European Food Safety Authority

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Safety of Synthetic Lycopene [1]

Scientific Opinion of the Panel on Scientific Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2007-119)

Adopted on 10 April 2008 by written procedure

PANEL MEMBERS

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SUMMARY

Following a request from European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific opinion on the safety of synthetic lycopene for use as a novel food ingredient taking into account the various EFSA opinions on all forms and proposed uses of lycopene.

The applicant proposes to use synthetic lycopene both as a food supplement and as a food ingredient. The novel food ingredient consists of synthetic (crystalline) lycopene to be marketed in three different formulations. These are lycopene 10 %, lycopene 10 cold water dispersion (CWD) and lycopene dispersion 20 %.

Synthetic lycopene is suggested by the applicant to be used in food supplements at levels of 8 or 15 mg/dosing, in beverages and dairy products at levels of up to 2.5 mg/100 g, in breakfast cereals up to 4 mg/100 g, in cereal bars up to 8 mg/100 g, in fats and dressings up to 4 mg/ 100 g and in dietary foods for special medical purposes at levels in accordance with the particular requirements of the person for whom the products are intended.

The applicant provides an intake estimate of lycopene based on three sources including 1) normal dietary intake from food, 2) intake from dietary supplements and 3) intake from proposed fortified food products. The Panel notes that an additional source is 4) use as a food colour.

[1] For citation purposes: Scientific Opinion of the Panel on Panel on Dietetic Products, Nutrition and Allergies on a request from the European Commission on the safety of synthetic lycopene. *The EFSA Journal* (2008) 676, 1-25

An overview of average dietary intakes of lycopene from foods in different populations was presented in previous EFSA evaluations. It was concluded that regular intakes of lycopene from natural dietary sources in different populations are, according to dietary surveys, estimated to be on average between 0.5 and 5 mg/day, with high exposures up to about 8 mg/day. High consumption of fruits and vegetables, especially tomato products, may result in occasional intakes of 20 mg lycopene/day or more.

The applicant indicates that intake of lycopene from supplements is not expected to be more than 21 mg/day among supplement users, based on the combined use of one lycopene supplement (providing maximal 20 mg of lycopene) and one multi-vitamin supplement (providing max 1 mg of lycopene).

Lycopene intake via lycopene fortified products is estimated by the applicant to be 28-30 mg/day for children up to 9y, 37 mg/day for males and 33 mg/day for females aged 10-18y, and 25 mg/day for males and 23 mg/day for females over 19y. Expressed per kg bw the estimated 95th percentile intakes will be highest for children (1-3y), being 2.2 mg/kg bw/day, intermediate for children (4-9y), 1.3 and 1.4 mg/kg bw/day, for girls and boys respectively, and lowest for men and women (19y) 0.32 and 0.35 mg/kg bw/day, respectively.

In a recent opinion the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food noted that total daily exposure to lycopene as a food colour could potentially range from 2 to 6 mg on average and up to 23 mg at the high level. The AFC Panel did not exclude an occasionally combined high exposure from both natural dietary sources and food colours up to 43 mg of lycopene per day.

Based on intake estimates from all these sources the Panel concludes that intake from the proposed uses and levels of use would lead to intake levels that will substantially increase the overall dietary intake of lycopene, and could lead to daily intakes from 10.5 - 30 mg/day at the mean and to 52 - 95 mg/day as high intakes. These values amount from 0.175 - 0.5 mg/kg bw/day and 0.87 - 1.58 mg/kg bw/day for a 60 kg person and are for the high intake estimates substantially higher than the ADI recently established by the AFC Panel as a group ADI of 0.5 mg/kg bw/day for lycopene from all sources (EFSA, 2008). This ADI is in line with the ADI of 0 - 0.5 mg/kg bw/day established by JECFA (JECFA, 2006).

The Panel considers that synthetic lycopene formulated as lycopene 10% and lycopene 10 CWD is as safe as lycopene from other accepted sources.

The Panel noted that the lycopene 20 % formulation was not formulated in the presence of an antioxidant and not tested in the toxicology tests. In the absence of these data the Panel cannot conclude on the safety in use of this formulation.

The Panel concludes that for the average user consumption of synthetic lycopene and from all other sources will be below the ADI. However, some users of lycopene products may exceed the ADI of 0.5 mg/kg bw/day.

Key words:

Synthetic lycopene, novel food ingredient, CAS Registry Number 502-65-8

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BACKGROUND AS PROVIDED BY THE COMMISSION

On 12 October 2005, the BASF AG submitted a request under Article 4 of the Novel Food regulation (EC) No 258/97 to the competent authorities of the Netherlands for placing on the market 'synthetic lycopene' (LycoVit^{R}) as a novel food ingredient.

On 23 October 2006, the competent authorities of the Netherlands forwarded to the Commission their initial assessment report, which had reached the conclusion that 'synthetic lycopene' for the proposed uses is acceptable.

On 10 November 2006, the Commission forwarded the initial assessment report to the other Member States. Several of these Member States submitted additional comments/objections.

In consequence, a Community Decision is now required under Article 7, paragraph 1 of Regulation (EC) No 258/97.

The concerns of a scientific nature raised by the Competent Authorities of Member States can be summarised as follows:

- Objections based on uncertainties related to the insufficient information on the long-term effects of potentially high intakes of lycopene.

- It is noted that many of the foodstuffs of interest are used especially by young consumers and children, e.g. fruit juices and soft drinks, milk-based fruit beverages, sports drinks, yoghurt and breakfast cereals.

- It is noted that since several applications have been submitted on lycopene as a novel food ingredient the safety of lycopene intake should be evaluated as a whole and should include intake estimates from natural sources, potential novel food applications, additive use and use in foods for special medical purposes.

- Reproduction and teratogenicity studies provided by the applicant were based on the assumption of temporary exposure to the novel ingredients, which might not be the case in reality at least for certain people.

- It should not be added to products that may be consumed by young children (1-3 years) and one Member State would welcome discussion on labelling stating; "Not recommended for young children" from a risk management perspective.

- One may question the nutritional value of using lycopene in foodstuffs at the proposed use levels, given the phenomenon of saturation, which makes any consumption in excess of 10 mg useless.

- The safety to health of synthetic lycopene (for use as a food additive) has already been assessed by the SCF which considered the toxicological information presented at that time to be insufficient and did not accept the product for use in food stuffs (SCF, 1999). It is argued that there has been no substantial change in the toxicological data for synthetic lycopene compared with the SCFs earlier assessment.

