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LYCOPENE (SYNTHETIC)
CHEMICAL AND TECHNICAL ASSESSMENT (CTA)

Prepared by Zofia Olempska-Beer, Ph.D.
Office of Food Additive Safety, Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
College Park, Maryland, USA

1. Summary

This Chemical and Technical Assessment summarizes the information about lycopene (synthetic) submitted to JECFA by BASF AG in a dossier dated 15 December, 2005, and by DSM Nutritional Products Ltd in a dossier dated 8 December, 2005. This document also discusses published information pertinent to lycopene in general.

Lycopene belongs to a group of naturally-occurring pigments known as carotenoids. Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. Tomatoes and tomato-based products are the major sources of lycopene in the human diet. In analogy to other carotenoids, lycopene occurs in various geometrical configurations. Lycopene present in fresh tomatoes consists predominantly of all-*trans*-lycopene. The synthetic lycopene described in this dossier contains approximately 70% of all-*trans*-lycopene, up to 23% of 5-*cis*-lycopene, and minor quantities of other *cis*-isomers.

Synthetic lycopene is produced by the Wittig condensation of synthetic intermediates that are also used in the production of other carotenoids used in food (Paust, 1996; Ernst, 2002). Lycopene is unstable when exposed to oxygen and light. To assure adequate stability, synthetic lycopene is stored under nitrogen or other inert gas in light-proof containers. Commercial lycopene preparations intended for use in food are formulated as suspensions in edible oils or as water-dispersible powders and are stabilized with antioxidants. Synthetic lycopene is intended for use in a wide range of foods at levels from 2 to 130 mg/kg.

2. Description

Lycopene is a red pigment that occurs naturally in certain fruits, vegetables, algae, and fungi. It belongs to a large group of pigments known as carotenoids, however, it has no provitamin A activity. Tomatoes and tomato-based products are the major sources of natural lycopene in the human diet. Other significant sources of lycopene include watermelon, pink grapefruit, pink guava, papaya, and apricots (Nguyen and Schwartz, 1999).

Synthetic lycopene occurs as a red to dark violet crystalline powder. It is insoluble in water and nearly insoluble in methanol and ethanol, but is freely soluble in chloroform and tetrahydrofuran. Lycopene is sparingly soluble in ether, hexane, and vegetable oils. A 1% solution of lycopene in chloroform is clear and has intensive orange-red colour. A solution in hexane shows an absorption maximum at approximately 470 nm.

3. Manufacturing

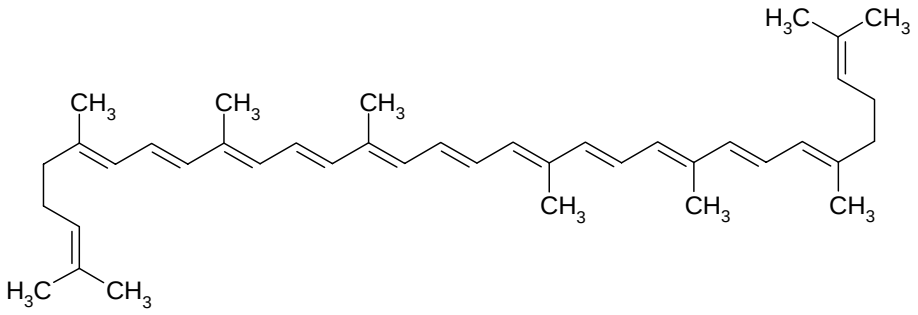
Synthetic lycopene is prepared from synthetic intermediates that are commonly used in the synthesis of other carotenoids used in food (Paust, 1996; Ernst, 2002). The production process

consists of several steps that may differ depending on the selection of the starting materials. Typically, the final production step includes a Wittig-type condensation between two intermediate compounds, one of which is usually C_{10}-dialdehyde, and the other is either lycopyl salt or another similar compound. Synthetic lycopene may contain low levels of triphenyl phosphine oxide (TPPO), *apo*-12'-lycopenal (known as lycopene C_{25}-aldehyde), and other lycopene-related substances, such as 1,2-dihydro-1-hydroxylycopene (rhodopin) or 1,2-dihydro-1-acetyllycopene (acetylrhodopin). Synthetic lycopene may also contain residues of volatile solvents.

4. Chemical characterization

Lycopene is an unsaturated acyclic hydrocarbon. It contains 13 double bonds, of which 11 are conjugated. The chemical name of lycopene is 2,6,10,14,19,23,27,31-octamethyl-2,6,8,10,12,14,16,18,20,22,24,26,30-dotriacontatridecaene. Common names include *Ψ,Ψ*-carotene, all-*trans*-lycopene, and (all-E)-lycopene. The chemical formula is $C_{40}H_{56}$.

The structural formula of all-*trans*-lycopene, which is the major isomer present in synthetic lycopene, is shown below:



The molecular weight of lycopene is 536.9 and the Chemical Abstract Service (CAS) number is 502-65-8.

