Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2016: 29

Risk assessment of "other substances" – Lycopene

Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

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Risk assessment of "other substances" – Lycopene

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Assessed and approved

The opinion has been assessed and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Members of the panel are: Inger-Lise Steffensen (Chair), Ellen Bruzell, Berit Granum, Ragna Bogen Hetland, Trine Husøy, Jens Rohloff, Trude Wicklund.

(Panel members in alphabetical order after chair of the panel)

Acknowledgment

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the risk of "other substances" in food supplements and energy drinks sold in Norway. VKM has assessed the risk of doses in food supplements and concentrations in energy drinks given by NFSA. These risk assessments will provide NFSA with the scientific basis while regulating the addition of "other substances" to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC *as substances other than vitamins or minerals that have a nutritional and/or physiological effect*. It is added mainly to food supplements, but also to energy drinks and other foods. VKM has not in this series of risk assessments of "other substances" evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of lycopene, and it is based on previous risk assessments and articles retrieved from a literature search.

According to information from NFSA, lycopene is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of 10 mg/day of lycopene in food supplements. The intake of lycopene was estimated for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Other sources of lycopene, such as foods and cosmetics, have not been included in the present risk assessment.

Lycopene belongs to a large group of naturally-occurring pigments known as carotenoids, and is known to have antioxidant properties. Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. The major sources of natural lycopene in the human diet are tomatoes and tomato-based products. Fruits like pink grapefruit, water melon, rosehip, papaya and guava are also sources of lycopene.

Lycopene can be obtained by solvent extraction of the natural strains of red tomatoes (*Lycopersicon esculentum* L.) with subsequent removal of the solvent. Synthetic lycopene can be produced by the Wittig condensation of synthetic intermediates commonly used in the production of other carotenoids used in food. Lycopene biosynthesis by the fungus *B. trispora* follows the same pathway as the synthesis of lycopene in tomatoes.

There are case reports of yellow-orange skin discoloration and/or gastrointestinal discomfort after prolonged high intakes of lycopene-rich food and supplements, those effects being reversible upon cessation of lycopene ingestion. The results from one study indicated that lycopene increased the incidence of the preterm labor and low birthweight babies. However, due to weaknesses in the reporting, VKM cannot use the results from this study in the risk characterisation.

An ADI of 0.5 mg/kg bw per day was established by EFSA in 2008. The ADI was derived from the NOAEL of 50 mg/kg bw per day from a 52-week toxicity study in rats, based on a partly reversible increased level of the liver enzyme alanine transaminase (ALT). An ADI is set to cover the general population, including children. This ADI-value was used for comparison with the estimated exposure in the risk characterization.

From a daily dose of 10 mg lycopene, the daily exposure is 0.23 mg/kg bw for children (10 to <14 years), 0.16 mg/kg bw for adolescents (14 to <18 years), and 0.14 mg/kg bw for adults (Table 3.1-1). Thus, the intakes are below the ADI of 0.5 mg/bw per day for all age groups.

VKM concludes that it is unlikely that a daily dose of 10 mg lycopene from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Short summary

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of lycopene in food supplements. For the risk characterisation, the value used for comparison with the estimated exposure is the ADI of 0.5 mg/kg bw per day established by EFSA. An ADI is set to cover the general population, including children. The ADI was used for comparison with the estimated exposure in the risk characterization.

VKM concludes that it is unlikely that a daily dose of 10 mg lycopene from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Key words: Adverse health effects, food supplement, lycopene, negative health effects, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, VKM

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetting av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Disse risikovurderingene vil gi Mattilsynet vitenskapelig grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC som stoffer som har en ernæringsmessig og/eller fysiologisk effekt, og som ikke er vitaminer og mineraler. De tilsettes i hovedsak til kosttilskudd, men også til energidrikker og andre næringsmidler. I disse risikovurderingene har VKM ikke vurdert påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Denne risikovurderingen av lykopen er basert på tidligere risikovurderinger og artikler funnet ved litteratursøk.

Ifølge informasjon fra Mattilsynet er lykopen en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere 10 mg/dag av lykopen i kosttilskudd for den generelle befolkningen fra 10 år og eldre.

Andre kilder til lykopen, som for eksempel mat og kosmetikk, er ikke inkludert i denne risikovurderingen.

