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Original Submission

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OFFICE OF
FOOD ADDITIVE SAFETY

Linda S. Kahl, Ph.D.
Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

November 13, 2002

Dear Dr. Kahl:

This letter is sent in compliance with proposed Sec. 170.36 of Part 21 of the *Code of Federal Regulations* (21 CFR 170.36) as published in the *Federal Register*, Vol. 62, No. 74, p. 18936 *et seq.*, April 17, 1997.

We wish to notify you that BASF Corporation has determined that the use of synthetic crystalline lycopene described in the enclosed notification is generally recognized as safe (GRAS), based on scientific procedures, and is thus exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act.

On behalf of BASF, an independent company assembled a panel of experts highly qualified by scientific training and experience to evaluate the safety of the intended uses of synthetic crystalline lycopene; the conclusions of these scientists regarding the safety and GRAS status of the material are also enclosed. Scientific nutrient safety evidence that formed, in part, the basis for GRAS status was published in Food and Chemical Toxicology; Volume 40, (2002) 1581-1588.

The information relied upon by BASF in making this determination is summarized in the enclosed materials, which are provided in triplicate. All of the data and information that serve as the basis for this GRAS determination will be available to FDA upon request or is available for FDA's review and copying at the offices of BASF Corporation in Mt. Olive, New Jersey.

Sincerely,

Herbert D. Woolf, Ph.D.
Technical Manager
BASF Corporation

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GRAS Synthetic Lycopene

BASF Corporation
3000 Continental Drive North
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I. GRAS EXEMPTION CLAIM

This is to notify you that BASF Corporation claims that the use of the substance described below (synthetic crystalline lycopene) is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because BASF has determined such use to be Generally Recognized As Safe (GRAS).

BASF convened an Expert Panel to review the available data and information on BASF's synthetic lycopene. The following individuals comprise the Expert Panel: Mildred S. Christian, Ph.D.; John W. Erdman, Jr., Ph.D.; Sanford A. Miller, Ph.D.; John A. Thomas, Ph.D. In addition, Gavin P. Thompson, Ph.D. served as the Panel's advisor on chemistry. After reviewing the available data, the Expert Panel concluded in its March 2002 statement that BASF's synthetic crystalline lycopene, to be used as in ingredient in breakfast cereals, juice drinks, energy drinks, dairy fruit drinks, instant soup, low fat dressings, meal replacements, meatless meat products, nutrient bars, salty snacks and crackers, and yogurt, resulting in an estimated mean intake of 4.7 mg lycopene per day and 90th percentile intake of 11.3 mg lycopene per day, is safe and GRAS for the general population.

This determination and notification are in compliance with proposed Sec. 170.36 of Part 21 of the Code of Federal Regulations (21 CFR § 170.36) as published in the Federal Register, Vol. 62, No. 74, FR 18937, April 17, 1997.

A. Name and Address of Notifier

BASF Corporation
3000 Continental Drive North
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Contact:	Herbert Woolf, Ph.D.
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B. Name of GRAS Substance

The substance that is the subject of this GRAS determination is synthetic crystalline lycopene prepared by BASF.

C. Intended Use and Consumer Exposure

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Synthetic crystalline lycopene is used in the manufacture of several products in commerce. These products include LycoVit®10%, Lycopene 10 Cold Water Dispersion

(CWD), and Lycopene Dispersion 20. Substances manufactured with synthetic crystalline lycopene are intended to be added to food as nutrient supplements (Code of Federal Regulations, Title 21 (21 CFR) §170.3(o)(20)) to increase the dietary intake of lycopene, an antioxidant carotenoid.

BASF intends use of LycoVit® 10%, Lycopene 10 CWD, and Lycopene Dispersion 20 in a variety of foods and beverages. The use categories and the maximum use levels per category are identified in Table 1.

Table 1. GRAS Uses of Synthetic Crystalline Lycopene in Foods and Beverages

Food Category	Maximum Use Level [a] (mg synthetic lycopene [b] per 100 g food as prepared)
Breakfast cereals (Ready-To-Eat and cooked)	0.5. 2.0, 3.5 or 7.0 [c]
Drinks (juice drinks, energy drinks, and dairy fruit drinks)	2.5
Instant soup	2.0
Low fat dressings	2.0
Meal replacements	2.5
Meatless meat products	5.0
Nutrient bars	5.0
Salty snacks and crackers	3.0
Yogurt	2.0

[a] The maximum use level of synthetic lycopene per 100 g food may be provided by any of the three synthetic lycopene-containing products (LycoVit® 10%, Lycopene 10 CWD, or Lycopene Dispersion 20)
[b] Total synthetic lycopene (*cis* + *trans* isomers)
[c] 7.0 mg synthetic lycopene per 100 g RTE for cereals weighing less than 20 g per cup, e.g., plain puffed cereal grains
3.5 mg synthetic lycopene per 100 g RTE for cereals weighing 20 g or more but less than 43 g per cup
3.5 mg synthetic lycopene per 100 g RTE for high fiber cereals containing 28 g or more of fiber per 100 g
2.0 mg synthetic lycopene per 100 g RTE for cereals weighing 43 g or more per cup or biscuit types
0.5 mg synthetic lycopene per 100 g cooked cereals

D. Basis for GRAS Determination

BASF Corporation's determination of the GRAS status of synthetic crystalline lycopene for use as a nutrient supplement as described in this document is based on scientific procedures as specified in 21 CFR §170.30(b).