Lycopene occurs in the all-*trans* and various *cis* configurations. Naturally-occurring lycopene consists predominantly of all-*trans*-lycopene. For example, lycopene present in red tomato fruits typically contains 94-96% of all-*trans*-lycopene (Schierle et al., 1997). However, lycopene may undergo *trans*-to-*cis* isomerization during tomato processing or preparation of tomato-based meals, thus increasing the proportion of *cis* isomers. The synthetic lycopene described in this dossier contains approximately 70% of all-*trans*-lycopene, up to 23% of 5-*cis*-lycopene, and minor quantities of other *cis* isomers, mainly 13-*cis*-lycopene and 9-*cis*-lycopene. In certain literature sources, all-*trans*-lycopene is referred to as (all-E)-lycopene and *cis* isomers are referred to as Z isomers. For example, 5-*cis*-lycopene is referred to as (5Z)-lycopene.

Lycopene occurs in human blood plasma at levels ranging from 0.2 to 1.0 µmol litre^{-1} (Schierle et al., 1997). The isomeric composition of lycopene present in human blood plasma is shifted towards *cis* isomers with 5-*cis*-lycopene being the predominant *cis* isomer. Table 1 below shows the isomer composition of lycopene in red tomato fruits, various tomato products, and human blood plasma (according to Schierle et al., 1997). Table 1 also shows the isomer composition of synthetic lycopene from two manufacturers.

Table 1. Isomer composition of lycopene from various sources (as % of total lycopene)

Sample	All-*trans*-lycopene	5-*cis*-lycopene	9-*cis*-lycopene	13-*cis*- and 15-*cis*-lycopene	Other *cis* isomers of lycopene
Raw red tomatoes*	94 – 96	3 – 5	0 – 1	1	<1
Cooked tomato-based foods	35 – 96	4 – 27	<1 – 14	<1 – 7	<1 – 22
Human blood plasma**	32 – 46	20 – 31	1 – 4	8 – 19	11 – 28
Synthetic lycopene produced by DSM Nutritional Products	>70	<23	<1	<1	<3
Synthetic lycopene produced by BASF AG	>70	<23			

*Unpublished results cited in Schierle et al., 1997.
**Four pooled samples and four single-donor samples

Lycopene is unstable when exposed to light, heat, and oxygen. Exposure to light and heat triggers isomerization from the *trans* to *cis* configurations. The c*is*-isomers of lycopene have different physical and chemical characteristics than all-*trans*-lycopene (Nguyen and Schwartz, 1999). Some of these differences include lower melting points, lower specific absorption, and a shift in the absorption maximum. Lycopene can also undergo oxidation when exposed to oxygen with the formation of many different oxidation products. To prevent isomerization and oxidation, synthetic lycopene is kept under inert gas in lightproof containers and stored in a cool place.

Synthetic lycopene is insoluble in water and is formulated into dispersible products before use in food. Formulated products include solutions or suspensions of lycopene in edible fats and oils, emulsions, and water-dispersible powders containing water-soluble food ingredients, such as proteins and/or carbohydrates. To prevent lycopene oxidation, antioxidants such as DL-α-tocopherol, or ascorbyl pamitate plus ascorbic acid are added to the formulated preparations (McClain and Bausch, 2003). Lycopene formulations are packed in tightly sealed, lightproof packaging.

5. Proposed specifications

The proposed specifications are based on the manufacturing process of synthetic lycopene. The assay is intended to define the content of total lycopenes (not less than 96%) and all-*trans*-lycopene (not less than 70%) in the final product. Purity specifications include limits on loss on drying (not more than 0.5%), lead (not more than 1 mg/kg), and potential reaction byproducts triphenyl phosphine oxide (TPPO) (not more than 0.01%) and *apo*-12'-lycopenal (not more than 0.15%). These limits are intended to ensure that lycopene used in food is equivalent to that evaluated in the toxicological tests.

The HPLC method of assay was developed on the basis of a published method (Schierle et al., 1997) and was designed to determine total lycopenes (as a sum of all detected lycopene isomers) and all-*trans*-lycopene in the lycopene product. The method includes spectrophotometric determination of lycopene in the lycopene standard (i.e., determination of standard purity).

The HPLC method for determination of *apo*-12'-lycopenal is described under PURITY TESTS. The analytical methods for other proposed specifications (solubility, spectrophotometry, loss on drying, and lead) are based on general tests for identity and purity published in the Combined Compendium of Food Additive Specifications, FAO JECFA Monographs 1, Volume 4. The HPLC method for determination of TPPO is also included in Volume 4.

6. Functional uses

Synthetic lycopene is intended for use as a food colour and food additive. Food categories in which lycopene would be used include baked goods, breakfast cereals, dairy products including frozen dairy deserts, dairy product analogs, spreads, bottled water, carbonated beverages, fruit and vegetable juices, soybean beverages, candy, soups, salad dressings, and other foods and beverages. Lycopene may also be used in multi-vitamin and multi-mineral tablets and other types of food supplements and in meal replacements. The use levels of lycopene depend on its intended function and may vary from 2 mg/l in bottled water to 130 mg/kg in ready-to-eat cereals. In general, lycopene will be used at substantially lower levels as a colour than as a food additive. Details on lycopene uses and use levels are provided in the attached Appendix 1.