Lykopen tilhører en gruppe med naturlig forekommende pigmenter som kalles karotenoider. Lykopen forekommer naturlig i røde frukter og grønnsaker og i noen alger og sopp. Hovedkildene til lykopen i kosten er tomater og tomat-baserte produkter. Frukt som rosa grapefrukt, vannmelon, nype, papaya og guava er også kilder til lykopen.

Lykopen ekstraheres fra røde tomater (*Lycopersicon esculentum* L.) ved hjelp av løsningsmidler, som så fjernes. Syntetisk lykopen kan fremstilles ved Wittig-kondensering. Lykopen syntetiseres også av soppen *B. trispora*, og synteseveien er da den samme som for lykopen som produseres i tomat.

Det er rapportert om tilfeller av gul-oransje misfarging av huden og/eller mage-tarm ubehag etter høyt inntak over lengre tid av lykopen fra mat og kosttilskudd. Disse effektene var reversible ved seponering av inntaket av lykopen. Resultatene fra en studie indikerte at lykopen ga økt forekomst av for tidlig fødsel og lav fødselsvekt, men VKM kan ikke bruke resultatene fra denne studien i risikokarakteriseringen på grunn av svakheter i rapporteringen.

I risikokarakteriseringen ble den estimerte eksponeringen sammenlignet med verdien for akseptabelt daglig inntak (ADI) på 0,5 mg/kg kroppsvekt per dag som er fastsatt av den europeiske myndighet for næringsmiddeltrygghet (European Food Safety Authority - EFSA). ADI-verdien ble fastsatt ut i fra en NOAEL-verdi (null-effektsnivå) på 50 mg/kg kroppsvekt per dag fra en rottestudie av 52 ukers varighet, basert på en økning i lever-enzymet alanin

transaminase (ALT) som kun var delvis reversibel. ADI er satt for å dekke den generelle befolkningen, inkludert barn.

Det estimerte daglige inntaket fra en dose på 10 mg/dag av lykopen var 0,23 mg/kg kroppsvekt for barn (10 til <14 år), 0,16 mg/kg kroppsvekt for ungdom (14 til <18 år) og 0,14 mg/kg kroppsvekt for voksne. Alle inntakene er under ADI-verdien på 0,5 mg/kg kroppsvekt per dag for alle aldersgrupper.

VKM konkluderer at det er usannsynlig at en daglig dose på 10 mg lykopen fra kosttilskudd forårsaker negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) eller voksne.

Kort sammendrag

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av lykopen i kosttilskudd. I risikokarakteriseringen ble den estimerte eksponeringen sammenlignet med verdien for akseptabelt daglig inntak (ADI) på 0,5 mg/kg kroppsvekt per dag som er fastsatt av den europeiske myndighet for næringsmiddeltrygghet (European Food Safety Authority – EFSA). ADI-verdien ble fastsatt ut i fra en NOAEL-verdi (null-effektsnivå) på 50 mg/kg kroppsvekt per dag fra en rottestudie av 52 ukers varighet, basert på en basert på en økning i lever-enzymet alanin transaminase (ALT) ved den høyeste testede dosen som kun var delvis reversibel.

VKM konkluderer at det er usannsynlig at en daglig dose på 10 mg lykopen fra kosttilskudd forårsaker negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) eller voksne.

Abbreviations and glossary

Abbreviations

ADI	- acceptable daily intake
ADME	- absorption, distribution, metabolism and excretion
AESAN	- the Spanish Agency for Food Safety and Nutrition
AST	- aspartate transaminase
ALT	- alanine transaminase
EFSA	- European Food Safety Authority
JECFA	- the Joint FAO/WHO Expert Committee on Food Additives
LDL	- low-density lipoprotein
NFSA	- Norwegian Food Safety Authority [*norw.*: Mattilsynet]
NOAEL	- no observed adverse effect level
OECD	- Organisation for Economic Co-operation and Development
VKM	- Norwegian Scientific Committee for Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet
WS	- water soluble

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (The European Parliament and the Council of the European Union, 2006).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition endorsed by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (EFSA, 2006; WHO, 1994).

Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to other foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

In Norway, a former practice of classification of medicines had constituted an effective barrier against the sale of potentially harmful "other substances". Ever since this practice was changed in 2009, it has become challenging to regulate and supervise foods with added "other substances". Meanwhile, in the recent years, the Norwegian market has witnessed a marked growth in the sales of products containing "other substances". In 2011, food supplements containing "other substances" constituted more than 50% of the market share.

