasma

65. Krinsky, NI., Molecular Aspects of Medicine 24:317-324 (2003) Human Requirements for Fat-soluble Vitamins, and Other Things Concerning These Nutrients

66. Krinsky, N.I., Mayne, S.T. and Sies, H. in CAROTENOIDS IN HEALTH AND DISEASE (Krinsky, N.I., Mayne, S.T. and Sies, H., eds.) in press Marcel Dekker, New York (2004) Carotenoids: Looking Forward

D. Books and Proceedings

1. Krinsky, NI, Mathews-Roth, MM and Taylor, RF, Eds., Carotenoids: *Chemistry and Biology* (Plenum Press, New York and London, 1989).

2. Canfield, LM, Krinsky, NI and Olson, JA, Eds., *Carotenoids in Human Health*, vol. 691 (New York Acad. Sci., New York, 1993).

3. Krinsky, NI and Sies, H, Eds., *Antioxidant Vitamins and Beta-Carotene in Disease Prevention*, Am J. Clin. Nutr. 62 (Suppl): 1299S-1540S (1995)

4. Olson, JA and Krinsky, NI, Eds., *Carotenoids*, FASEB J. 9: 1547-1558 (1995).

5. Krinsky, N.I., Guest Editor, Proceedings of Symposium to Honor the Memory of James Allen Olson: Functions and Actions of Retinoids and Carotenoids: Building on the Vision of James Allen Olson J. Nutr. 134 (Suppl 1S) 218S-293S (2004)

6. Krinsky, N.I., Mayne, S.T. and Sies, H. (eds.) CAROTENOIDS IN HEALTH AND DISEASE in press Marcel Dekker, New York (2004)

E. Letters

1. Krinsky, NI and Leff, J, Visible Light: Mutagen or Killer? Science 160:1255-1256 (1968).

2. Krinsky, N.I., Peacocke, M. and Russell, R.M. Antioxidant Vitamins, Cancer and Cardiovascular Disease. New Engl. J. Med. 335: 1066-1067 (1996).

3. Krinsky, NI and Russell, RM, Regarding the Conversion of ß-Carotene to Vitamin A. Nutr. Rev. 59: 309 (2001).

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September 19, 2007

Laura Tarantino, Ph.D.
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: Lyc-O-Mato® 6% Oleoresin, 1.5% / 70% Oleoresin GRAS Notification (GRN 000156) Amendment

Dear Dr. Tarantino:

1. Introduction

As representative of the notifier, LycoRed Ltd. [LycoRed Natural Products Industries, Ltd.], Hebron Road – Industrial Zone, P.O. Box 320, Beer Sheva – 84102 Israel; Burdock Group, by this letter, is providing the Food and Drug Administration (FDA) a notice of intention to market tomato lycopene extract 6 *percent* (Lyc-O-Mato® 6% Oleoresin), tomato lycopene extract 1.5 *percent* (Lyc-O-Mato® 1.5%), and crystallized tomato lycopene extract (Lyc-O-Mato® 70% Oleoresin), the subjects of a prior Generally Recognized As Safe (GRAS) notification (GRN 000156[1]), as ingredients to be added to products that have been previously determined as medical foods.[2,3] This addition of these oleoresin ingredients to medical food products does not

000299

[1] See attached copy of the Notification Letter.

[2] 21 CFR 101.9(j)(8) Nutrition labeling of food. Medical foods as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)). A medical food is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. A food is subject to this exemption only if: (i) It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube; (ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone; (iii) It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation; (iv) It is intended to be used under

increase the Estimated Daily Intake of lycopene in the general population, and is supported by the safety studies cited in the previous GRAS notification (GRN 000156).

2. History of regulatory activity of tomato lycopene extract

The FDA has previously reviewed the GRAS status of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract for use as ingredients in baked goods, breakfast cereals, cheeses, condiments and relishes, confections, dairy product analogs, frozen dairy desserts, gelatins, puddings and fillings, grain products, gravies and sauces, jams and jellies, meat products, milk products, processed vegetables and vegetable juices, snack foods, soft candies, soups and soup mixes (GRN 000156). The GRN 000156 letter, dated February 7, 2005, acknowledged that the Agency had no further questions concerning the determination that these substances were GRAS for the proposed uses. The substances, tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract, are composed of tomato oleoresin, containing a standardized concentration of lycopene, with the balance consisting of other tomato lipids including total fatty acids, phytosterols, tocopherols, and other carotenoids, such as phytoene, phytofluene, and *beta*-carotene. The specifications for the tomato oleoresins have not changed from the original notification.