- EFSA's Panels concluded previously that the toxicological information on lycopene was insufficient to determine an ADI and the NDA Panel in an opinion on lycopene from *Blakeslea trispora* considered that only an additional lycopene intake of 2 mg per day (but not 20 mg per day) was acceptable (EFSA, 2005a).

- In agreement with previous SCF and EFSA opinions the total lycopene intake should not substantially exceed the amount obtained from natural foods in a balanced diet. The proposed uses and use levels lead to daily intake levels at the 95th percentile in adolescents excluding food supplements, 26 times higher than the average lycopene intake obtained from non-fortified foods (52 mg as opposed to 2 mg).

- Highly concentrated lycopene is sensitive to oxygen and light and forms degradation products with mutagenic activity (SCF, 1999). Appropriate quality assurance and control measurements must be taken.

- Synthetic lycopene is often referred to as the first example of a food ingredient that will be marketed in a nanopartical form, and lycovit 10 % consists of particles < 0.5 micrometer in diameter. This aspect requires additional information to demonstrate that there are no safety concerns.

- The JECFA has set an ADI of 0 - 0.5 mg/kg bw/day. This value is 3 to 4 times lower than the proposed estimated intake for the synthetic lycopene. The toxicological data used by JECFA to set the ADI should be taken into consideration.

- The test materials used in the toxicological studies contained 2 % of related compounds of the synthetic crystalline lycopene, whereas the specifications indicate that this should be no more than 9 %. An explanation of this discrepancy between what is tested and what is in the specifications is needed.

- It is important to include studies on factors which might affect the bio-availability of lycopene, evaluating its interaction with other carotenoids present in the diet, in order to assess whether there is any difference from food naturally rich in lycopene.

- There is insufficient support for the health claims presented.

- While lycopene is also allowed as a food additive, this additional use of lycopene could lead to circumvention of the regulations made for food additives.

- The limits on use proposed by the applicant would exceed those already authorised for other sources of lycopene.

In addressing Member States' comments of a scientific nature, and considering the overall safety of synthetic lycopene the Panel has used information from the original dossier provided by the applicant, the initial assessment carried out by the authorities of the Netherlands, the comments given by the Member States, the response from the applicant to the issues raised by the Member States and the recent opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on the use of lycopene as a food additive (EFSA, 2008).

Existing authorisations and evaluations

Lycopene, extracted from tomatoes, is authorised as food colouring agent within the EU (E160d) (Directive 94/36/EC) and the US (CDR 21 73.295).

Lycopene was evaluated by the SCF in 1975 (SCF, 1975) when it was unable to allocate an ADI but felt able to accept the use of lycopene prepared from natural foods by physical processes, without further investigations, as a colouring matter in food, provided that the amount consumed did not differ significantly from the amount consumed through the relevant foodstuffs. This Opinion was reiterated in 1989 (SCF, 1989). When JECFA evaluated lycopene from natural sources in 1977 they postponed a decision because of lack of data (JECFA, 1978).

In 1999 the SCF evaluated synthetic lycopene, but the available data were not sufficient to allow for an acceptance. The SCF concluded (SCF, 1999): " The proposed specification 'not less than 96 %' lycopene is not acceptable because highly concentrated lycopene is sensitive to oxygen and light, forms degradation products with mutagenic activity, and is not identical with the beadlet formulation that has been tested toxicologically," and "The toxicological data provided on the beadlet formulation are insufficient. Therefore the Committee is not able to allocate an ADI and considers its use in food unacceptable at present."

Synthetic lycopene is currently not approved for colouring matters within the EU. It is considered generally recognised as safe (GRAS) for use as a food ingredient in the US (GRAS notice No GRN 000119).

Recently the Panel evaluated the use of an α-tocopherol-containing oil suspension of lycopene, obtained from *Blakeslea trispora* for use as a novel food (NDA, 2005). It was concluded that the α-tocopherol-containing oil suspension of lycopene obtained from *B. trispora* at an additional intake of up to about 2 mg/day is not of concern from a safety point of view. It was also concluded that this does not hold for the proposed levels of use of lycopene in foods that would give rise to an additional intake of 20 mg per day.

In July 2006, the Joint FAO/WHO Expert Evaluation Committee on Food Additives (JECFA, 2006) derived an ADI of 0 - 0.5 mg/kg bw/day based on a 104-week study in rats using a safety factor of 100 for synthetic lycopene. This ADI was made into a group ADI to include lycopene from *B. trispora*. In both cases the ADI was considered to be 0 - 0.5 mg/kg bw/day. JECFA therefore proposed that this level be considered a group ADI for lycopene. This level equates to 30 mg lycopene/day for a 60 kg individual.

The Panel noted that the ADI set by JECFA (JECFA, 2006) does not include lycopene from tomatoes. This was due to the fact that JECFA was not evaluating lycopene from tomatoes.

In a recent opinion the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (EFSA, 2008) evaluated the new toxicological data on lycopene and derived an ADI of 0.5 mg/kg bw/day using a safety factor of 100. This ADI refers to lycopene from all sources.

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 9 (1) (a) of Regulation (EC) No 178/2002, the European Food Safety Authority is asked to carry out the additional assessment for 'synthetic lycopene' in the

context of Regulation (EC) No 258/97 and taking into account the various requests concerning lycopene currently under consideration.

In particular, EFSA is asked to consider the elements of a scientific nature in the comments/objections raised by the other Member States.

ACKNOWLEDGEMENTS

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ASSESSMENT

In accordance with the Commission Recommendation 97/618/EC, the ingredient concerned by the application belongs to Class 6. "Foods produced using a novel process". For this reason the Opinion will be an assessment of the safety data provided by the applicant to comply with the information required for novel foods of Class 6, i.e. information requirements I, II, III, IX, X, XI, XII and XIII as detailed in the following text. It does not include an assessment of the possible nutritional benefits of synthetic lycopene.

