

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

SYNTHETIC LYCOPENE

**Issue**

The Dutch Competent Authority has prepared an initial opinion on an application for the authorisation of synthetic lycopene as a novel food ingredient under the Novel Food Regulation (EC) No. 258/97. The Committee is asked whether it agrees with the initial opinion and whether it has any further comments or objections to make on the application. The Committee's advice will form the basis for the UK's formal response.

**Introduction**

1. On 10 November 2006, the European Commission forwarded the Dutch Competent Authority's (CA) initial opinion on an application made by BASF Corporation Ltd under Article 4(1) of Regulation (EC) 258/97, for the authorisation of a synthetic lycopene (Lycovit®) as a novel food ingredient. Under the time scales set out in the regulation, the UK and other Member States have until 10 January 2007 to provide objections to the initial opinion.
2. The Dutch CA has sought advice from their Committee on Safety Assessment of Novel Foods. The Dutch Initial Assessment Report is attached as **Annex 1**. The full dossier provided by the applicant is attached as **Annex 2** (restricted).

**Background**

3. This application from BASF Corporation Ltd is for the placing on the market of a synthetic lycopene (Lycovit®) as a novel food ingredient (NI) for use in a number of food categories and as a food supplement in the EU. Lycopene (C<sub>40</sub>H<sub>56</sub>) is an aliphatic branched hydrocarbon with a molecular weight of 536.9 Daltons. It is found in tomatoes and other foodstuffs, predominantly in the trans- form, and pure

lycopene is a red crystalline powder that is soluble in fats and organic solvents, but virtually insoluble in water, methanol or ethanol.

4. This is the third application submitted under the novel food regulation for lycopene. The two other applications were for lycopene purified from a fungal source (*Blakeslea trispora*) and for a lycopene-containing extract from a natural source (lycopene-rich tomatoes). Both applications were submitted to the UK CA (papers ACNFP/63/3 and 69/2). The marketing of the fungal lycopene produced by Vitatene Antibiotics SAU was recently approved under Commission Decision 2006/721/EC<sup>1</sup>. The natural lycopene produced by LycoRed was considered safe for human consumption by the UK CA in June 2005<sup>2</sup> but other Member States have raised objections to this application. The response provided by the applicant to these concerns in September 2006 is currently being considered by the Member States.
5. Lycopene (from tomatoes) is also approved for use as a food colour (E160d) in the EU. The safety of lycopene as a food additive was considered by the Joint FAO/WHO Expert Committee on Food Additives at its 67<sup>th</sup> meeting in June 2006<sup>3</sup>. BASF has highlighted that the package of toxicological tests submitted for the JECFA evaluation was the same as the one provided in this novel food application. JECFA also received data from another manufacturer of synthetic lycopene and from the manufacturer of the fungal-derived product. JECFA established an Acceptable Daily Intake of 0-0.5 mg/kg bodyweight which covers both synthetic lycopene and lycopene purified from *Blakeslea trispora*. The detailed report of the JECFA evaluation is not yet published.
6. Members may also wish to be aware that the use of synthetic lycopene as a food additive was reviewed by the Scientific Committee on Food (SCF) in 1999. The SCF highlighted a number of issues related to the stability of the product and the formation of potentially toxic degradation products; differences between the product tested and the form to be marketed; and the limited number of toxicology studies.

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<sup>1</sup> See at: [http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l\\_296/l\\_29620061026en00130016.pdf](http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_296/l_29620061026en00130016.pdf)

<sup>2</sup> See at: <http://www.acnfp.gov.uk/assess/fullapplies/lycotom>

<sup>3</sup> See at: <http://www.fao.org/ag/agn/jecfa-additives/details.html?id=918>.

7. In accordance with the European Commission Regulation 258/97, the Dutch CA considers that the NI falls under the category described under Article 1(2)(f), which is a food produced using a novel process. This corresponds to class 6 under Commission Recommendation 97/518/EC which sets out the guidelines for novel food applications. The requirements for a submission for this class are as follows:

<b>I</b>	<b>Specification of the NF</b>	<b>X</b>
<b>II</b>	<b>Effect of the production process applied to the NF</b>	<b>X</b>
<b>III</b>	<b>History of the organism used as the source of the NF</b>	<b>X</b>
IV	Effect of the genetic modification on the properties of the host organism	-
V	Genetic stability of the GMO	-
VI	Specificity of expression of novel genetic material	-
VII	Transfer of genetic material from GM microorganisms	-

VIII	Ability to survive in and colonise the human gut	-
<b>IX</b>	<b>Anticipated intake/extent of use of the NF</b>	<b>X</b>
<b>X</b>	<b>Information from previous human exposure to the NF or its source</b>	<b>X</b>
<b>XI</b>	<b>Nutritional information on the NF</b>	<b>X</b>
<b>XII</b>	<b>Microbiological information on the NF</b>	<b>X</b>
<b>XIII</b>	<b>Toxicological information on the NF</b>	<b>X</b>

8. The key issues for consideration are presented below under the headings taken from the European Commission guidelines on scientific information necessary to support applications for placing on the market of novel foods or novel food ingredients.