3. Consumption of tomato lycopene extract

Tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract (as indicated in GRN 000156) are intended to be used to increase the consumption of lycopene in the diet of the general population, when incorporated into specific food products as food ingredients. These foods are identified in GRN 000156, according to food codes given in the U.S. Department of Agriculture (USDA) 1994-1996, 98 Continuing Survey of Food Intakes by Individuals (CSFII, 94-96, 98), and these codes have been used to calculate the Estimated Daily Intake (EDI) values for lycopene consumption (Table 1). Other GRAS Notices concerning lycopene have been filed with the FDA, but due to the self-limiting nature of lycopene addition to food (*i.e.*, an undesirable red color or tomato-like taste), lycopene from more than one source would not likely be added to a food product. GRN 000156 identified the Acceptable Daily Intake (ADI) of lycopene at 120 mg/day.

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medical supervision; and (v) It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

[3] Because there is no specific deficiency, disease, syndrome or symptom arising from an absence of lycopene, the addition of lycopene, in and by itself, cannot render a food a "medical food" simply as the result of its addition to the food. In this GRAS Notification, tomato extract of lycopene is to be added to foods already determined to be medical foods.

Table 1. Current lycopene intake, predicted lycopene intake following supplementation of selected foods at the levels indicated in GRN 000156 and total lycopene intake (predicted + current) for individuals consuming selected supplemented foods

	Per User (mg/day)	
Lycopene intake from:	**Mean**	**90th Percentile**
A. Current consumption from food[a]	8.2	15.7
B. Possible maximum consumption with Tomato extracts (1.5%, 6%) or crystallized tomato lycopene extract as an added ingredient to food[a]	10.4	17.7
C. Consumption as a color additive[b]	5.3	9.2
D. Total consumption from conventional food (current + added)	23.9	42.6
E. Potential consumption from dietary supplement use	30.0	60.0
F. Total consumption from all sources (food + dietary supplements)	53.9	102.6

[a]Levels calculated using consumption values from CSFII 1994-1996, 1998 (2000) and food lycopene concentrations from Holden *et al.* (1999).
[b]GRN 000156

4. Proposed new use of tomato lycopene extract as an ingredient in products previously determined to be medical foods

Lycopene is a natural constituent of the typical U.S. diet, with mean lycopene consumption at approximately 8 mg/day.[4] The available information indicates that current commercial enteral formulas do not provide lycopene to patients comparable to that which would be derived from a typical diet (Olmedilla *et al.*, 1996). LycoRed, Ltd. intends to market tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract as ingredients for addition to products previously determined to be medical foods at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day.[5]

The term "medical food" means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Medical foods are in some cases, the sole source of calories and nutrients for a patient, but as often as not, certain medical foods are consumed as a caloric and nutritive supplement (*i.e.*, may be taken to supplement the typical diet), as a result of the patient not eating or being able to eat normally due to the patient's specific disease or condition.[2]

The addition of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract to products previously determined as medical foods intended to supplement the patient's diet was evaluated and determined GRAS by scientific procedures when

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[4]GRN000156 Notification.
[5]The energy content of a supplemental product is typically in the range of 200 – 400 kcal *per* serving, with a suggested intake of 1 to 3 servings *per* day, depending on the product. The maximum daily intake of lycopene from products previously determined as medical foods taken as a supplement to the typical diet would be 36 mg/day.

added to medical foods at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day.[5] While there is no question that patients receiving such a medical food as a sole source of nutrition would not exceed the ADI of lycopene because of the absence of other lycopene sources, the Expert Panel determined supplemental uses to the typical diet to also be consistent with the safe use of lycopene the following reasons:

- The original lycopene consumption calculation (see table above), indicating a potential total consumption of lycopene from all sources was 53.9 mg/day (mean) and 102.6 mg/day (90th percentile). This total stipulated that consumption from food [*i.e.,* as a natural constituent of food, as an added ingredient (with limitations to specific foods) and as a color additive] was 23.9 mg/day (mean) and 42.6 at the 90th percentile. The Expert Panel reasoned that if a patient is receiving medical food to supplement his/her caloric intake, it is unlikely that the patient will be consuming enough conventional food to achieve the mean or 90th percentile intakes of lycopene.
- This total (above, 53.9 and 102.6 mg/day) also assumed an exaggerated consumption of lycopene as a dietary supplement at 30 mg/day (mean) and 60 mg/day (90th percentile). Because medical foods are administered under supervision of a physician, the Expert Panel reasoned that patients who receive medical food to supplement their caloric and nutritive intake would be unlikely to consume dietary supplements, at least to the extent of the exaggerated estimates identified above.
- Lastly, the only documented effect of over-consumption of lycopene is a skin color change and to this extent, consumption of lycopene is self-limiting. In addition, because a patient consumes medical foods under the supervision of a physician, the physician, as a trained observer, would notice the skin color change, investigate this phenomenon and subsequently caution the patient about over consumption of lycopene.

5. Additional information in the scientific literature developed since the original GRAS (GRN 000156)

Tomato oleoresins are composed of the same substance previously notified, and reference is made to the original GRAS submission (GRN 000156). Summaries of safety data relevant to lycopene consumption are also referenced in GRN 000156, as a general recognition of safety. From the time of the first GRAS notification (August 4, 2004), additional preclinical and clinical studies have been published that evaluate the effects of lycopene or tomato extract consumption. Those studies are summarized in the attached GRAS 156 Amendment document. No adverse effects were noted in any of the preclinical or clinical studies published since the original GRAS submission. The Expert Panel that initially evaluated the available information on the tomato oleoresins and concluded that tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract were GRAS by scientific procedures for supplementing the diet with lycopene, was requested to reassess the GRAS status of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract in light of the proposed use as ingredients in products previously determined as medical foods. The Expert Panel evaluated information generated since the first GRAS review, and found that this information is consistent with that provided in the first GRAS determination and fully supports the GRAS status of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract for use in products previously determined to be medical foods, as indicated in the attached GRAS dossier Amendment document.

6. Conclusion

In consideration of the facts and reasoning presented above, it was concluded by the GRAS Expert Panel that the use of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day as ingredients in products previously determined as medical foods, and remains consistent with the safety data cited in GRN 000156.

This GRAS notification was based on published, generally available and accepted scientific data, information, methods and principles, as well as experience based on common use in foods. LycoRed has determined that the use of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract as ingredients to supplement medical foods with lycopene, are GRAS, and therefore, exempt from the premarket approval requirements of the U.S. Food, Drug and Cosmetic Act.

Sincerely,

George A. Burdock, PhD., D.A.B.T., F.A.C.N.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition

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October 12, 2007

Laura Tarantino, Ph.D.
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: Lyc-O-Mato® 6% Oleoresin, 1.5% / 70% Oleoresin GRAS Notification (GRN 000156) Amendment

Dear Dr. Tarantino:

1. Introduction

As agent of the notifier, LycoRed Ltd. [LycoRed Natural Products Industries, Ltd.], Hebron Road – Industrial Zone, P.O. Box 320, Beer Sheva – 84102 Israel; Burdock Group, by this letter, is providing the Food and Drug Administration (FDA) a notice of intention to market tomato lycopene extract 6 *percent* (Lyc-O-Mato® 6% Oleoresin), tomato lycopene extract 1.5 *percent* (Lyc-O-Mato® 1.5%), and crystallized tomato lycopene extract (Lyc-O-Mato® 70% Oleoresin), the subjects of a prior Generally Recognized As Safe (GRAS) notification (GRN 000156[1]), as ingredients to be added to products that have been previously determined as medical foods.[2,3]

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[1] See attached copy of the Notification Letter.