I. Specification of the novel food (NF)

Lycopene is a carotenoid with the formula $C_{40}H_{56}$. It has a molecular weight of 536.85 and the CAS Registry Number 502-65-8. Its structural formula is:

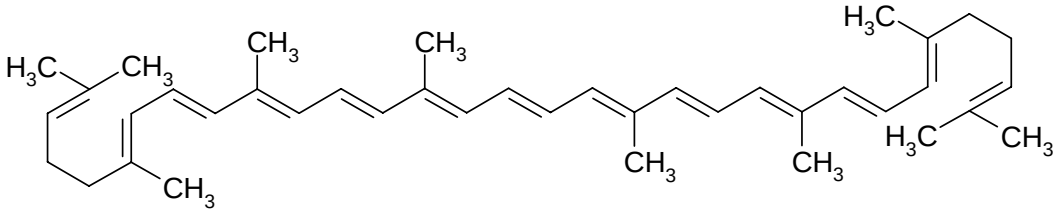

Fig 1. **Structural Formula**

Lycopene occurs in food predominantly in an all-*trans* form (Cronin, 2000; Boileau *et al.*, 2002). Tomatoes and tomato products contain the all-E (*trans*-)isomers of lycopene (between 35-96 % of total lycopene content), but also some Z (*cis*-)isomers, mainly as 5Z, 9Z, 13Z and 15Z in percentages varying between 1-22 % (Schierle *et al.*, 1997).

Synthetic lycopene consist mainly of the all *trans*-lycopene (>70 %) with 5-*cis*-lycopene (max. 20 %) and up to 3.5 % other *cis* isomers. It contains the same *cis* isomers found in tomatoes and tomato products (Table 1).

Table 1. **Cis/trans isomer ratios of lycopene in tomatoes, foodstuffs, synthetic lycopene and in human blood after consumption of lycopene (in % total lycopene).**

	Synthetic[1]	**Synthetic[2]**	**Natural[1]**	**Tomatoes[2]**	**Cooked tomato based foodstuffs[2]**	**Blood plasma[2]**
All-*trans* (%)	>70	73-77	94-96	35-96	16-96	38-40
5-*cis* (%)	Max 25	19-22	3-5	3-5	4-27	27
9-*cis* (%)	1	2-4	0-1	0-1	<1-14	4-5
13-*cis* (%)	1	1-2	1	1	1-7	7-8
Other *cis* (%)	3	-	<1	<1	<1-22	22

[1] SCF/CS/ADD/COL/160 Final 6/12/99 opinion on synthetic lycopene as a colouring matter for use in foodstuffs SCF, 1999.
[2] McClain, 2003

The novel food ingredient (LycoVit^R) consists of synthetic (crystalline) lycopene to be marketed as of three different formulations. These are lycopene 10 %, lycopene 10 cold water dispersion (CWD) and lycopene dispersion 20 %.

Lycopene 10 %
Lycopene 10 % is a dark red powder in which white particles of starch may be visible. The powder consists of spherical particles with a uniform particle size. The particles consist of synthetic lycopene embedded in a starch-coated matrix of fish gelatine and sucrose. They contain tocopherol (E307), sodium ascorbate (E301) and ascorbyl palmitate (E304) as antioxidants and tricalcium phosphate (E341) as an anti-caking agent. The level of synthetic lycopene is 10-12 %.

Lycopene 10 CWD
Lycopene 10 CWD is a dark red powder, which is easily dispersible in cold water. The powder consists of micronised synthetic lycopene embedded in a matrix of fish gelatine and glucose syrup. It contains DL-alpha-tocopherol (E307), ascorbyl palmitate (E304) and ascorbic acid as antioxidants. The level of the synthetic lycopene is 10-12 %.

Lycopene dispersion 20 %
Lycopene dispersion 20 % is a red-violet oily dispersion of milled synthetic crystalline lycopene. The product contains 20-22 % of the microcrystalline lycopene dispersed in food grade sunflower oil. No additional stabilizers are used in the product.

The applicant indicates that the lycopene formulations of the present opinion did not fall under the term nanoparticles. The powder particles typically have a size well above 100 micrometer. They contain lycopene particles sized about 300 nanometers on average embedded in a powder matrix. The applicant also indicates that on dissolution of the powder or in the digestive tract the powder matrix dissolves and releases the ingredient in the form of very fine emulsion droplets or suspension particles and the lycopene is subject to normal metabolism of carotenoids in the human body. The applicant also indicates that the finely dispersed carotenoid particles can be incorporated more easily into the mixed micelles containing fat, lipidoids and bile acids and that the toxicological tests performed with the synthetic lycopene formulations indicate no specific risk from the material used.

An overview of the specifications proposed by the applicant for the three lycopene formulations is given in Table 2. Synthetic crystalline lycopene is at least 96 % pure. For lycopene 10 CWD and lycopene dispersion 20 % the applicant provides the following specifications for heavy metals: heavy metals (as lead) are $\leq$ 10 mg/kg, arsenic $\leq$ 3 mg/kg and lead $\leq$ 5 mg/kg and for lycopene 10 CWD also cadmium $\leq$ 1 mg/kg and mercury $\leq$ 1 mg/kg are indicated.

Table 2. **Specifications for lycopene 10 %, lycopene 10 CWD and lycopene dispersion 20 %.**

Substance	**Composition (%)**
LycoVit® 10 %	
Synthetic crystalline lycopene	10-12
Gelatin	25-35
Sucrose	20-35
Native corn starch	20-30
Sodium ascorbate	0.5-2.5
d,l-α-tocopherol (E307)	0.5-2.0
Ascorbyl palmitate (E304)	0.1-1.2
Tri-calcium phosphate (E341)	0.4-0.6
Water	2-5

LycoVit® 10 CWD	
Synthetic crystalline lycopene	10-12
Fish gelatin	20-25
Glucose	55-60
d,l-α-tocopherol	1-2
Ascorbylpalmitate	1-2
Ascorbic acid	1-2
Tri-calcium phosphate (E341)	0.1-0.5
LycoVit® Dispersion 20 %	
Synthetic crystalline lycopene	20-22
Sunflower oil (food grade)	78-80

The applicant provided data on the stability of crystalline lycopene in the lycopene 10 % formulation at respectively 25°C and 60 % relative humidity for 36 months, of lycopene 10 CWD at 25°C and 60 % relative humidity for 12 months and at 40°C and 75 % relative humidity for 6 months, and of lycopene dispersion 20 % at 30°C and 70 % relative humidity for 9 months and at 40°C and 75 % relative humidity for 6 months. The products were stored in tightly closed containers and at each time point new aliquots containing the formulation were opened for the stability test. The results demonstrated that lycopene in these formulations and under these conditions was stable.

II. Effect of the production process applied to the NF

Synthetic lycopene is manufactured using a three stage process which is adequately described by the applicant. The ultimate product is stored and shipped in air-tight containers under inert gas. This crystalline synthetic lycopene is the starting material for the three formulations.

The other ingredients present in these formulations are common dietary ingredients or approved food additives such as cornstarch, gelatine and stabilizers such as ascorbyl palmitate and alpha-tocopherol.