### **I. Specification of the novel food**

Annex 2, p.9-p[21

9. The NI is a chemically synthesised crystalline lycopene and will be marketed in three different formulations:

- **LycoVit 10%:** powder preparation with 10-12% lycopene, fish gelatin, sucrose, and maize starch

- **LycoVit 10 CWD<sup>4</sup>**: powder preparation with 10-12% lycopene, fish gelatine and glucose
- **LycoVit Dispersion 20%**: suspension of 20-22% of lycopene in sunflower oil.

10. The specification of the three proposed synthetic lycopene formulations are provided in the dossier (p.9, table 3.1.1). Compositional data of representative batches produced in 2003 of the synthetic crystalline lycopene itself and the three formulations are provided in the dossier (p.9-11 and table 3.1.2). In response to request by the Dutch CA, the applicant also provided additional compositional data on batches produced in 2004. All batches comply with their respective specifications.

11. The synthetic crystalline lycopene used in the three formulations contains approximately 75% *all-trans* lycopene, 20% 5-*cis* lycopene and 6-9% related compounds (*cis*- isomers, rhodopin, acetyl-rhodopin). The applicant has suggested setting an upper limit of 14% for related compounds, to be consistent with the international specifications for synthetic lycopene used as a food additive (see para. 15 below).

12. No measurable quantities of heavy metals were found in the synthetic lycopene or in the three NI formulations, at the limit of detection of the analytical method used.

13. The applicant was asked to provide further information on the stability of the NI and its storage life when added into foods. No measurable signs of degradation was observed in LycoVit 10% stored for 3 years at room temperature and normal relative humidity and for LycoVit 10 CWD and LycoVit Dispersion 20% stored for 12 months under standard conditions or 6 months at elevated temperature and relative humidity. The applicant has also investigated the stability of LycoVit 10% in multivitamin tablets stored dry, at room temperature and under normal conditions of use. The level of lycopene stayed stable during the first six months and then decreased by 5 and 10% after respectively six and 18 months. The applicant was of the view that the obtained results were comparable to that of other components in the food that are susceptible to oxidation, such as certain vitamins and beta-carotene. The applicant has also found that after pasteurisation for one minute at 90°C, LycoVit 10 CWD- enriched squash and

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<sup>4</sup> CWD: Cold Water Dispersable

lemonade stored for a year at room temperature, both in daylight and under neon light, contained the same levels of lycopene.

14. In response to a request by the Dutch CA, the applicant has provided additional information on the presence of C25-aldehyde lycopene in the NI. The applicant explains that this degradation product can be potentially genotoxic but the low levels present in their product do not pose any health risk.
15. The Dutch CA was satisfied with the compositional data provided for the NI but stressed that, for the synthetic crystalline lycopene in the NI, the levels of related compounds should be no more than 9% because this corresponds to the level of related compounds in the preparations tested in toxicological studies presented in this dossier. The Dutch CA noted that the applicant should be able to comply with this requirement because the compositional analyses of batches of the NI met this specification.
16. The Dutch CA was also content that the applicant has demonstrated the absence of undesirable substances in the NI and that the level of C25-aldehyde lycopene present in the NI gives no cause for safety concern for the proposed uses of the NI.
17. The Dutch CA is of the opinion that the NI will be stable and, although the stability tests did not involve the analysis of individual isomers of lycopene, the isomerisation processes occurring during storage are not fundamentally different from the chemical changes seen in natural lycopene when processing or cooking tomato products. However, the Dutch CA would like the applicant to advise producers of foods containing the NI regarding the susceptibility of lycopene to oxygen and light. In addition, although the applicant has not provided any information on potential degradation of lycopene in products containing the NI which are cooked or baked at high temperatures, the Dutch CA highlights that heating products containing lycopene above 100°C is not recommended as this leads to the degradation of lycopene. The Secretariat notes that the request from Dutch CA for additional information on the effect of storage on the safety of the product helps to address the concerns raised by the SCF in 1999 (para. 6 above).