[2] 21 CFR 101.9(j)(8) Nutrition labeling of food. Medical foods as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)). A medical food is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. A food is subject to this exemption only if: (i) It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube; (ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone; (iii) It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation; (iv) It is intended to be used under medical supervision; and (v) It is intended only for a patient receiving active and ongoing medical supervision

This addition of these oleoresin ingredients to medical food products does not increase the Estimated Daily Intake of lycopene in the general population, and is supported by the safety studies cited in the previous GRAS notification (GRN 000156).

2. History of regulatory activity of tomato lycopene extract

The FDA has previously reviewed the GRAS status of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract for use as ingredients in baked goods, breakfast cereals, cheeses, condiments and relishes, confections, dairy product analogs, frozen dairy desserts, gelatins, puddings and fillings, grain products, gravies and sauces, jams and jellies, meat products, milk products, processed vegetables and vegetable juices, snack foods, soft candies, soups and soup mixes (GRN 000156). The GRN 000156 letter, dated February 7, 2005, acknowledged that the Agency had no further questions concerning the determination that these substances were GRAS for the proposed uses. The substances, tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract, are composed of tomato oleoresin, containing a standardized concentration of lycopene, with the balance consisting of other tomato lipids including total fatty acids, phytosterols, tocopherols, and other carotenoids, such as phytoene, phytofluene, and *beta*-carotene. The specifications for the tomato oleoresins have not changed from the original notification.

3. Consumption of tomato lycopene extract

Tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract (as indicated in GRN 000156) are intended to be used to increase the consumption of lycopene in the diet of the general population, when incorporated into specific food products as food ingredients. These foods are identified in GRN 000156, according to food codes given in the U.S. Department of Agriculture (USDA) 1994-1996, 98 Continuing Survey of Food Intakes by Individuals (CSFII, 94-96, 98), and these codes have been used to calculate the Estimated Daily Intake (EDI) values for lycopene consumption (Table 1). Other GRAS Notices concerning lycopene have been filed with the FDA, but due to the self-limiting nature of lycopene addition to food (*i.e.*, an undesirable red color or tomato-like taste), lycopene from more than one source would not likely be added to a food product. GRN 000156 identified the Acceptable Daily Intake (ADI) of lycopene at 120 mg/day.

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wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

[3] Because there is no specific deficiency, disease, syndrome or symptom arising from an absence of lycopene, the addition of lycopene, in and by itself, cannot render a food a "medical food" simply as the result of its addition to the food. In this GRAS Notification, tomato extract of lycopene is to be added to foods already determined to be medical foods.

Table 1. Current lycopene intake, predicted lycopene intake following supplementation of selected foods at the levels indicated in GRN 000156 and total lycopene intake (predicted + current) for individuals consuming selected supplemented foods

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D. Total consumption from conventional food (current + added)	23.9	42.6
E. Potential consumption from dietary supplement use	30.0	60.0
F. Total consumption from all sources (food + dietary supplements)	53.9	102.6

[a]Levels calculated using consumption values from CSFII 1994-1996, 1998 (2000) and food lycopene concentrations from Holden *et al.* **(1999).**
[b]GRN 000156

4. Proposed new use of tomato lycopene extract as an ingredient in products previously determined to be medical foods

Lycopene is a natural constituent of the typical U.S. diet, with mean lycopene consumption at approximately 8 mg/day.[4] The available information indicates that current commercial enteral formulas do not provide lycopene to patients comparable to that which would be derived from a typical diet (Olmedilla *et al.*, 1996). LycoRed, Ltd. intends to market tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract as ingredients for addition to products previously determined to be medical foods at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day.[5]

The term "medical food" means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Medical foods are in some cases, the sole source of calories and nutrients for a patient, but as often as not, certain medical foods are consumed as a caloric and nutritive supplement (*i.e.*, may be taken to supplement the typical diet), as a result of the patient not eating or being able to eat normally due to the patient's specific disease or condition.[2]

The addition of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract to products previously determined as medical foods intended to supplement the patient's diet was evaluated and determined GRAS by scientific procedures when