While within the European Economic Area, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list, i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods (FVM, 2014).

The Norwegian Food Safety Authority (NFSA) is working on the establishment of a regulation on the addition of "other substances" to foods at a national level. The regulation will include a list of substances with permitted maximal doses, based on the substances and doses found in products on the Norwegian market. In preparation for a regulation, NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, in consultation with the industry, has compiled a list of "other substances" found in products marketed in Norway. Only substances with a purity of minimum 50% or concentrated 40 times or more have been included in the list. Substances regulated by other legislations like those for novel foods, food additives, flavourings, foods for special medical purposes etc., have been excluded from the list.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of lycopene in food supplements at the following dose: 10 mg lycopene/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance to the guidance document developed in Phase 2) at the doses specified (Phase 3). Safety assessments of "other substances" present in food supplements shall be carried out for a general population, ages 10 years and above.

Assessment

1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC *as substances other than vitamins or minerals that have a nutritional or physiological effect,* and may be added to food supplements or e.g. energy drinks (The European Parliament and the Council of the European Union, 2006).

This risk assessment regards the substance lycopene per se, and no specific products.

VKM has in this series of risk assessments of "other substances" not evaluated documentation of any claimed beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway. Thus, potential high intake consumer groups of the substance may not be identified and included in this assessment.

According to information from the Norwegian Food Safety Authority (NFSA), lycopene is an ingredient in food supplements purchased in Norway. NFSA has requested a risk assessment of the intake of 10 mg/day of lycopene from food supplements. The total exposure to lycopene from other sources than food supplements, such as foods and cosmetics, is not included in the risk assessment.

Lycopene belongs to a large group of naturally-occurring pigments known as carotenoids, and is known to have antioxidant properties (EFSA, 2008). Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. The major sources of natural lycopene in the human diet are tomatoes and tomato-based products. Fruits like pink grapefruit, water melon, rosehip, papaya and guava are also sources of lycopene (Nguyen and Schwartz, 1999). Lycopene from tomatoes, synthetic lycopene and lycopene synthesized by the fungus *B. trispora* is authorised as a food additive (registered as E160d).

In humans, lycopene is not transformed to vitamin A in contrast to e.g. ß-carotene (JECFA, 2009). The exposure to lycopene from dietary sources varies between different European populations. According to dietary surveys, regular intakes of lycopene from natural dietary sources in different populations were estimated to be on average between 0.5 and 5 mg/day, with high intakes up to about 8 mg/day (EFSA, 2008). High consumption of fruits and vegetables, especially tomato products, may result in occasional intakes of 20 mg lycopene/day or more (EFSA, 2008). EFSA noted that total daily exposure to lycopene from *Blakeslea trispora* as a food additive (as food colour) could potentially range from 2 to 6 mg on the average and go up to 11 to 23 mg at the high level. Thus, EFSA did not exclude an occasionally combined high exposure from both natural dietary sources and food additives (as food colours) up to 43 mg of lycopene per day (EFSA, 2008).

There are case reports of yellow-orange skin discoloration and/or gastrointestinal discomfort after prolonged high intakes of lycopene-rich food and supplements, those effects being reversible upon cessation of lycopene ingestion (JECFA, 2006).

In this risk assessment, the intake of 10 mg/day from food supplements is assessed.

2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on previous risk assessments of lycopene and articles retrieved from a literature search.

2.1.1 Previous risk assessments

Safety evaluation of certain food additives and contaminants. Prepared by the Sixty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006)

In previous safety evaluations of lycopene as a food colour by JECFA, an acceptable daily intake (ADI) was not established due to lack of data. In this meeting, the safety of synthetic lycopene and lycopene from the fungus *B. trispora* was evaluated using a large number of studies of pharmacokinetics and metabolism, acute toxicity, short- and long-term toxicity, carcinogenicity, genotoxicity and reproductive toxicity.

Reported negative effects after prolonged consumption of high doses of lycopene were yellow-orange skin discoloration and/or gastrointestinal discomfort.