## **II. Effect of the production process applied to the novel food**

Annex 2, p.20-22

18. The chemical synthesis of the crystalline lycopene involves three steps:

- a) synthesis of C15 - phosphonium methane sulfonic acid which is then dissolved in methanol
- b) synthesis of C10 - dialdehyde in crystalline form
- c) synthesis of lycopene by mixing the two above intermediate compounds at 90°C, in the presence of a catalyst (sodium methoxide solution). The crude product undergoes further filtration and purification steps using water and methanol to be finally dried using warm nitrogen.

The crystalline lycopene obtained is stored in airtight containers, under inert gas and shielded from daylight to avoid degradation.

19. The synthetic lycopene will be milled to less than 0.5µm in diameter for the formulation of LycoVit 10% and less than 20µm in diameter for the formulation of LycoVit 10 CWD and LycoVit Dispersion 20%. Details of the preparation of the three formulations is provided in the dossier (Annex 2, p.25-26). LycoVit 10% and LycoVit 10 CWD contain antioxidants to improve their storage stability.

20. The Secretariat notes that synthetic lycopene from BASF is mentioned in various publications<sup>5</sup> as an example of a food ingredient produced in nanoparticulate form. Although there is no fixed definition of "nanoparticle", the term is generally taken to refer to substances with a particle size less than 100nm (0.1µm). The applicant has not provided information on the distribution of particle sizes in their product, other than the upper limits of 0.5 and 20µm.

21. The Dutch CA notes that the applicant will produce the NI in accordance with recognised quality control procedures, such as Good Manufacturing Practice, and HACCP and assumes these measures will be appropriate for the risk management of preparation and processing of the NI. The Dutch CA also states that the maximum permitted concentration of residual methanol should be 10 mg/kg, as required under Directive 88/334 (as amended) on extraction solvents used in the production of foods.

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<sup>5</sup> e.g. Information Statement on Nanotechnology, Institute of Food Science and Technology (February 2006)

### **III. History of the organism used as a source of the novel food**

Annex 2, p. 27

22. The Dutch CA notes that the NI is chemically synthesised and does not have a biological source.

### **IX. Anticipated intake/extent of use of the novel food**

Annex 2, p.33-37

23. The NI is intended to be added into food supplements, dietary foods intended for special medical purposes and various types of foods including drinks, meal replacements, dairy products excluding milk, breakfast cereals, spreadable fats and salad dressings. The applicant proposes to incorporate the NI at 2.5 to 8mg/100g in a range of food products and 15 mg per tablets or capsule in the case of food supplements.

24. Using the most recent Dutch Food Consumption survey data carried out by TNO in 1997-98, the applicant has estimated that the average daily lycopene intake will be 15 mg for children aged 4 to 9, 18 mg for teenagers and 9 mg for adults. Boys aged 10-18 years are the highest consumers with an estimated daily intake of 37 mg of synthetic lycopene at the 95<sup>th</sup> percentile. In comparison, the estimated daily intake of synthetic lycopene for adult men and women at 95<sup>th</sup> percentile are 25 mg and 23 mg respectively. When the estimated intake values for lycopene are compared in terms of kg bodyweight, young children aged 1-3 years are the highest consumers with 2.2 mg/kg bw/day. These estimates are calculated using the conservative assumption that all foods in the relevant categories contain the Ni at the maximum proposed levels of addition.

25. The Dutch CA notes that these estimated intake values for lycopene may not be representative of the intake of lycopene by consumers elsewhere in the EU. The Dutch CA also notes that the applicant did not include the use of foods intended for a particular nutritional purpose containing the NI and that it is not known whether the consumption of such food products will increase the anticipated daily lycopene intake. Given that the lycopene intake for young children is the highest, and that the Health Council of the Netherlands has identified a clear increase in the consumption of soft drinks (particularly sugar free) and fruit juices by people aged 13-35 years since 1988, the Dutch CA recommends that lycopene content should be expressed per unit of energy in order to prevent the overconsumption

of lycopene in low calorie drinks. Finally, the Dutch CA highlights that the daily consumption of food enriched with the NI, together with food supplements with 15mg of synthetic lycopene/capsule and multivitamin preparations with 1mg synthetic lycopene, could result in high level (95th percentile) intakes of synthetic lycopene of 41 mg/day for adult men and women and 53 mg/day for boys aged 10-18 years old.