Lycopene 10 %

The formulation process is carried out under a nitrogen atmosphere and using aqueous solutions containing sodium acetate and/or ascorbyl palmitate.

Lycopene 10 CWD

For applications in aqueous systems lycopene is formulated as a so-called cold water dispersible (CWD) powder in the micronization process by controlled precipitation.

Lycopene dispersion 20 %

The coarse crystalline lycopene is poured under nitrogen into sunflower oil and further processed to result in a formulation where 90 % of the crystalline lycopene particles have a diameter of less than 20 micrometer. A nitrogen stream is passed through the dispersion and the formulation is packed under nitrogen atmosphere.

The applicant indicates that the production process is not expected to result in undesirable products and that the production process and the production of the final formulations are expected to be micro-organism free.

III. History of the organism used as the source of the NF

Synthetic lycopene is obtained via chemical synthesis.

IX. Anticipated intake/extent of use of the NF

Table 3 presents the uses and use levels proposed by the applicant for lycopene in fortified foods (lycopene added to foods). Synthetic lycopene is suggested by the applicant to be used in food supplements at levels of 8 or 15 mg/dosing, in beverages and dairy products up to 2.5 mg/100 g, in breakfast cereals at up to 4 mg/100 g, in cereal bars up to 8 mg/100 g, in fats and dressings up to 4 mg/100 g and in dietary foods for special medical purposes at levels in accordance with the particular requirements of the person for whom the products are intended.

Table 3. **Uses and maximum use levels of synthetic lycopene suggested by the applicant**

Food Category	Maximum Content Level[a]
Food Supplements	
Multi-vitamin, multi-mineral tablets	8 mg/tablet
Soft gelatine capsules	15 mg/capsule
Hard gelatine capsules	15 mg/capsule
Effervescent tablets	15 mg/tablet
Waver/strips	15 mg/waver or strip
Condition-specific supplements	15 mg/tablet or capsule
Beverages	
Fruit & vegetable juice	2.5 mg/100g
Fruit juice drinks (including multi-vitamin drinks & ACE drinks)	2.5 mg/100g
Soft drinks (carbonated and non-carbonated)	2.5 mg/100g
Squash	2.5 mg/100g
Sport & Energy drinks	2.5 mg/100g
Dairy fruit drinks	2.5 mg/100g
Meal Replacements (e.g. foods intended for use in energy-restricted diets for weight reduction)	8 mg/meal replacement
Dairy Products (Except milk)	
Yoghurts, drink yoghurts	2.5 mg/100g
Breakfast Cereals	
Cereals (cold)	4 mg/100g
Cereal Bars	8 mg/100g
Fats & Dressings	
Margarine (used as spread)/ spreads	4 mg/100g

Dietary Foods for Special Medical Purposes	In accordance with the particular nutritional requirements of the persons for whom the products are intended

[a] The maximum content level of synthetic lycopene (total synthetic lycopene :cis + trans isomers) per 100 g food as prepared or tablets/capsules for supplements. Maximum content level may be provided by any of the three synthetic lycopene-containing products (LycoVit® 10 %, LycoVit® 10 CWD or LycoVit® Dispersion 20 %)

The applicant provides an intake estimate of lycopene based on three sources including 1) normal dietary intake from food, 2) intake from dietary supplements and 3) intake from proposed fortified food products. The Panel notes that an additional source is 4) use as a food colour.

Intake of lycopene from normal dietary sources

An overview of average dietary exposure to lycopene from foods in different populations was presented in previous EFSA evaluations (EFSA, 2005a and b). It was concluded that regular exposure to lycopene from natural dietary sources in different populations are, according to dietary surveys, estimated to be on average between 0.5 and 5 mg/day, with high exposures up to about 8 mg/day. High consumption of fruits and vegetables, especially tomato products, may result in occasional exposure to 20 mg lycopene/day or more.

Intake of lycopene from proposed supplement use

The applicant indicates that no data on supplement use are available, but that use of the lycopene formulations of the present opinion is likely to replace the use of other lycopene supplements. Synthetic lycopene is suggested by the applicant to be used in food supplements at levels of 8 or 15 mg/dosing.

Intake of lycopene from fortified food at the proposed uses and use levels.

For estimating the intake from fortified food products, information on the consumption of the products intended for fortification was taken from the Dutch National Food Consumption Survey that provided data on the food consumption by individuals based on a two-day dietary record method (DNFCS-3, 1998).

Tables 4 and 5 present the estimated daily intakes expressed in respectively mg/day and on a mg/kg bw/day basis provided by the applicant.

Table 4. **Estimated daily intake of lycopene (mg/day) from proposed LycoVit® fortified food products based on consumption data taken from Dutch population groups (DNFCS-3, 1998).[a]**

	All-Person intake					**All-User intake**				
Population group	N	Mean	sd	P50	P95	N	Mean	sd	P50	P95
Children, 1-3y	254	13.2	8.0	11.8	29.2	253	13.2	8.0	11.8	29.2
Boys,4-9y	242	15.9	8.3	15.0	29.6	241	16.0	8.3	15.0	29.6
Girls, 4-9y	272	15.0	7.3	14.1	28.4	272	15.0	7.3	14.1	28.4
Males, 10-18y	391	18.9	10.1	17.7	36.8	390	18.9	10.0	17.7	36.8
Females, 10-18	380	16.5	9.2	14.9	32.7	380	16.5	9.2	14.9	32.7

Males, 19+y	2117	8.8	8.5	6.5	24.9	2042	9.1	8.4	6.7	25.2
Females, 19+y	2544	8.3	8.0	6.2	22.7	2431	8.7	7.9	6.6	22.9

[a] Assuming the maximum content level is applied in the products and the consumers use only the fortified products.

Table 5. **Estimated daily intake of lycopene (mg/kg bw/day) from proposed LycoVit® fortified food products based on consumption data taken from Dutch population groups (DNFCS-3, 1998).[a]**

	All-Person intake					**All-Users intake**				
Population group	N	Mean	sd	P50	P95	N	Mean	sd	P50	P95
Children, 1-3y	254	0.98	0.61	0.89	2.2	253	0.98	0.61	0.89	2.2
Boys,4-9y	242	0.69	0.40	0.64	1.3	240	0.69	0.40	0.64	1.4
Girls, 4-9y	272	0.65	0.36	0.59	1.3	271	0.66	0.36	0.59	1.3
Males, 10-18y	391	0.35	0.20	0.33	0.68	389	0.36	0.19	0.33	0.68
Females, 10-18	380	0.33	0.19	0.31	0.67	379	0.33	0.19	0.31	0.69
Males, 19+y	2117	0.11	0.11	0.08	0.32	2041	0.11	0.11	0.09	0.32
Females, 19+y	2544	0.12	0.11	0.09	0.34	2427	0.13	0.11	0.10	0.35

[a] Assuming the maximum content level is applied in the products and the consumers use only the fortified products.