An ADI of 0–0.5 mg/kg bw per day for synthetic lycopene was established, and the ADI was made into a group ADI to include lycopene from *B. trispora*, which was considered to be toxicologically equivalent to synthetic lycopene. The ADI was based on the highest dose identified as the No Observed Adverse Effect Level (NOAEL) of 50 mg/kg bw per day tested in a 104-week study in rats (no adverse effects relevant to humans were induced) and a safety factor of 100. The study was performed by Edwards et al., 2006 (unpublished report No. 2285/001 (DSM No. 2500022) from Covance Laboratories Ltd., Harrogate, United Kingdom; described by JECFA), and followed OECD guideline 451. Wistar rats, 50 males and 50 females, were given lycopene (2, 10 and 50 mg/kg bw per day) in the diet for 104 weeks. Two control groups of 50 males and 50 females received either a diet mixed with placebo beadlets or pure diet. In addition to the standard observations, plasma and liver samples were analysed for total lycopene content (i.e. sum of all determined isomers), and liver, mesenteric and mandibular lymph nodes from all animals in the study were examined microscopically, as well as kidneys from all female rats. Analysis of plasma and liver samples demonstrated systemic absorption of lycopene in all groups receiving Lycopene 10% WS (water soluble) beadlets. There was no influence of treatment on incidences and causes of morbidity and mortality. Food consumption, overall body-weight gain and food conversion efficiency of males and females given lycopene in the diet were similar to that of the

standard control and placebo groups. Erythrocyte and leukocyte counts were not consistently affected by treatment. The treatment resulted in liver pigmentation with associated histopathological alterations of hepatocellular foci, in particular eosinophilic, normochromic and basophilic foci, and mainly at the intermediate and highest dose. The significance of these treatment-related alterations for humans is unclear, given that there was no apparent sign of liver dysfunction, they were without a consistent dose–response relationship, and placebo controls were in some cases also affected. Moreover, in contrast to humans, hepatocellular foci are commonly found in the ageing rat at high incidences, and while experimental models suggest that some foci may be precursors of hepatocellular neoplasia, it is also known that only a very small proportion of foci progress to neoplasia even after continued administration. Indeed, treatment with lycopene did not result in an increase in liver tumors. However, it was noted that the alterations were observed in a single, non-standardized liver section investigated, which would not necessarily be representative for other sections of the liver.

Use of Lycopene as a food colour. Scientific Opinion of the Panel on Food additives, Flavourings, Processing Aids and Materials in Contact with Food. The European Food Safety Authority (EFSA, 2008)

The safety in use of lycopene as a food colour was evaluated, and the included sources of lycopene were tomatoes, synthetic lycopene and lycopene synthesized by the fungus *B. trispora.* Studies of acute oral toxicity, subchronic toxicity, chronic toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity were included.

The oral LD_{50} value of lycopene in mice was reported to be higher than 3000 mg/kg bw (the source of lycopene was not specified by the authors) (Milani et al., 1970).

Studies on lycopene extracted from *B. trispora*

- The NOAEL value from a 90-day oral toxicity study with lycopene extracted from *B. trispora* was 600 mg/kg bw per day (Milani et al., 1970).

Studies (all guideline studies) on formulated, synthetic lycopene. The following NOAELs were established:

- Oral toxicity study:
    - 500 mg/kg bw per day (the highest dose level tested) in a 14-week rat study (unpublished study; Buser & Urwyler, 1996. Ro 01-9251/008 (Lycopene).
- Developmental toxicity studies:
    - 500 mg/kg bw per day (the highest dose level tested) in a rat study. Mated female rats were administered lycopene orally from day 5 (implantation) to day 21 post coitum (unpublished study; Edwards et al., 2004. Lycopene 10% WS beadlets (Ro01-9251) Prenatal Developmental Toxicity Study in the Han Wistar Rat, RCC Study Number: 848973, RDR Report No. 1016176).

- 500 mg/kg bw per day (the highest dose level tested) in a two-generation study in the rat (unpublished study; Edwards et al., 2005. Lycopene 10% WS beadlets (Ro 01-9251), Two generation reproduction study in rats by the oral route (dietary admixture), MDS Study Number 161/582, RDR Report No. 2500018).
- 400 mg/kg bw per day (the highest dose level tested) in a study in rabbits (unpublished study; Edwards et al., 2004d. Lycopene 10% WS beadlets (Ro 01-9251) Prenatal Developmental Toxicity Study in the Himalayan Rabbit, RCC Study Number: 848972, RDR Report No. 1014560).