Synthetic crystalline lycopene intake resulting from the intended use is safe and is also GRAS under the Federal Food, Drug, and Cosmetic Act (FDCA) based on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food.

This determination of the safety of lycopene in the synthetic crystalline lycopene is based on the generally accepted safety of naturally occurring lycopene as established in the available scientific literature, on the determination of substantial equivalence of the

synthetic crystalline lycopene with naturally occurring lycopene, and on the potential exposures to the general population that are associated with the intended use. Safety of consumption of the whole material, synthetic crystalline lycopene, is determined by evaluating the production process, the nature and quantity of impurities, and product specifications. Corroboration of safety is provided by animal toxicology studies and human clinical studies.

1. Description of Substance

a) Identity

Lycopene is a naturally occurring aliphatic hydrocarbon of the carotenoid class. Lycopene is the most abundant carotenoid in ripe tomatoes and comprises 80-90% of the pigment. Lycopene contains thirteen double bonds. The all-*trans* isomer is predominant in tomatoes and other natural sources. Storage, cooking, food processing, and exposure to light may result in some isomerization of the all-*trans* form to various cis forms including the 5-*cis*, 9-*cis*, 13-*cis*, and 15-*cis* forms.

(1) Common or Usual Names

The substance that is the subject of this GRAS determination is synthetic crystalline lycopene prepared by BASF and used in the following products: LycoVit® 10%, Lycopene 10 Cold Water Dispersion (CWD), and Lycopene Dispersion 20. The lycopene in these products is predominantly the all *trans*-lycopene (>80%) with some 5-*cis*-lycopene and other *cis* isomers.

(2) Chemical Names

Other chemical names for lycopene are Ψ,Ψ-carotene and (all-E)-all-*trans*-lycopene. It is commonly known as all-*trans*-lycopene. The systematic name for the all-*trans*-lycopene is (all-E)-2, 6, 10, 14, 19, 23, 27, 31-octamethyl-2, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30-dotricaconta-tridecaene.

(3) CAS Registry Number, Empirical Formula, and Molecular Weight

The Chemical Abstracts Service (CAS) Registry Number for lycopene is 502-65-8. The empirical formula is $C_{40}H_{56}$, and the molecular weight is 536.88.

b) Manufacturing Process

(1) Raw Materials

BASF generates a variety of products from the base material, synthetic crystalline lycopene. Because the crystalline is unstable due to its sensitivity to oxygen (exposure results in rapid isomerization and oxidation), the crystalline material is stored under inert gas (nitrogen) or is suspended in an aqueous solution containing antioxidants.

(2) Production Process: Overview

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Synthetic lycopene is manufactured using a three stage process:

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2. Figure 3. Synthesis of Lycopene

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c) Characteristics and Composition of Crystalline Material

(1) Side Reactions, Residuals, Impurities and By-Products

A variety of organic solvents are used in the synthesis reaction steps, in the separation and concentration of intermediates, and in the clean-up and formulation of the various products derived from the crystalline lycopene. Therefore, batches of the crystalline material and the formulated product have been analyzed for these solvents, namely, methanol, acetone, n-heptane, methylene chloride, and isopropanol.

Chemical characterization of batches of products containing synthetic lycopene crystalline material identify 100 ± 1.6% of the components in the crystalline material. Approximately 98% of the identified components are lycopene, including both *cis* and *trans*-isomers. An additional 0.9% is identified as lycopene-related substances (e.g., rhodopin); the remainder includes approximately 0.3% residual solvents.

(2) Isomer Profiles: Comparability of Natural Lycopene and Synthetic Lycopene

Approximately 79 – 84 percent of the lycopene in BASF synthetic crystalline lycopene is the all-*trans* isomer; in extracts of natural lycopene, the range is 67 – 98 percent all-*trans* isomer (Schierle et al. 1997, Nguyen and Schwartz 1998, BASF October 4, 2001). The characterization of the synthetic crystalline lycopene demonstrates the substantial equivalence of the synthetic lycopene to lycopene extracts from natural sources (FDA 1997).

d) Specifications for Food-grade Products

The specifications for the food-grade crystalline material and products formulated with it are presented in Table 2. Other components of the formulated products are food-grade materials.