The 95th percentile values may be considered as a high intake scenario since the estimates assume that the consumers use only the fortified products. From the results presented in Tables 4 and 5 it can be concluded that the highest 95th percentile intake of added lycopene on an absolute basis is expected among males aged 10-18y, being 36.8 mg/day, equivalent to 0.68 mg/kg bw/day. On a bodyweight basis, children (1-3y) are expected to have the highest 95th percentile intake of added lycopene, being 2.2 mg/kg bw/day.

Altogether the 95th percentile lycopene intake via lycopene fortified products is estimated to be 28-30 mg/day for children up to 9y, 37 mg/day for males and 33 mg/day for females aged 10-18y, and 25 mg/day for males and 23 mg/day for females over 19y. Expressed per kg bw estimated 95th percentile intakes will be highest for children (1-3y), being 2.2 mg/kg bw/day, intermediate for children (4-9y), 1.3 and 1.4 mg/kg bw/day, for girls and boys respectively, and lowest for men and women (19y) 0.32 and 0.35 mg/kg bw/day, respectively.

Intake of lycopene resulting from use of lycopene as a food colour

An overview of average dietary exposure to lycopene from its use as a food colour in different populations was presented in a previous EFSA evaluation (EFSA, 2008). It was concluded that total daily exposure to lycopene as a food colour could potentially range from 2 to 6 mg on average and up to 23 mg at the high level.

The AFC Panel did not exclude an occasionally combined high exposure from both natural dietary sources and food colours of up to 43 mg of lycopene per day.

An overview of the estimates, compared to the exposure to naturally occurring lycopene is presented in Table 6.

Table 6. **Summary of typical lycopene exposure estimates**

Source of lycopene	Average (mg/day)	High (mg/day)	reference
Naturally occurring	0.5 - 5	8 - 20	AFC 2008
Fortified foods	8 - 19	23 – 37	Present opinion
Supplements	0 (no supplement use)	8-15	Present opinion
Food Colour	2 - 6	11 – 23*	AFC 2008

* based on the 97.5th percentile intake estimates

Overall, the Panel concludes that intake from the proposed levels of use would lead to intake levels that will substantially increase the overall dietary intake of lycopene, and could lead to mean daily intakes from 10.5 - 30 mg/day and to 52 - 95 mg/day as high intakes. The estimates for the high intakes are based on conservative assumptions. These values amount to 0.175 to 0.5 mg/kg bw/day and 0.87 - 1.58 mg/kg bw/day for a 60 kg person and are for the high intake estimates substantially higher than the ADI recently established by the AFC Panel as a group ADI of 0.5 mg/kg bw/day for lycopene from all sources (EFSA, 2008). This ADI is in line with the ADI of 0 - 0.5 mg/kg bw/day established by JECFA (JECFA, 2006).

X. Information from previous human exposure to the NF or its source

The applicant indicates that the synthetic lycopene 10 % formulation of the present opinion has been used in two small intervention studies of short duration.

In the first study 12 subjects (3 men and 9 women) used the lycopene 10 % formulation as gelatine beadlets in an amount equivalent to 15 mg total lycopene per day, for 28 days (Hoppe *et al.*, 2003). In the second study 8 postmenopausal females used synthetic lycopene in an amount equivalent to 12 mg per day for 57 days (Zhao *et al.*, 2006).

Two other human intervention studies have been published using synthetic lycopene. In one study, 6 healthy male subjects received 20 mg of lycopene (synthetic lycopene tablets) per day for 8 days (Cohn *et al.*, 2004). In the other study, 12 healthy subjects received 10 mg of synthetic lycopene per day for 12 weeks (Aust *et al.*, 2005).

No nutritional, microbial, toxicological and/or allergenicity problems were noted in these studies.

According to the applicant, supplements containing lycopene in amounts up to 20 mg are on the market in Europe and the USA.

XI. Nutritional information on the NF

The Panel considers that synthetic lycopene does not have a nutritional impact.

Bioavailability

No information on the kinetics of the synthetic lycopene formulations was provided by the applicant.

Plasma responses in man and experimental animals upon intake of synthetic lycopene or lycopene from tomatoes have been investigated frequently and data on the bioavailability of these forms of

lycopene have been presented in previous opinions from EFSA on lycopene from various sources (EFSA 2005a and b, 2008).

Lycopene absorption from purified or synthetic sources has been demonstrated to be comparable to that of tomato-based lycopene (Böhm and Bitsch 1999; Cohn *et al.,* 2004; Hoppe 2003).

In addition, interactions, both competitive and synergistic, between carotenoids have been shown to occur during the various stages of absorption (e.g., incorporation into mixed micelles, intracellular transport within enterocytes, and chylomicron assemblage), as well as during post-absorptive distribution (Furr and Clark, 1997; Van den Berg, 1999). However, the mechanisms *via* which this occurs are not clear, and definite relationships between specific carotenoids have not been established. However, as long as intake levels are within normal dietary intake, such interactions are unlikely to have a significant impact on the systemic bio-availability of an individual component.

Metabolism

Very little is known about the metabolism or degradation of lycopene in mammals (Clinton, 1998; Parker 1996). It has been shown that lycopene does not exhibit provitamin A activity (Van Vliet *et al.,* 1996; Agarwal and Rao, 2000). Furthermore, few metabolites of lycopene have been documented in human plasma or tissues. For example, two oxidative lycopene metabolites, identified as epimeric 2,6-cyclolycopene-1,5-diols, have been detected in breast milk and serum of three lactating mothers (Khachik *et al.,* 1997). It is postulated by the authors that these compounds may result via an *in vivo* metabolic oxidation of lycopene to lycopene epoxide. Upon oral administration of ^{14}C labelled lycopene to rats and monkeys no evidence for any metabolic products of lycopene was observed (McClain and Bausch, 2003).

XII. Microbiological information on the NF

Synthetic lycopene is obtained from a chemical synthetic process. The applicant indicates that the manufacturing of the formulations is a hygienic procedure performed according to HACCP, and that therefore contamination with micro-organisms is not expected.