- Carcinogenicity and long-term studies
  - 50 mg/kg bw per day in a one-year rat study based on the non-reversible increase in alanine transaminase (ALT) (unpublished study; Smith et al., 2005. Lycopene 10% WS Beadlets (Ro 01-9251), 52-Week Oral (Dietary) Administration Toxicity Study in the Rat, RDR Report No. 2500020). **EFSA (2008) derived the ADI of 0.5 mg/kg bw per day for lycopene from this study**. From the EFSA opinion: "*Daily administration of lycopene at 10, 50 or 250 mg/kg bw/day to rats for 52 weeks was generally well tolerated with only minimal liver changes observed. These changes involved increases in aspartate transaminase (AST) and alanine transaminase (ALT), mainly noted at 250 mg/kg/day, with the increases in ALT in this highest dose group not being fully reversible upon a 13 week treatment free period. Minor microscopic changes were observed histologically in the liver, mainly in females. Hepatocyte pigment was increased with no obvious dose relationship and therefore considered not treatment-related. Pigmented histiocytes were increased in males fed intermediate and high doses of lycopene and in all treated females receiving lycopene. Greater incidence and severity of basophilic foci was observed in high dose females. Hepatocyte pigment, pigmented histiocytes, and basophilic foci are all seen as background findings in the aging rat, especially in females (Eustis et al., 1990; Popp 2006) and were therefore considered by the Panel not to be of toxicological relevance. The Panel considers the effects on ALT and AST levels to be treatment-related. For the highest dose group of 250 mg/kg bw per day the increases in AST appeared reversible upon a 13 week treatment-free period, but the increases in ALT appeared to be only partially reversible upon a 6 and 13 week treatment-free period. The Panel considers the non-reversible effect on ALT as the effect on which to base the NOAEL for the study. The Panel concludes that the NOAEL of this study amounts to 50 mg/kg bw per day, a dose level where the effects on the AST and ALT levels were considered not toxicologically significant*."
  - 50 mg/kg bw per day in a two-year rat carcinogenicity study (unpublished study; Smith et al, 2006. Lycopene 10% WS Beadlets (Ro 01-9251), 104 Week Oral (Dietary) Administration Carcinogenicity Study in the Rat (2285/001) RDR Report No. 2500022). In this study, no carcinogenic potential

was observed after exposures up to 50 mg/kg bw per day (the highest tested dose).

Studies on lycopene from tomatoes

- Several toxicity studies on lycopene from tomatoes showed no adverse effects up to the highest dose levels tested, including a 10-week study in rats (Zhao et al., 1998) and a 28-week study in mice (Black, 1998), revealing NOAEL values of 60 mg/kg bw per day and 35 mg/kg bw per day, respectively. Both NOAEL values were the highest tested doses.

In conclusion, an ADI for lycopene from all sources of 0.5 mg/kg bw per day was derived by EFSA, using a safety factor of 100 based on the NOAEL of 50 mg/kg bw per day.

Safety evaluation of certain food additives. Prepared by the seventy-first meeting of the JECFA Food Additives series 62 (JECFA, 2009)

In this evaluation, lycopene from all sources were evaluated. All the toxicity studies that were included in the 2006 report by JECFA were reconsidered in addition to new studies.

It was concluded that, based on lycopene's low toxicity, there was no need to establish a numerical ADI. The Committee decided to revise the group ADI previously established (for synthetic lycopene and lycopene from *B. trispora*) and replace it with a group ADI "not specified" for lycopene from all sources. Hence, the previous group ADI of 0–0.5 mg/kg bw for lycopene was replaced with the group ADI "not specified" for synthetic lycopene, lycopene derived from the fungus *B. trispora* and lycopene extract from tomato.

Statement of the divergence between the risk assessment of lycopene by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The European Food Safety Authority (EFSA, 2010)

In this statement, the divergence between the ADI-values established by EFSA (2008) and JECFA (2009) was addressed.

EFSA concluded that the divergence of the scientific opinions was not based on data that were not available to EFSA during its evaluation of lycopene, but rather on diverging interpretation of the results in a study by Smith et al. (unpublished study; Smith et al., 2005. Lycopene 10% WS Beadlets (Ro 01-9251), 52-Week Oral (Dietary) Administration Toxicity Study in the Rat, RDR Report No. 2500020).

Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements (1) (AESAN, 2012)

In this report, a proposal of the use of a maximum of 15 mg lycopene per day was addressed.

The Spanish Scientific Committee concluded, based on the information available and taking into account the general considerations reflected in their report, that the AESAN proposal of a maximum amount of 15 mg/day of lycopene is acceptable from the safety point of view for use as a food supplement.

2.1.2 Literature search

2.1.2.1 Search strategy

To retrieve publications on adverse effects caused by lycopene, literature searches were performed in Embase and Medline. The search strategy is included in Appendix 1.

2.1.2.2 Publication selection and data extraction

The literature search identified 213 articles. In the primary screening, titles and abstracts of all publications retrieved were independently screened by two persons against the inclusion criteria checklist.

Inclusion criteria checklist:

- Adverse effects in relation to the substance alone are addressed
- Route of exposure for humans is oral
- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetics is equal to oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of the assessed substance
- Animal model studies address adverse effects relevant to human health

The inclusion criteria checklist was developed by members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Articles that did not appear to meet the inclusion criteria were excluded from further analysis. In situations where it was unclear whether the publication was of relevance to the study, it was retained for further screening. The primary screening was performed independently by two persons.

The full text of articles that passed the primary screening was retrieved for secondary screening. In this screening, the full text articles were reviewed and compared against the inclusion criteria checklist. The secondary screening was performed by one person.

The secondary screening resulted in one publication. Additionally, 2 publications from a manual search were identified and included. A final total of 3 publications were identified and included in the results in this report (see Figure 2.1.2.2-1).