Table 2. Specifications for Food-Grade Products of Synthetic Lycopene

Parameter	Specification	Test Method
Synthetic Lycopene Crystalline		
Assay (for total carotenoids)	min. 96 %	AM 0087 DA 0 (photometric assay)
Identity	Profile must conform to standard	M 98/0021-02e (HPLC analysis)
Arsenic	max. 3 ppm	PM 0160/04e
Lead	max. 0.5 ppm	PM 0160/04e
Copper and Zinc	max. 50 ppm	PM 0160/04e
Zinc	max. 25 ppm	PM 0160/04e
Heavy metals (as lead)	max. 10 ppm	PM 0160/04e
Loss on drying	max. 0.2 %	KON 131.1
Residue on ignition	max. 0.1 %	PM 0107/01e
LycoVit® 10%		
Assay (for total carotenoids)	min. 10 %	AM 1037 DF 01 (photometric assay)
Lycopene 10 CWD		
Assay (for total carotenoids)	10.5 - 12.5 %	AM 1032 DF01 (photometric assay)
Lycopene Dispersion 20		
Assay (for total carotenoids)	20.4 - 22.0 %	AM 1037 DF 01 (photometric assay)

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3. Safety Determination of Synthetic Crystalline Lycopene Exposure: Comparison of Estimated Daily Intake to Background Exposure

a) Background Exposure to Lycopene in the American Diet

Tomatoes and tomato products are the primary natural sources of lycopene in the American diet. These foods have been consumed throughout history by individuals of all ages. Based on food consumption data reported in the Third National Health and Nutrition Examination Survey (NHANES III) and carotenoid data compiled by the U.S. Department of Health and Human Services, National Center for Health Statistics and the Nutrition Coordinating Center, the mean estimated per capita intake of lycopene by the U.S. population age 2 and older is 7.9 mg/day; the 90th percentile intake is 22.8 mg/day (U.S. DHHS 1997, U.S. DHHS-NCC 2000).

In NHANES III, slightly more than 70 percent of the U.S. population age 2 years and older reported consumption of a lycopene-containing food on the survey day. Their mean intake of lycopene was 10.9 mg, and the 90th percentile of intake was 27.8 mg; these levels of intake roughly correspond to the amount of lycopene provided in a standard serving of a tomato-based food such as lasagna or vegetable juice. Estimates of lycopene intake from select foods that contain processed tomato products (including commonly consumed foods such as catsup, pizza, spaghetti sauce and pasta mixtures, tomato juice, tomato paste/puree/sauce, and tomato soup) indicate that among users, the mean intake of lycopene from any one of these food categories ranges from 4.7 to 29.2 mg per day, and intake at the 90th percentile ranges from 11.6 to 60.9 mg per day. Intake of lycopene from naturally occurring sources by the U.S. population therefore may range from none to approximately 30 mg or more per day depending on the specific foods consumed.

b) Estimated Daily Intake of BASF Synthetic Lycopene from GRAS Uses

Using food intake data reported in the United States Department of Agriculture's 1994-96 Continuing Survey of Food Intakes by Individuals (CSFII) and its 1998 Supplemental Children's Survey (USDA 2000), exposure to BASF synthetic lycopene that will result from the GRAS uses was estimated. The CSFII provides the most current food consumption data available for the American population.

The CSFII was conducted between January 1994 and January 1997 with non-institutionalized individuals in the United States. In each of the three survey years, data were collected from a nationally representative sample of individuals of all ages. The CSFII 1998 survey was a survey of children ages 0 through 9 years which was supplemental to the CSFII 1994-96. It used the same sample design as the CSFII 1994-96 and was intended to be merged with CSFII 1994-96 to increase the sample size for children. The merged surveys are designated as CSFII 1994-96, 1998. In the CSFII 1994-96, 1998, dietary intakes were collected through in-person interviews using 24-hour recalls on two nonconsecutive days approximately one week apart. A total of 21,662 individuals provided data for the first day; of those individuals, 20,607 provided data for a second day. The food record for each individual includes the gram weight and nutrient data for all foods consumed during the day of the recall.

Estimates of 2-day average intakes of synthetic lycopene were calculated from the food code list and the survey database of diet recalls. All estimates were generated with USDA sampling weights to adjust for differences in representation of subpopulations.

Results of the exposure estimates for the U.S. population ages 2 years and older are presented in Table 3; estimates are presented for each food category, and all categories combined. These estimates were calculated from 2-day average intakes of BASF synthetic lycopene by all individuals who consumed one or more foods from the proposed use categories at least once during the recall period. The mean intake of BASF synthetic lycopene from all GRAS proposed use categories by users of one or more foods is 4.7 mg/day and the 90th percentile intake of BASF synthetic lycopene is 11.3 mg/day.