XIII. Toxicological information on the NF

Lycopene, either natural or synthetic has been thoroughly studied in both animals and humans. Toxicological information on lycopene from different sources including lycopene from tomatoes, synthetic lycopene and lycopene from *B. trispora* has been evaluated in several previous opinions by SCF (1975, 1989, 1999), EFSA (2005; 2008) and JECFA (2006).

In July 2006, the Joint Evaluation Committee on Food Additives (JECFA, 2006) derived an ADI for synthetic lycopene and lycopene from *B. trispora* (JECFA, 2006). In both cases the ADI was considered to be 0 - 0.5 mg/kg bw/day. JECFA therefore proposed that this level be considered a group ADI for lycopene. This level equates to 30 mg lycopene/day maximum for a 60 kg individual.

Recently EFSA also evaluated the new toxicological data for lycopene and derived an ADI of 0.5 mg/kg bw/day. This ADI refers to lycopene from all sources (EFSA, 2008).

The present opinion only presents the studies specific for the synthetic lycopene formulations of the present opinion.

Acute oral toxicity

The applicant described results from an acute oral toxicity study, an acute dermal irritation/corrosion study and an acute eye irritation/corrosion study, performed with the synthetic lycopene 10 % formulation. In the acute oral toxicity study, no mortality, clinical signs, changes in body weight or abnormalities were observed. The LD50 for the test substance test substance LycoVit® 10 CWD (purity of 9.81 %), was ≥ 5000 mg/kg bw (about 500 mg lycopene/kg bw). The skin and eye irritation tests showed no toxic effects. Thus, the acute oral toxicity of the synthetic lycopene 10 % formulation is low.

Subacute and subchronic toxicity

The applicant reports a repeated dose 90-day oral toxicity study with the synthetic lycopene in rats performed according to OECD guidelines (application dossier; Mellert *et al.*, 2002). In this study, groups of 10 male and 10 female Wistar rats were exposed to 0, 500, 1500, 3000 mg/kg bw/day LycoVit® 10 CWD (purity 9.81 % lycopene) or to LycoVit® 10 % (purity 10.8 % lycopene) by gavage for 3 months.

For an interim sacrifice, additional groups of 5 male and 5 female Wistar rats were administered by gavage for 4 weeks lycopene 10 CWD at doses of 0 and 3000 mg/kg bw/day, and lycopene 10 % at 3000 mg/kg bw/day. Food consumption and body weights were determined weekly. The animals were examined for clinical signs of toxicity or mortality at least once a day. Additionally, general clinical observations were carried out before and after daily treatment. Detailed clinical examinations were conducted prior to the start of the administration and weekly thereafter. A functional observational battery (FOB) and measurement of motor activity was carried out towards the end of the 3-month administration period. Ophthalmological examinations were carried out with the animals of the 3-months administration prior to the start and towards the end of the 3 months administration period. Clinical chemistry and haematological examinations were carried out towards the end of the 4-week and 3-month administration period. Urine analysis was carried out towards the end of the 3 months administration period. All animals were assessed forgross pathology, followed by histopathological examinations.

The mean absolute thymus weight was slightly although significantly decreased after 4 weeks of application in females that received 3000 mg/kg lycopene 10 %. The applicant indicates that this was not regarded as treatment related, because a comparable effect was not noted in males and because no microscopy finding was obtained that may correlate with this weight change. Moreover, a comparable effect was not seen after the 3 month application period in either sex. The same was true for the slight but significant increased mean kidney weights after 4 weeks of application seen in males receiving 3000 mg/kg bw/day lycopene 10 CWD or 3000 mg/kg bw/day lycopene 10 %, as the females were not affected, morphology failed to detect a meaningful morphologic correlate for the increased weights and no such observation was made after the 3-month application period in either sex.

All significant weight changes, all gross lesions and all microscopic findings recorded after 4-week and 3-month application periods were either single observations or they were recorded at low or comparable incidence and graded severity in males and/or females of control and investigated treatment groups.

It was concluded that no treatment related effects were observed, except for a red discoloration of the faeces as well as the contents of the gastrointestinal tract of the animals treated with both formulations. This effect is not considered to be an adverse effect but is due to the red colour of the test substance. The no observed adverse effect level (NOAEL) was at least 3000 mg/kg bw/day, the highest dose tested for both formulations.

The applicant concludes that the NOAEL of this study amount to at least 3000 mg 10 % lycopene formulation/kg bw/day, the highest dose tested for both formulations, amounting to approximately 300 mg lycopene/kg bw/day.

An overview of other subchronic studies with oral administration of synthetic or natural lycopene or lycopene from *B. trispora* to experimental animals can be found in previous evaluations on the safety of lycopene from *B. trispora* or lycopene from tomatoes or synthetic lycopene, made by the SCF (1999), EFSA (2005, 2008) and JECFA (2006).

Reproductive toxicity and teratogenicity

No reproductive toxicity study was performed with the synthetic lycopene formulations. In the 90 day toxicity study with the synthetic lycopene 10 % and 10 CWD formulations in rats no histopathological changes were observed in the reproductive organs.

Two prenatal developmental toxicity studies were performed with the synthetic lycopene 10 % and 10 CWD formulations (Richards 2001a, Richards 2001b; Christian *et al*., 2003).

In the first study groups of 25 time-mated female KBL New Zealand White strain rabbits were exposed to synthetic lycopene 10 CWD or lycopene 10 %, vehicle or matrix control by oral gavage once a day from day 6 to day 28 post-coitum. Due to the difficulty of administering, the number of animals in some groups was increased in order to have at least 16 litters/group for foetal examination. The test substances were administered in the vehicle (purified water) at dose levels of 0 (vehicle control), 500, 1500 and 2000 mg lycopene 10 CWD/kg bw/day (amounting to 0, 50, 150 and 200 mg synthetic lycopene/day), to 2000 mg lycopene 10 %/kg bw/day (amounting to 200 mg synthetic lycopene/kg bw/day) and to placebo controls consisting of the matrix of lycopene 10 CWD at 2000 mg/kg bw, or the matrix of lycopene 10 % at 2000 mg/kg bw/day.