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[4]GRN000156 Notification.
[5]The energy content of a supplemental product is typically in the range of 200 – 400 kcal *per* serving, with a suggested intake of 1 to 3 servings *per* day, depending on the product. The maximum daily intake of lycopene from products previously determined as medical foods taken as a supplement to the typical diet would be 36 mg/day.

added to medical foods at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day.[5] While there is no question that patients receiving such a medical food as a sole source of nutrition would not exceed the ADI of lycopene because of the absence of other lycopene sources, the Expert Panel determined supplemental uses to the typical diet to also be consistent with the safe use of lycopene the following reasons:

- The original lycopene consumption calculation (see table above), indicating a potential total consumption of lycopene from all sources was 53.9 mg/day (mean) and 102.6 mg/day (90th percentile). This total stipulated that consumption from food [*i.e.*, as a natural constituent of food, as an added ingredient (with limitations to specific foods) and as a color additive] was 23.9 mg/day (mean) and 42.6 at the 90th percentile. The Expert Panel reasoned that if a patient is receiving medical food to supplement his/her caloric intake, it is unlikely that the patient will be consuming enough conventional food to achieve the mean or 90th percentile intakes of lycopene.
- This total (above, 53.9 and 102.6 mg/day) also assumed an exaggerated consumption of lycopene as a dietary supplement at 30 mg/day (mean) and 60 mg/day (90th percentile). Because medical foods are administered under supervision of a physician, the Expert Panel reasoned that patients who receive medical food to supplement their caloric and nutritive intake would be unlikely to consume dietary supplements, at least to the extent of the exaggerated estimates identified above.
- Lastly, the only documented effect of over-consumption of lycopene is a skin color change and to this extent, consumption of lycopene is self-limiting. In addition, because a patient consumes medical foods under the supervision of a physician, the physician, as a trained observer, would notice the skin color change, investigate this phenomenon and subsequently caution the patient about over consumption of lycopene.

5. Additional information in the scientific literature developed since the original GRAS (GRN 000156)

Tomato oleoresins are composed of the same substance previously notified, and reference is made to the original GRAS submission (GRN 000156). Summaries of safety data relevant to lycopene consumption are also referenced in GRN 000156, as a general recognition of safety. From the time of the first GRAS notification (August 4, 2004), additional preclinical and clinical studies have been published that evaluate the effects of lycopene or tomato extract consumption. Those studies are summarized in the attached GRAS 156 Amendment document. No adverse effects were noted in any of the preclinical or clinical studies published since the original GRAS submission. The Expert Panel that initially evaluated the available information on the tomato oleoresins and concluded that tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract were GRAS by scientific procedures for supplementing the diet with lycopene, was requested to reassess the GRAS status of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract in light of the proposed use as ingredients in products previously determined as medical foods. The Expert Panel evaluated information generated since the first GRAS review, and found that this information is consistent with that provided in the first GRAS determination and fully supports the GRAS status of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract for use in products previously determined to be medical foods, as indicated in the attached GRAS dossier Amendment document.

6. Conclusion

In consideration of the facts and reasoning presented above, it was concluded by LycoRed Ltd., that the use of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract at a level not to exceed 3 mg/100 kcal or 36 mg of lycopene/day as ingredients in products previously determined as medical foods, is (are) generally recognized as safe (GRAS), and remains consistent with the safety data cited in GRN 000156. LycoRed Ltd. bases its conclusion of GRAS status and assumes responsibility for this conclusion following close consultation with, and based on, the opinion of an Expert Panel (in compliance with the definition and description of Expert Panel actions in section 201(s) of the Federal Food Drug and Cosmetic Act) and, whose opinion is attached to this Notification.

This GRAS notification was based on published, generally available and accepted scientific data, information, methods and principles, as well as experience based on common use in foods. LycoRed Ltd. has determined that the use of tomato lycopene extract 6 *percent*, tomato lycopene extract 1.5 *percent*, and crystallized tomato extract as ingredients to supplement medical foods with lycopene, is (are) GRAS, and therefore, exempt from the premarket approval requirements of the U.S. Food, Drug and Cosmetic Act.

Sincerely,

George A. Burdock, PhD., D.A.B.T., F.A.C.N.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition

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