The salty snacks and crackers, breakfast cereals, and drinks use categories represent the most frequently consumed proposed uses in the population ages 2 years and older. Results of the estimates of exposure from all use categories combined indicate that approximately 83 percent of the population ages 2 years and older consume one or more of the foods and beverages included in the list of proposed GRAS uses in a 2-day period. This is likely an overestimate of exposure to foods with BASF synthetic lycopene, as these estimates assume that all foods in the proposed use categories are manufactured with BASF synthetic lycopene at the maximum proposed use level.

Table 3. Estimated Intake of Synthetic Lycopene from Proposed GRAS Uses by Use Category: All Individuals 2 and Older

	Consumers of GRAS Uses		Synthetic Lycopene Intake [a] (mg/d)	
Food Category	**n**	**%**	**Mean**	**90th Percentile**
Breakfast cereals	10336	47	1.2	2.1
Drinks [b]	6557	29	7.8	15.4
Instant soup	1205	6	3.2	5.8
Low fat dressing	872	6	0.4	0.9
Meal replacements	252	2	7.0	12.6
Meatless meat products	367	2	0.5	1.8
Nutrient bars	748	4	1.4	2.3
Salty snacks and crackers	10050	52	0.9	2.0
Yogurt	1324	7	2.2	4.3
All categories	15773	83	4.7	11.3

Data source: U.S. Department of Agriculture, Agricultural Research Service. Continuing Survey of Food Intakes by Individuals 1994-96, 1998. Estimates represent the 2-day average intake reported per individual; data are limited to individuals who provided two 24-hour dietary recalls. A "user" is an individual who reported consumption of one or more foods in a use category during the recalls. All results were generated with USDA sampling weights to adjust for differences in representation of subpopulations.

[a] Total lycopene (*cis* + *trans* isomers)

[b] Includes juice drinks, energy drinks, and dairy fruit drinks.

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Results of the exposure estimates to all proposed uses of synthetic lycopene combined by select subpopulations are presented in Table 4. These estimates were calculated from 2-day average intakes of BASF synthetic lycopene by all individuals who consumed one or more foods from the proposed GRAS use categories at least once during the recall period. The population with the highest potential intake of synthetic lycopene from the proposed GRAS supplement uses is teenagers. The mean daily intake of BASF synthetic lycopene from all GRAS uses combined by teenagers is 6.9 mg/day and the 90th percentile intake of BASF synthetic lycopene is 15.9 mg/day.

Table 4. Estimated Intake of Synthetic Lycopene from All Proposed GRAS Uses Combined and Future Uses as a Color Additive

	Consumers of GRAS Uses		Synthetic Lycopene Intake [a] (mg/d)			
			From GRAS Uses		From GRAS Uses and Future Color Additive Uses [b]	
Population	**n**	**%**	**Mean**	**90th Percentile**	**Mean**	**90th Percentile**
Infants 0-11 m	318	31	2.1	5.0	2.1	5.0
Infants 1 y	908	94	3.6	9.3	3.8	9.4
Children 2-5 y	5312	98	5.1	11.6	5.6	12.3
Children 6-12 y	1996	95	5.8	12.8	6.6	14.2
Teenagers 13-19 y	1069	87	6.9	15.9	7.6	16.8
Adults ≥20 y	7396	80	4.1	9.8	4.6	10.7
Population ≥2 y	15773	83	4.7	11.3	5.3	12.0

Data source: U.S. Department of Agriculture, Agricultural Research Service. Continuing Survey of Food Intakes by Individuals 1994-96, 1998. Estimates represent the 2-day average intake reported per individual; data are limited to individuals who provided two 24-hour dietary recalls. A "user" is an individual who reported consumption of one or more foods in a use category during the recalls. All results were generated with USDA sampling weights to adjust for differences in representation of subpopulations.

[a] Total lycopene (*cis* + *trans* isomers)

[b] Proposed uses of synthetic lycopene as a color additive include 4% in hard candy, 2% in ice cream and frozen yogurt, 2% in pudding mixes, and 6% in sugar coated drops (percent refers to weight of synthetic lycopene per 100 g food (as consumed)). These color additive uses are not the subject of this GRAS determination.