7. Reactions and fate in food

Lycopene is used in foods in the form of suitable formulations (see section 4 above). To prevent lycopene loss due to oxidative degradation, appropriate conditions during processing and storage of food should be assured including controlled atmosphere, where possible. Addition of antioxidants may also be necessary.

DSM Nutritional Products Ltd performed several studies on lycopene stability during storage of lycopene-containing foods. Generally, lycopene stability was above 70% after a typical storage time for most tested foods (see Appendix 2 for details).

8. References

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McClain, R.M., and Bausch, J., 2003. Summary of safety studies conducted with synthetic lycopene. Regul. Toxicol. Pharmacol. 37, 274-285.

Nguyen, M.L., and Schwartz, S.J., 1999. Lycopene: Chemical and biological properties. Food Technol., 53, 38-45.

Paust, J., 1996. Part VII: Technical Syntheses. In "Carotenoids, Volume 2: Synthesis." Britton, G., Liaaen, S., and Pfander, H., eds. Birkhäuser Verlag, Basel, Boston, Berlin.

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APPENDIX 1

Intended uses and use levels of synthetic lycopene (based on data provided by BASF AG and DSM Nutritional Products Ltd)

Food category[1]	Food	Use level (mg/kg)
01.1.2	Flavoured milk and milk drinks	30
01.2.1	Fermented milk beverages	30
01.3.3	Imitation milks	30
01.5	Dry milk	30
01.5.2	Soy milks	30
01.7	Yoghurt	20-40
01.7	Frozen Yoghurt	20-40
02.2.1.2	Margarine-like spreads	20
05.2	Chewy and nougat candy	15
05.2	Fruit Snacks	15
05.2	Hard candy	20-70
05.3	Chewing gum	15
06.3	Ready-to-eat cereals	30-130
06.5	Instant and regular hot cereals	9-20
07.1.2	Crackers and crisp breads	60
07.2.1	Cakes, cookies	30
10.4	Egg-based desserts	20
12.5.1	Soups	30
12.6.1	Salad dressings	30
12.6.2	Tomato-based sauces	30
12.9.1.1	Soybean beverage	20-40
13.4	Milk-based meal replacements	9-40
13.4	Meal replacements	9-40
14.1.1.1	Bottled water	2-15
14.1.2.1	Fruit juice	4-20
14.1.2.2	Vegetable juice	4-20
14.1.3	Nectars	4-20
14.1.4	Energy, sport, and isotonic drinks	4-15
14.1.4.1	Carbonated beverages	4-20
14.1.4.2	Fruit-flavoured drinks	9-15
14.1.5	Tea, ready-to-drink	3-15
15.1	Cereal and energy bars	40-80

[1] Food category system (Annex B) of the General Standard for Food Additives (GSFA) of the Codex Alimentarius Commission *[CODEX STAN 192-1995 (Rev. 6-2005)] (CODEX, 2005).*

Synthetic lycopene is also intended for use in multi-vitamin and multi-mineral tablets at 8 mg/tablet and in food supplements at 15 mg/unit.

APPENDIX 2

Lycopene stability in food (based on data provided by DSM Nutritional Products Ltd)

Product	**Storage time**	**Retention of lycopene**
UHT-Milk drink[2]	3 months	100%
Ice Cream	3 months	81%
Yoghurt	3 weeks	83%
Soft drink (stored in glass bottles)	3 months	98%
Soft drink (stored in aluminium cans)	3 months	88%
Soft drink (stored in PET bottles)	3 months	100%
Multi-fruit drink (stored in glass bottles)	12 months	130%
Whey juice drink (stored in glass bottles)	12 months	102%
Tropical nectar (stored in glass bottles)	3 months	100%
Breakfast cereals uncoated (PE bags translucent)	3 months	77%
Breakfast cereals sugar coated (PE bags translucent)	3 months	68%
Chocolate cookies	6 months	72%
Instant soup powder (ambient conditions)	12 months	73%
Tomato based sauce (ambient conditions)	12 months	76%
Thousand island dressing 25% oil (ambient conditions)	2 months	72%
Thousand island dressing 25% oil + mixed tocopherols (ambient conditions)	2 months	76%
Thousand island dressing mayonnaise based 54% oil (ambient conditions)	2 months	70%
Hamburger patties (stored as frozen patties)	6 months	69%
Meatless sausages (stored as frozen sausages)	6 months	89%
Hard candies	12 months	115%
Dragees (sugar coated chocolate drops; stored at ambient temperature)	12 months	102%
Dragees (sugar coated chocolate drops; stored at 45°C)	12 months	77%