26. The Secretariat notes that the intended uses of the NI will, in all likelihood, lead to significantly higher likely levels of lycopene intake compared with the recently authorised lycopene from *B. trispora*. The applicant is of the view that the toxicological assessment of the NI provides the necessary reassurance of safety at these levels of consumption (see paras 38-41 below), and this appears to have been accepted by the Dutch CA.

27. The 2003 UK initial opinion for lycopene from *B. trispora* did not highlight any concerns with the proposed levels of consumption which included the use of fungal lycopene in dietary supplements and indicated that consumption could exceed 20mg day<sup>6</sup>.

#### **X. Information from previous human exposure to the novel food or its source**

Annex 2, p.38

28. The applicant has provided a summary of the estimated daily intake of lycopene from natural sources, based on food consumption data obtained in different Member States. The average daily intake of lycopene for Dutch men and women in 1986 was 1.05 mg and 1.33 mg, respectively (95<sup>th</sup> percentile was 2.8 and 3.5 mg/day). An other European research project found that the median intake of lycopene for Dutch men and women was 4.9 mg/day which was similar to the values found for British, Irish and French consumers.

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<sup>6</sup> The EFSA Panel on Dietetic Products, Nutrition and Allergy Panel subsequently expressed some concern that no long term feeding studies had been carried out and that the available toxicological data on lycopene from *B. trispora* (a 90-day oral feeding study in rats) were not sufficient to derive an acceptable daily intake (ADI). In view of this the Panel concluded that:

“whilst use as a novel food ingredient in foodstuffs leading to an additional intake of up to about 2 mg/day is not of concern from the safety point of view, 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”.

The net result of this opinion was that the authorisation for lycopene from *B. trispora* did not extend to use in supplements, so that consumption of the fungal-derived lycopene is unlikely to exceed 2mg/day.

29. The applicant has also provided intake estimates for naturally-occurring lycopene in Canada and the USA. This shows that Canadians consume an average of 25 mg of lycopene/day through the consumption of tomatoes and tomato products. In the USA, consumers ingest considerably more lycopene per day than their European counterparts (e.g.: the lycopene intake for American men aged 19-30 years at the 95<sup>th</sup> percentile is 47.5mg/day).
30. Lycopene from natural sources is also available in Europe as a food supplement in doses of up to 20 mg/day. The applicant is currently marketing food supplements with added synthetic lycopene in the USA with a recommended daily dose of 5 to 15 mg lycopene/day.
31. The Dutch CA concludes that the applicant has clearly shown that lycopene is a normal component of our daily diet and has indicated the current level of exposure. It also states the consumption of 15 mg of lycopene per day is common. Finally, the Dutch CA notes that lycopene intake in individuals who are particularly fond of lycopene-rich natural products is of the same magnitude as the highest intake that would result from synthetic lycopene added to foods.

## **XI. Nutritional information on the novel food**

Annex 2, p.39-41

32. Lycopene is a carotenoid with no pro-vitamin A activity. Its major role in the human body is as an antioxidant, it can also protect membranes and DNA against harmful effects.
33. The applicant has described how the lycopene is absorbed and metabolised in the human body (Annex 2, Appendix A). After digestion, lycopene ends up in different body tissues with the highest levels found in the liver.
34. The applicant has carried out a study with LycoVit 10% which showed that the bioavailability of synthetic lycopene does not differ from that of natural lycopene from tomatoes processed into a food supplement.
35. In response to a request by the Dutch CA, the applicant has provided additional information on the potential effects that carotenoids and other fat-soluble vitamins may have on one another's absorption. Three recent studies on human subjects, a daily intake of 15 mg of lycopene did not have any adverse effect on the

absorption of other carotenoids such as zeaxanthin, beta-carotene and lutein. Additionally, it has been demonstrated that a daily intake of tomato extracts containing 13 or 15mg lycopene did not reduce the level of vitamins A and E in the blood plasma.

36. *Cis*- lycopene is more easily absorbed in the human body than *trans*-lycopene. *All-trans* lycopene have a relative faster clearance rate in the blood.

37. The Dutch CA concludes that the daily consumption of 15 mg of lycopene does not affect the absorption of other carotenoids and fat-soluble vitamins, in conjunction with a varied diet. It is also of the opinion that there is no evidence that *cis*- and *trans*- lycopene isomers have a different biological activity. Additionally, synthetic and natural lycopene is considered to be equivalent by the Dutch CA, in terms of nutritional function. Finally, it is of the view that a daily dose of 15 mg of synthetic lycopene will not have any adverse effects on human health.