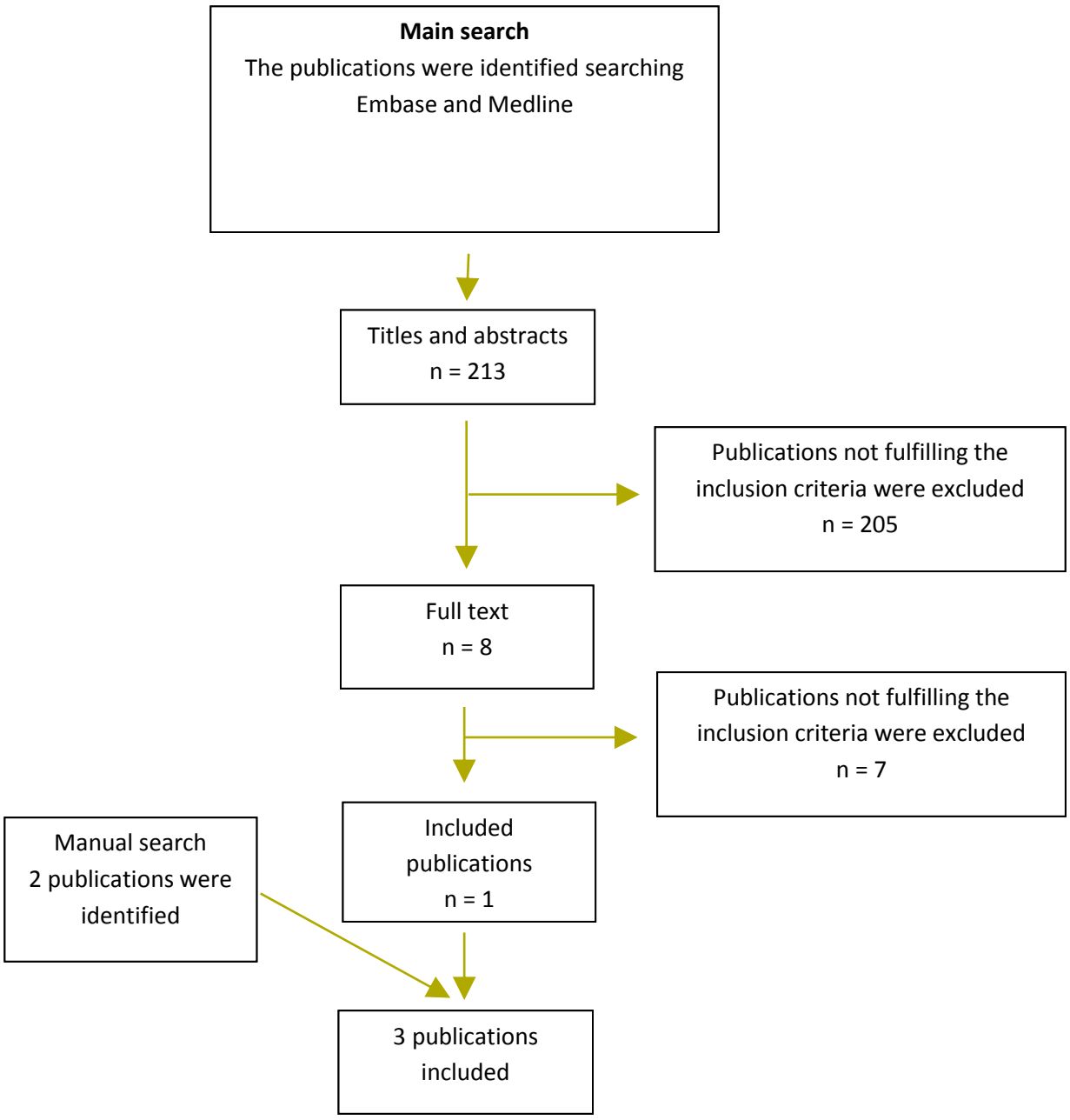

Figure 2.1.2.2-1: Flow chart for the literature search for lycopene and the subsequent publication selection.

2.2 General information

2.2.1 Chemistry

Lycopene (EINECS no. 207-949-1) belongs to a group of naturally-occurring pigments known as carotenoids. Lycopene is a constituent of red fruits and vegetables and of certain algae and fungi. The molecular formula is $C_{40}H_{56}$ and the molecular weight is 536.85 g/mol (EFSA, 2008). The chemical name for 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 (JECFA, 2006). Lycopene is an unsaturated acyclic hydrocarbon. Lycopene occurs in various geometrical configurations. In food, all-*trans*-lycopene (CAS no. 502-65-8) is the predominant form of lycopene.

Lycopene from tomatoes consists predominately of all-*trans*-lycopene (35-96% of the total lycopene content) and low levels of *cis*-lycopene (1-22% of the total lycopene content). Synthetic lycopene contains approximately 70% of all-*trans*-lycopene, up to 23% of 5-*cis*-lycopene and minor quantities of other *cis*-isomers. Lycopene from *B. trispora* contains at least 90% all-*trans*-lycopene and minor quantities of 13-*cis*-lycopene and β- and γ-carotene.

Lycopene is water insoluble, but can be dissolved in organic solvents and oils. The structure formula of all-*trans*-lycopene is shown in Figure 2.2.1-1.

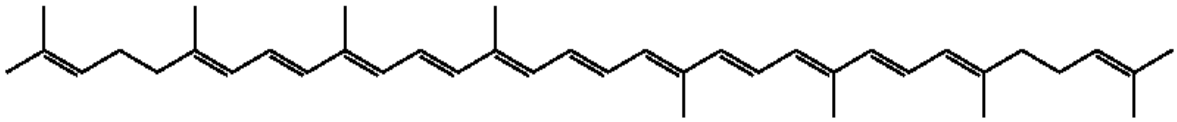

Figure 2.2.1-1 The structural formula of all-*trans*-lycopene.

Lycopene can be obtained by solvent extraction of the natural strains of red tomatoes (*Lycopersicon esculentum* L.) with subsequent removal of the solvent (EFSA, 2008). Synthetic lycopene can be produced by the Wittig condensation of synthetic intermediates commonly used in the production of other carotenoids used in food. Lycopene biosynthesis by the fungus *B. trispora* follows the same pathway as lycopene synthesis in the tomato (EFSA, 2008).

2.2.2 Occurrence

The major sources of natural lycopene in the human diet are tomatoes and tomato-based products. Fruits like pink grapefruit, water melon, rosehip, papaya and guava are also sources of lycopene (Nguyen and Schwartz, 1999). Lycopene from tomatoes, synthetic lycopene and lycopene synthesized by the fungus *B. trispora* is authorised as a food additive (registered as E160d).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

After ingestion, synthetic lycopene is considered to be equivalent to naturally-occurring dietary lycopene (JECFA, 2006).