Lycopene imparts color to foods and synthetic lycopene may in the future be approved for use as a color additive. Therefore, Table 4 also presents estimated exposure to synthetic lycopene from the proposed GRAS uses and future color additive uses combined. These results are based upon the population of individuals who reported consumption of foods that are proposed for nutrient supplementation with synthetic lycopene. The color additive uses are not included in this GRAS determination but may provide additional sources of synthetic lycopene in the future. The mean daily intake of BASF synthetic lycopene from all proposed GRAS (nutrient) and color additive uses combined is 5.3 mg/d for the population of users ages 2 and older, and the 90th percentile

intake is 12.0 mg/d. In the population of teenagers, mean intake of synthetic lycopene from the combined nutrient and color additive uses is 7.6 mg/day for teenagers, while the 90th percentile intake for this population is 16.8 mg/day.

c) Relative Bioavailability of Lycopene

Several dietary factors are known to affect the bioavailability of carotenoids. Factors believed to have the greatest influence on lycopene bioavailability include the type of food matrix in which the carotenoid is located and mechanical homogenization and/or heat treatment associated with processing. The lycopene isomer profile of the product, presence and type of dietary fat, and presence of dietary fiber may also influence absorption (Williams et al. 1998, van het Hof et al. 2000b, Erdman et al. 1993, Stahl and Sies 1992, Riedl et al. 1999).

In order to understand the bioavailability of the synthetic lycopene products as compared to a natural source of lycopene, BASF conducted a clinical trial comparing BASF synthetic lycopene product with natural lycopene material.

A single-blind, randomized, placebo-controlled, parallel and free living trial was conducted by TNO Nutrition and Food Research from April 3, 2000 through May 2, 2000 to determine the relative bioavailability of LycoVit 10% and lycopene naturally occurring in tomatoes (Steenge et al. 2001). The natural lycopene material tested was Lyc-O-Mato™ Beads 5%, tomato lycopene in beadlets produced by LycoRed Natural Products Industries, Ltd.

Results of this study suggest that daily ingestion of capsules containing 15 mg lycopene from LycoVit10% or Lyc-O-Mato5% has a comparable effect on raising serum levels of total lycopene. Additionally, neither form of lycopene appeared to have an effect on serum levels of other carotenoids as observed under the conditions of this study, nor were any other potentially adverse effects noted.

d) Safety Determination

Tomatoes and tomato products are concentrated sources of lycopene in the American food supply, and individuals consume this carotenoid as part of a varied and normal diet. The synthetic lycopene created by BASF has been shown to be chemically substantially equivalent to natural lycopene and therefore can be regarded as interchangeable with natural lycopene in the diet. As with other nutrients, it is recognized that adverse health effects can be produced if intakes of lycopene from natural or synthetic sources are excessive. Unlike the situation for assessing risk of an environmental chemical, nutrients are essential for human well-being and often life itself within a certain range of intakes (IOM 2000).

A principal feature of the safety assessment process for nutrients such as lycopene is that no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded. Therefore, the approach to evaluating the safety of increased lycopene intake

from consumption of synthetic lycopene is based on an evaluation of the incremental increase this ingestion will produce compared to background exposure. The estimated daily intake (EDI) of lycopene from the intended uses of BASF synthetic lycopene is compared to background intake levels of lycopene from foods. A reasonable assurance of safety is provided when the ingestion of lycopene from the intended uses of BASF synthetic lycopene results in only a moderate increase in the total background intake of this carotenoid. Corroboration of safety is provided by human clinical studies and animal toxicology studies.

Exposure to dietary lycopene is provided through a small number of foods, primarily tomatoes and processed tomato products. As a result, lycopene intakes may vary widely from day to day. In the United States, the mean per capita lycopene intake of all individuals 2 years and older is 7.9 mg/day. Given that only a limited number of foods contain more than trace amounts of lycopene and that lycopene-rich foods are not necessarily daily staples in the diet, as previously indicated, only slightly more than 70 percent of the population consumes any lycopene-containing food on a random day. Per capita estimates based on one day of intake therefore are likely to underestimate the amount of lycopene consumed by individuals who do include lycopene-containing foods and beverages in their diet.

The estimated mean intake of BASF synthetic lycopene from all GRAS use categories by users of one or more foods is 4.7 mg per day and the 90th percentile intake of BASF synthetic lycopene is 11.3 mg per day. The population with the highest potential intake of synthetic lycopene is teenagers. The estimated mean daily intake of BASF synthetic lycopene from all use categories by teenagers is 6.9 mg per day and the 90th percentile intake of BASF synthetic lycopene is 15.9 mg per day.

Based on data from bioavailability studies, the bioavailability of synthetic lycopene appears to approximate to the bioavailability of lycopene from processed tomato products. Therefore, an intake of BASF synthetic lycopene in the range of 10 to 15 mg would be roughly comparable to the intake of lycopene from a typical serving of lasagna or slightly less than the amount of lycopene provided in a serving of spaghetti sauce. This amount of lycopene results in a moderate increase in background intake of lycopene, which is estimated to be nearly 30 mg per day or more for some consumers of lycopene-rich foods, and is therefore regarded as a safe level of intake.