Clinical signs and mortality were checked daily. Body weight and food consumption were recorded at designated intervals. On day 29 post-coitum, the dams were sacrificed. A macroscopic post-mortem, which included examination of the principal thoracic and abdominal organs and the placenta, was performed. The foetuses were removed by hysterectomy. For each of the females the litter parameters, including the number of corpora lutea, implantation sites, early and late resorptions, dead and live foetuses were recorded. All the foetuses were weighed and subjected to an external examination. Fresh dissection of all live foetuses allowed a detailed examination of soft tissue. Half of the foetuses were processed for evaluation of designated tissues. The brains of the remaining half of the foetuses were examined by serial

sectioning. The carcasses of all the foetuses were fixed and detailed skeletal examination of the bone and cartilage structures was performed.

None of the test groups showed treatment related effects indicative of maternal or foetal toxicity, or influences on gestation parameters. It is concluded that the NOAEL of the study amounts to 2000 mg /kg bw/day (amounting to 200 mg synthetic lycopene/kg bw/day), the highest dose tested.

In the second study lycopene 10 CWD and lycopene 10 % were administered by daily oral gavage to pregnant female Sprague Dawley rats from implantation to 1 day prior to the expected day of parturition (day 6 to day 19 post-coitum inclusive). Groups of 25 mated female rats were exposed to 0 (vehicle control), 500, 1500 or 3000 mg lycopene 10 CWD/kg bw/day or to 3000 mg lycopene 10 %/kg bw/day or to placebo controls consisting of the matrix of lycopene 10 CWD at 3000 mg/kg bw, or the matrix of lycopene 10 % at 3000 mg/kg bw/day.

Clinical signs and mortality were checked daily. Body weight and food consumption were recorded at designed intervals. On day 20 post-coitum, the dams were sacrificed and subjected to a macroscopic examination. The pregnant uterus weight was recorded to allow the calculation of the net body weight of the dams. The foetuses were removed by hysterectomy. The litter parameters were recorded including the number of corpora lutea, implantation sites, uterine scars, early and late resorptions, dead and live foetuses. The foetuses were weighed, their sex determined and submitted to an external examination. Half of the foetuses were subjected to a detailed examination of the soft tissues and the other half of the foetuses was subjected to a detailed examination of the skeleton and cartilage.

None of the test groups showed treatment related effects indicative of maternal or foetal toxicity, or influences on gestation parameters. It is concluded that the NOAEL for the study amounts to 3000 mg /kg bw/day (amounting to 300 mg synthetic lycopene/kg bw/day), the highest dose tested.

Additional developmental and reproduction studies with oral administration of synthetic lycopene can be found in the opinion of the AFC, which describes studies revealing (EFSA, 2008):

- A NOAEL of 500 mg lycopene/kg bw/day (the highest dose level tested) in a 14-week rat study
- A NOAEL of 500 mg lycopene/kg bw/day (the highest dose level tested) in a developmental toxicity study in the rat
- A NOAEL of 500 mg lycopene/kg bw/day (the highest dose level tested) in a two-generation study in the rat
- A NOAEL of 400 mg lycopene/kg bw/day (the highest dose level tested) in a developmental toxicity study in the rabbit.

Chronic toxicity and carcinogenicity

In a most recent AFC Opinion two long term studies in rats with synthetic lycopene are described (51 and 104 weeks respectively) (EFSA, 2008).

Additional long term studies with oral administration of synthetic lycopene can be found in the AFC opinion which describes studies revealing:

- A NOAEL of 50 mg lycopene/kg bw/day in a one year rat study, and
- A NOAEL of 50 mg lycopene/kg bw/day (the highest dose level tested) in a two year rat carcinogenicity study.

Mutagenicity

The applicant provided results from genotoxicity studies performed with the lycopene 10 CWD formulation. The preparation was negative in bacterial tests with *Salmonella enterica var.* Typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 and *E.coli* WP2uvrA all with and without metabolic activation (Engelhardt and Hoffman 2000).

Synthetic lycopene 10 CWD formulation tested positive in the chromosome aberration test in Chinese hamster cells (V79 cell line) without metabolic activation, but was negative in the same test in the presence of metabolic activation (Engelhardt and Hoffman 2001b). The applicant indicates that this positive effect may be the result of an indirect mechanism due to extreme culture conditions.

No genotoxicity was observed as well for the lycopene 10 CWD formulation in two *in vivo* tests including a test for DNA repair in rat hepatocytes (Engelhardt and Hoffmann 2001c) and a mouse bone marrow micronucleus test (Engelhardt and Hoffmann 2001a).

Previously the SCF (SCF, 1999), EFSA (EFSA, 2005a; EFSA 2008) and JECFA (JECFA, 2006) have evaluated the genotoxicity of lycopene from various sources including natural lycopene from tomatoes, synthetic lycopene and lycopene from *B. trispora*, and concluded that genotoxicity data do not give reason for concern.

An important issue in the potential genotoxicity of lycopene is the degradation of pure crystalline lycopene into mutagenic products when exposed to air and light. These studies revealed that lycopene in a beadlet formulation and pure crystalline lycopene surrounded by the antioxidant alpha-tocopherol were not mutagenic (McClain and Bausch, 2003). The applicant indicates that in order to avoid degradation of lycopene in the synthetic lycopene formulations, several measures are taken, such as the addition/presence of antioxidants and specific storage conditions.

Altogether it is concluded that the present database on genotoxicity of lycopene from various sources indicates that there is no reason for concern with respect to genotoxicity.

Allergenicity and Irritancy

The skin and eye irritation tests with the synthetic lycopene 10 % formulation showed no toxic effects.

According to the applicant, there is no information in public literature on allergenic reactions associated with lycopene and no information was submitted on the possible allergenic potential of (synthetic) lycopene. In theory an allergic reaction due to the additive fish gelatine in the synthetic lycopene 10 CWD formulation is possible. However, the applicant indicates that in a double-blind placebo-controlled food challenge study of 30 patients with clinical allergy to fish, no patients reacted to a cumulative dose of fish gelatine, except for one patient showing a reaction at a very high dose in the gram range (EFSA, 2004).

DISCUSSION

The applicant proposes to use synthetic lycopene both as a food supplement and as a food ingredient. Synthetic lycopene is suggested by the applicant to be used in food supplements at levels of 8 or 15 mg/dosing/day, in beverages and dairy products up to 2.5 mg/100 g, in breakfast cereals up to 4 mg/100 g, in cereal bars up to 8 mg/100 g, in fats and dressings at levels up to 4 mg/100 g and in dietary foods for special medical purposes at levels in accordance with the particular requirements of the person for whom the products are intended.

The applicant provides an intake estimate of lycopene based on three sources including 1) normal dietary intake from food, 2) intake from dietary supplements and 3) intake from proposed fortified food products. The Panel notes that an additional source is 4) use as a food colour.