## **XII. Microbiological information on the novel food**

Annex 2, p.42

38. The applicant has provided microbiological analytical results of several batches of LycoVit 10% and LycoVit 10 CWD. The applicant states that the LycoVit preparations are produced under specific hygienic conditions and it is therefore unlikely that a microbiological contamination occurs. The applicant will carry out check for the presence of micro-organisms on a regular basis for LycoVit 10% and LycoVit 10 CWD but this will be unnecessary for LycoVit 20% Dispersion due to the use of food-grade sunflower oil in the matrix and the nature of the production process.

39. The Dutch CA was content that the NI will be of microbiological quality which complies with food safety standards.

## **XIII. Toxicological information on the novel food**

Annex 2, p.43-44, Appendix B

40. LycoVit 10 CWD has been tested for its potential genetic, acute, subchronic and reproduction toxic properties. LycoVit 10% was only tested for its potential subchronic, teratogenic and embryo toxicological effects. Although the company has not responded directly to concerns raised in the SCF's 1999 opinion on

synthetic lycopene (see para 6) the toxicological analyses carried out, and the additional evaluation, and setting of an ADI by JECFA may go some way to alleviating the SCF's concerns.

41. In response to a request by the Dutch CA, the applicant has provided further data on the test materials used in the toxicological studies. It contained 82% *all-trans* lycopene, 16% 5-*cis* lycopene and 0.06% C25-aldehyde lycopene. Details of the total synthetic lycopene content of all the tested preparations have also been provided.
42. No adverse effects related to the consumption of the NI have been observed in any of the toxicological studies presented in this application. Based on the 13-week rat study (highest dose = 3000mg of a preparation containing 10% of the NI per kg bw per day), the applicant has calculated that the intake of synthetic lycopene is approximately a factor of 1200 higher than the proposed daily lycopene intake of 15 mg for adults weighing 60 kg. Based on the 95<sup>th</sup> percentile of the estimated intake of the NI added to foods and combined with various types of lycopene supplements, the safety margin is approximately 450 for adults and 300 for boys aged 10 to 18 years. For children aged 1 to 3 years, the safety margin is between 100 and 150, depending on whether the consumption of food supplements has been taken into account.
43. The Dutch CA accepted that the test materials in the toxicological studies are representative of the synthetic lycopene used in the NI. It also agrees that the safety margins calculated by the applicant are adequate and show that there are no safety concerns over the proposed uses of the NI.
44. The Dutch CA highlights that the safety margin for lycopene derived from *B. trispora* (i.e. the difference between the dose of fungal lycopene which produces no adverse effects in animals and the intake through the use of food supplements with 20 mg added lycopene) was 2000. It also notes that JECFA concluded that lycopene from *B. trispora* was equivalent to chemically synthesised lycopene in toxicological terms. JECFA also set an ADI of 0-0.5 mg/kg bw/day for synthetic lycopene and lycopene from *B. trispora*. The Dutch CA comments that ADI value is based on continuous exposure and that it can be described as "cautious". They note also that JECFA had access to additional safety data on a synthetic

lycopene preparation from another manufacturer and the ADI is derived from a 2-year rat feeding study with that product. The Dutch CA finally concludes that the daily consumption of high doses of lycopene is unlikely to give rise to long-term adverse effects.

## **Labelling**

Annex 2

45. The applicant has not indicated how the NI would be declared on food labels. The Dutch CA highlights that the labelling of the NI will have to comply with Directive 2000/13/EC relating to food labelling but does not offer any further comment, referring to other procedures under their national legislative system.

## **Committee Action Required**

46. The Committee is asked whether it agrees with the initial opinion from the Dutch CA that synthetic lycopene produced by BASF should be granted authorisation as a novel food ingredient in food supplements and in other foods, and whether it wishes to make any additional comments on the application.

**Secretariat**

**January 2007**

### **Annexes attached:**

- Annex 1 – Dutch initial assessment report.  
Available from: <http://www.cbg-meb.nl/uk/nwvoeding/index.htm>
- Annex 2 - Application dossier submitted by BASF Corporation Ltd for the approval of a synthetic lycopene (Lycovit) as a novel food ingredient (**restricted**).

**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

Dutch Competent Authority's Initial Assessment Report

Available from: <http://www.cbg-meb.nl/uk/nwvoeding/index.htm>

**Secretariat  
January 2007**

**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

**RESTRICTED**

Application dossier submitted by BASF Corporation Ltd for the approval of a synthetic lycopene (LycoVit) as a novel food ingredient.

**Secretariat  
January 2007**