4. Corroborative Safety Studies

a) Toxicology Studies of Synthetic Lycopene Products

Results from toxicology studies provide corroborative evidence of the safety of ingestion of the synthetic crystalline lycopene products. A rat toxicology study of BASF's synthetic crystalline lycopene products demonstrated the safety of ingestion of synthetic crystalline lycopene. In a 13-week oral dosing study, no adverse effects were observed at doses of 0, 500, 1,500 and 3,000 mg/kg-bw/day of the products tested. The no observed adverse effect level (NOAEL) for this study was concluded to be 3,000

mg/kg-bw/day (highest dose tested) for the synthetic crystalline lycopene products tested, which is equivalent to 324 mg synthetic lycopene/kg-bw/day based on a lycopene content of 10.8% in the synthetic lycopene product. At the highest dose tested, the dose of synthetic crystalline lycopene given was approximately 4,000 fold higher, on a body weight basis, than the mean EDI of lycopene in humans from BASF synthetic crystalline lycopene products. This dose of BASF synthetic crystalline lycopene products did not produce any adverse effects.

A genotoxicity battery (including the Ames assay, an *in vivo* micronucleus assay, an *in vitro* chromosome aberration assay, and *in vivo/in vitro* unscheduled DNA synthesis assays) indicated no concern for mutagenic potential of the BASF synthetic crystalline lycopene products.

Developmental (embryo-fetal) toxicity studies of synthetic crystalline lycopene products revealed no developmental toxicity in rats at maximum feasible doses as high as 3,000 mg/kg-bw/day, or in rabbits at maximum feasible doses as high as 2,000 mg/kg-bw/day.

Estimates of daily intake of lycopene-related substances, process residuals, and impurities in the synthetic crystalline lycopene product at the mean level of intake (4.7 mg/day), were less than 3.75×10^{-2} mg/day, the limit for FDA's Concern Level I. The toxicology data package for synthetic crystalline lycopene exceeds the FDA guideline for testing at this level of exposure.

b) Human Clinical and Epidemiology Studies of Lycopene Intake

Normal serum concentrations of lycopene are variable, and physiologic, lifestyle, and dietary habits are thought to be associated with plasma lycopene concentrations (Johnson 1998). No adverse effects were noted in human trials in which intake of 5 to 150 mg lycopene daily was observed for up to 24 weeks (Böhm and Bitsch 1999, Bowen et al. 1993, Cohn et al. 2001, Micozzi et al. 1992, Paetau et al. 1998, Porrini et al. 1998, Porrini and Riso 2000, Rao and Agarwal 1998, Riso et al. 1999, Steenge et al. 2001). Epidemiology studies of lycopene intake suggest that intake of lycopene, serum levels of lycopene, and adipose levels of lycopene may be associated with reduced risk for some chronic diseases (Clinton 1998).

c) Adverse Effects of Carotenoid Intake

Excessive intake of foods or supplements high in carotenoids has been associated with changes in skin color; the effects are identified as carotenodermia and are harmless but clearly documented biological effects of high carotene intake (IOM 2000). Carotenodermia is characterized by yellowish discoloration of the skin. It is considered harmless and is readily reversible when carotenoid ingestion is discontinued. A related condition that is unique to high intake of the carotenoid lycopene is lycopenodermia. Lycopenodermia results from high intakes of lycopene-rich foods such as tomatoes and is characterized by a deep orange discoloration of the skin. Case reports of individuals with lycopenodermia indicate that the skin discoloration is reversible when dietary intake of tomatoes is restricted (Reich et al. 1960; La Placa et al. 2000).

At the intended levels of use in food, intake of lycopene has not been shown to adversely impact absorption of other carotenoids (Johnson et al. 1997, van den Berg and van Vleit 1998, van den Berg 1999).

E. Availability of Information

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times at the office of Herbert D. Woolf, Ph.D., BASF Corporation, 3000 Continental Drive-North, Mount Olive, New Jersey 07828-1234, telephone (973) 426-5378 and facsimile (973) 426-5399, email woolfh@basf.com.

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ENVIRON

CONCLUSIONS OF THE EXPERT PANEL: THE GENERALLY RECOGNIZED AS SAFE STATUS OF SYNTHETIC CRYSTALLINE LYCOPENE IN BASF LYCOVIT® 10%, LYCOPENE 10 CWD, AND LYCOPENE DISPERSION 20

Prepared for
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March 18, 2002

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FORWARD

The following summary was prepared by an Expert Panel organized by ENVIRON International Corporation at the request of BASF. The charge of the Expert Panel was to review the data collected by ENVIRON to determine the generally recognized as safe (GRAS) status of synthetic crystalline lycopene in the BASF products LycoVit® 10%, Lycopene 10 CWD, and Lycopene Dispersion 20. The Expert Panel participants and the Panel's advisor on chemistry were:

Dr. Mildred S. Christian
President, Argus International, Inc.
Horsham, Pennsylvania