An overview of average dietary exposure to lycopene from foods in different populations was presented in previous EFSA evaluations (EFSA, 2005a and b). It was concluded that regular exposure to lycopene from natural dietary sources in different populations is, according to dietary surveys, estimated to be on average between 0.5 and 5 mg/day, with high exposures up to about 8 mg/day. High consumption of fruits and vegetables, especially tomato products, may result in occasional exposure to 20 mg lycopene/day or more.

The 95th percentile intake via lycopene fortified products is estimated to be 28-30 mg/day for children up to 9y, 37 mg/day for males and 33 mg/day for females aged 10 -18y, and 25 mg/day for males and 23 mg/day for females over 19y. Expressed per kg bw estimated 95th percentile intakes will be highest for children (1-3y), being 2.2 mg/kg bw/day, intermediate for children (4-9y), being 1.3 and 1.4 mg/kg bw/day, for girls and boys respectively, and lowest for men and women (19y) being 0.32 and 0.35 mg/kg bw/day, respectively.

In a recent opinion the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food noted that total daily exposure to lycopene as a food colour could potentially range from 2 to 6 mg on the average and up to 23 mg at the high level (EFSA, 2008). The AFC Panel did not exclude an occasionally combined high exposure from both natural dietary sources and food colours up to 43 mg of lycopene per day.

No mutagenic potential of formulated synthetic lycopene was observed in a battery of mutagenicity assays. Ames test data for crystalline, synthetic lycopene showed no mutagenic activity.

Synthetic lycopene 10 CWD formulation tested positive in the chromosome aberration test in Chinese hamster cells (V79 cell line) without metabolic activation, but was negative in the same test in the presence of metabolic activation. However no genotoxicity was observed for the lycopene 10 CWD formulation in two *in vivo* tests including a test for DNA repair in rat hepatocytes and a mouse bone marrow micronucleus test.

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food recently evaluated the safety of lycopene from all sources for uses and use levels as a food colour, including lycopene from tomatoes, *B. trispora* and synthetic lycopene (EFSA, 2008).

The AFC Panel concluded that the safety of synthetic lycopene was demonstrated in subchronic and chronic toxicity studies in rats, a carcinogenicity study and a two-generation study in rats, and developmental toxicity studies in the rat and rabbit. Mutagenicity has been

studied in an extensive program using formulated forms of lycopene and demonstrated no concern. The following no observed adverse effect levels (NOAELs) for formulated, synthetic lycopene, were established in guideline-conforming toxicity studies:

- 500 mg lycopene/kg bw/day (the highest dose level tested) in a 14-week rat study and in a developmental toxicity study in the rat
- 500 mg lycopene/kg bw/day (the highest dose level tested) in a two-generation study in the rat
- 400 mg lycopene/kg bw/day (the highest dose level tested) in a developmental toxicity study in the rabbit
- 50 mg lycopene/kg bw/day in a one year rat study and
- 50 mg lycopene/kg bw/day (the highest dose level tested) in a two year rat carcinogenicity study.

The NOAEL from a 90 day oral toxicity study with lycopene extracted from *B. trispora* amounted to about 600 mg/kg bw/day.

From the lowest NOAEL of 50 mg/kg bw/day the AFC Panel derived an ADI of 0.5 mg/kg bw/day using a safety factor of 100. This ADI refers to lycopene from all sources (EFSA, 2008).

This ADI is in line with the ADI of 0 - 0.5 mg/kg bw/day established by JECFA (JECFA, 2006) The Panel noted that the ADI set by JECFA does not include lycopene from tomatoes. This was probably due to the fact that JECFA was not evaluating lycopene from tomatoes.

The present opinion presents data from toxicity studies with synthetic lycopene 10 % and 10 CWD formulations. The NOAEL derived from a 90-day oral toxicity study in rats amounted to at least 3000 mg 10 % lycopene formulation/kg bw/day, the highest dose tested. The NOAELs for developmental toxicity studies in rabbits and rats amounted to respectively at least 2000 and 3000 mg 10 % lycopene formulation)/kg bw/day, the highest doses tested in both studies, amounting to approximately 300 mg lycopene/kg bw/day. The Panel notices that the NOAELs derived for these studies with the synthetic lycopene 10 % formulations are in the same range as those reported for the studies summarised in the AFC opinion (EFSA, 2008). Therefore, the Panel concludes that the data provided do not give reason for re-evaluation of the ADI recently derived.

Overall, the Panel concludes that intake from the proposed levels of use would lead to intake levels that will substantially increase the overall dietary intake of lycopene, and could lead to mean daily intakes from 10.5 - 30 mg/day at the mean and to 52 - 95 mg/day as high intakes. These values amount to 0.175 - 0.5 mg/kg bw/day and 0.87 - 1.58 mg/kg bw/day for a 60 kg person and are, for the high intake estimates, substantially higher than the ADI recently established by the AFC Panel as a group ADI of 0.5 mg/kg bw/day for lycopene from all sources (EFSA, 2008). This ADI is in line with the ADI of 0 - 0.5 mg/kg bw/day established by JECFA (JECFA, 2006).

CONCLUSIONS AND RECOMMENDATIONS

The Panel considers that synthetic lycopene formulated as lycopene 10 % and lycopene 10 CWD is as safe as lycopene from other accepted sources provided appropriate safety measures are taken to prevent oxidative deterioration of crystalline lycopene.

The Panel noted that the lycopene 20 % formulation was not formulated in the presence of an antioxidant and not tested in the toxicology tests. In the absence of these data the Panel cannot conclude on the safety in use of this formulation.

The Panel concludes that for the average user consumption of synthetic lycopene and from all other sources will be below the ADI. However, some users of lycopene products may exceed the ADI of 0.5 mg/kg bw/day.

DOCUMENTATION PROVIDED TO EFSA

1) Letter from the European Commission to the Chairman of the European Food Safety Authority with the request for an opinion on the safety of 'synthetic lycopene'. SANCO E4/Ak/bs (2007) D/540328

2) Initial assessment report by the Bureau Nieuwe Voedingsmiddelen (NL) concerning the assessment of 'synthetic lycopene',

3) Letters from Member States with comments on the initial assessment report on synthetic lycopene from Bureau Nieuwe Voedingsmiddelen (NL)

4) Response to Member States comments on the Netherland Opinion for synthetic lycopene as a novel food ingredient.

5) Application under regulation No 258-97 for the use of synthetic lycopene as a novel food ingredient.

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