Signature: Date: 3/28/02

Dr. John W. Erdman, Jr.
Professor
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Dr. Sanford A. Miller
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Signature: Date: 4/7/02

Dr. John A. Thomas
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University of Texas Health Science Center
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Senior Science Advisor
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Signature: Date: 04/12/02

CONCLUSIONS OF THE EXPERT PANEL: THE GENERALLY RECOGNIZED AS SAFE STATUS OF SYNTHETIC CRYSTALLINE LYCOPENE IN BASF LYCOVIT® 10%, LYCOPENE 10 CWD, AND LYCOPENE DISPERSION 20

We, the members of the Expert Panel, have performed a comprehensive and critical review of the GRAS status of BASF's synthetic crystalline lycopene. Our collective conclusions follow:

- The substance that is the subject of this generally recognized as safe ("GRAS") determination is crystalline lycopene produced by chemical synthesis. The carotenoid lycopene constitutes approximately 98% by weight of the crystalline material. This material is used in the manufacture of products in commerce ("BASF synthetic crystalline lycopene products"), including LycoVit® 10%, Lycopene 10 CWD, and Lycopene Dispersion 20, which are intended to be added to foods as nutrient supplements to increase the dietary intake of lycopene.

- The safety of consumption of synthetic crystalline lycopene used as an ingredient in food is determined by evaluating the safety of ingestion of the whole product, as well as safety of ingestion of the major constituent, lycopene. Safety of consumption of the whole product is determined by evaluating the source of the product, production process, nature and quantity of impurities, and product specifications. Compositional analysis of the product identifies 100.0 ± 1.6% of the components. Appropriate product specifications are set to assure food grade product.

- Carotenoids, including lycopene, occur naturally in fruits and vegetables and are part of the normal diet. Our approach to evaluating the safety of increased lycopene intake from consumption of BASF synthetic crystalline lycopene products is based on an evaluation of the incremental increase this ingestion will produce in lycopene compared to background exposure. The estimated daily intake (EDI) of lycopene from BASF synthetic crystalline lycopene products is compared to background levels of intake of lycopene from foods. A reasonable assurance of safety is provided when the ingestion of lycopene from the proposed uses of BASF synthetic crystalline lycopene products results in a moderate increase in the intake of lycopene. Corroboration of safety is provided by animal toxicology studies and human clinical studies.

- Tomatoes and tomato products are the primary natural sources of lycopene in the American diet. In the Third National Health and Nutrition Examination Survey, slightly more than 70 percent of the U.S. population age 2 and older reported consumption of a lycopene-containing food on the survey day. Their mean intake of lycopene was 10.9 mg, and the 90th percentile of intake was 27.8 mg. The mean estimated per capita intake of lycopene by the U.S. population age 2 and older is 7.9 mg/day; the 90th percentile intake is 22.8 mg/day.

- The mean estimated intake of lycopene from all proposed use categories of BASF synthetic crystalline lycopene products by users of one or more foods is 4.7 mg/day and the 90th percentile of intake is 11.3 mg/day. The proposed product uses, proposed levels of addition of lycopene, and EDI's are given in the following table:

Proposed Uses of BASF Synthetic Crystalline Lycopene Products and Estimated Daily Intake of Synthetic Crystalline Lycopene by Users Age 2 Years and Older

Food Category	Proposed Maximum Use Level of Synthetic Lycopene [a] (mg per 100 g food as prepared)	Synthetic Lycopene Intake (mg/day)	
		Mean	90th Percentile
Breakfast Cereals (Ready-To-Eat and cooked)	0.5 – 7.0[b]	1.2	2.1
Drinks (energy, dairy fruit, and juice drinks)	2.5	7.8	15.4
Instant soup	2.0	3.2	5.8
Low fat dressings	2.0	0.4	0.9
Meal replacements	2.5	7.0	12.6
Meatless meat products	5.0	0.5	1.8
Nutrient bars	5.0	1.4	2.3
Salty snacks and crackers	3.0	0.9	2.0
Yogurt	2.0	2.2	4.3
All categories combined		4.7	11.3

[a] The proposed maximum use level of synthetic lycopene per 100 g food may be provided by one of the three synthetic lycopene-containing products (LycoVit® 10%, Lycopene 10 CWD, or Lycopene Dispersion 20); synthetic lycopene includes *cis* + *trans* isomers

[b] 7.0 mg synthetic lycopene per 100 g for Ready-To-Eat (RTE) cereals weighing less than 20 g per cup, e.g., plain puffed cereal grains
3.5 mg synthetic lycopene per 100 g for RTE cereals weighing 20 g or more but less than 43 g per cup
3.5 mg synthetic lycopene per 100 g for RTE high fiber cereals containing 28 g or more of fiber per 100 g
2.0 mg synthetic lycopene per 100 g for RTE cereals weighing 43 g or more per cup or biscuit types
0.5 mg synthetic lycopene per 100 g for cooked cereals

- Approximately 79 – 84 percent of the lycopene in BASF synthetic crystalline lycopene is the all-*trans* isomer; in extracts of natural lycopene, the range is 67 – 98 percent all-*trans* isomer.

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- The literature suggests that the bioavailability of lycopene from processed tomato products approaches that of purified natural sources or synthetic forms of lycopene. It is therefore reasonable to assume that the bioavailability of BASF synthetic lycopene approximates the bioavailability of naturally occurring lycopene as provided by highly processed tomato products.

- Intake of 4.7 to 11.3 mg lycopene/day from consumption of foods containing BASF synthetic crystalline lycopene products is considered to be a moderate increase in the level of intake of natural lycopene. Human clinical and epidemiology studies of lycopene intake show no adverse effects over a wide range of exposures. At the proposed levels of use in food, intake of lycopene has not been shown to adversely impact absorption of other carotenoids.

- A genotoxicity battery (including the Ames assay, an *in vivo* micronucleus assay, an *in vitro* chromosome aberration assay, and *in vivo/in vitro* unscheduled DNA synthesis assays) indicated no concern for mutagenic potential of the BASF synthetic crystalline lycopene products. A rat toxicology study of BASF synthetic crystalline lycopene products demonstrated the safety of ingestion of synthetic crystalline lycopene. In a 13-week oral dosing study, no adverse effects were observed at doses of 0, 500, 1,500 and 3,000 mg/kg-bw/day of the products tested. The no observed adverse effect level (NOAEL) for this study was concluded to be 3,000 mg/kg-bw/day (highest dose tested) for the synthetic crystalline lycopene products tested, which is equivalent to 324 mg synthetic lycopene/kg bw/day based on a lycopene content of 10.8% in the synthetic lycopene product. At the highest dose tested, the dose of synthetic crystalline lycopene given was approximately 4,000 fold higher, on a body weight basis, than the mean EDI of lycopene in humans from BASF synthetic crystalline lycopene products. This dose of BASF synthetic crystalline lycopene products did not produce any adverse effects.

- Developmental (embryo-fetal) toxicity studies of synthetic crystalline lycopene products revealed no developmental toxicity in rats at maximum feasible doses as high as 3,000 mg/kg-bw/day, or in rabbits at maximum feasible doses as high as 2,000 mg/kg-bw/day.

- Estimates of daily intake of lycopene-related substances, process residuals, and impurities in the synthetic crystalline lycopene product at the mean level of intake (4.7 mg/day), were less than 3.75×10^{-2} mg/day, the limit for FDA's Concern Level I.

The toxicology data package for synthetic crystalline lycopene exceeds the FDA guideline for testing at this level of exposure.

- In conclusion, synthetic crystalline lycopene, used in the manufacture of BASF synthetic crystalline lycopene products, has been sufficiently characterized to assure both a food grade product and no toxicity concerns from impurities. Ingestion of BASF synthetic crystalline lycopene products results in a moderate increase in intake of lycopene over existing levels of intake from naturally occurring sources such as tomatoes and tomato products. Further, at the proposed levels of use in foods, it has no adverse impact on absorption of other carotenoids. Corroboration of safety is provided by animal toxicology studies and clinical and epidemiology studies of lycopene intake. Therefore, synthetic crystalline lycopene, to be used as an ingredient in breakfast cereals, juice drinks, energy drinks, dairy-fruit drinks, instant soup, low fat dressings, meal replacements, meatless meat products, nutrient bars, salty snacks and crackers, and yogurt, resulting in a mean intake of 4.7 mg lycopene/day and a 90th percentile intake of 11.3 mg lycopene/day, is safe and GRAS for the general population.

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BASF Corporation

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Facsimile Cover Sheet

To:	Dr. Robert Martin FDA/CFSAN GRAS Notification Program	**From:**	Dr. Herbert Woolf BASF Corporation 3000 Continental Drive-North Mount Olive, New Jersey 07828-1234
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Date:	November 26, 2002		
Pages:	one		

Subject: BASF Synthetic Lycopene GRAS Notification: Clarification of intended uses

cc:

Comments:

Dear Dr. Martin:

This communication is in response to your request for clarification of BASF's "Intended Use and Consumer Exposure" of synthetic lycopene as described in Section C on page one of BASF's GRAS Notification letter on November 13, 2002. BASF synthetic lycopene is not intended for use in meat or poultry. The intended uses and use levels for BASF's synthetic lycopene are stated in Table 1, page two "GRAS uses of synthetic crystalline lycopene in foods and beverages"

Yours truly,

Herbert D. Woolf; Ph.D.
BASF Corporation

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End Submission