Lycopene is water insoluble. Studies have demonstrated that the absorption of lycopene is increased when it is ingested with a high-fat diet. The addition of oil to tomato juice before heating also improves the bioavailability of lycopene (Stahl and Sies, 1992). Lycopene from food supplements generally have higher bioavailability than lycopene from food sources such as fruits and vegetables as it is usually combined with a lipid substance (Tang et al., 2005).

Fat soluble carotenoids such as lycopene are absorbed in the intestine and transported in chylomicrons to the blood stream via the lymphatic system (Parker, 1996). Lycopene absorption can be facilitated by a cholesterol membrane transporter known as scavenger receptor class B type I (During et al., 2005; Moussa et al., 2008). Heat treatment in the processing of raw tomatoes results in the release of lycopene from the cellular matrix, making it more bioavailable (Gartner et al., 1997).

Lycopene is primarily transported by low-density lipoprotein (LDL) (Erdman et al., 1993; Holloway et al., 2000; Parker, 1996) and accumulates in tissues rich in LDL receptors, such as liver, adrenals and testes (Holloway et al., 2000). It reaches its maximum concentration in the plasma 24–48 hours after dosing (Stahl and Sies, 1992), and with repeated dosing the blood concentration continues to rise until a steady state is reached. Rao and Agarwal (1999) reported a half-life of lycopene in plasma in the order of 2–3 days, whereas Cohn et al. (2004) reported estimated half-lives of 5 days and 9 days for all-*trans*-lycopene and 5-*cis*-lycopene, respectively.

The metabolic pathway of lycopene has not been fully described (JECFA, 2009). In EFSA (2008) the following was reported: *"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."*

2.3.2 Animal studies

A study in lymph duct cannulated ferrets showed that the *cis*-isomers of lycopene are more bioavailable than the *all-trans* isomer (Boileau et al., 1999). It was speculated that it might be due to the shorter length of the molecule, the greater solubility in mixed micelles and their lower tendency to aggregate cis-isomers (Boileau et al., 2002).

From a summary of studies on synthetic lycopene by McClain and Bausch (2003): *"There is little information in the scientific literature regarding the absorption, distribution, and*

metabolism of lycopene. In a published study, Mathews-Roth et al. (1990) reported the distribution of [^{14}C]-labeled lycopene (specific activity 101 µCi/mg) in rats and monkeys dosed by gavage with 20 and 50 µCi, respectively. After the administration of [^{14}C]lycopene, peak accumulation of radioactivity in plasma occurred between 4 and 8 hours in rats and between 8 and 48 hours in monkeys. In rats, the liver contained the largest amount of radioactive pigment. In monkeys, with the exception of one stomach sample, liver was also the main depot organ for lycopene. The other organs tested accumulated various amounts of pigment. No labeled metabolic products of lycopene were found. In these studies, however, the investigators did not measure the urinary excretion of radioactivity and did not calculate the radioactive balance. Furthermore, the lack of radiolabeled metabolic compounds reported by the investigators was probably due to analytical methods used in this study. In an ADME study in rats, lycopene, like other carotenoids, was poorly absorbed after oral (gavage) administration (0.2 or 2 mg/kg bw in a beadlet formulation), however, absorption was fairly rapid with a peak at 2 hours following administration. On average, 8.7% of the administered dose was absorbed. High levels of radioactivity were found in the feces, representing mainly non-absorbed [^{14}C]lycopene. Of the amount of lycopene that was absorbed, 44% was excreted in the urine, 20% in the bile, 13% was expired in the air, and 24% remained in organs and tissues 96 hours after administration. Low absolute amounts of radioactivity (<1.0 µg parent equivalents/g) were measured in organs/tissues, blood, and plasma at any time. The amount of residual radioactivity was lower after pretreating the animals for 14 days with unlabeled lycopene. Otherwise, no significant differences in excretion patterns were observed between males and females, between dose groups, or between non-pretreated and pretreated rats. The overall recovery of radiolabel was approximately 97.5% of the administered dose."

EFSA (2008) reported that a series of polar lycopene metabolites was found in urine in studies of ADME of lycopene in rats and rabbits: "*The petitioner reports that in ADME studies in rats with synthetic lycopene, a series of polar metabolites in urine was found which were not further identified (Mair et al., 2005). In another study provided by the petitioner it was demonstrated that radioactivity of 14C labelled lycopene was excreted after a single dose in urine (44%), bile (20%) and air (13%), while 24% remained in the body at 96 hours after administration (Wendt and Bausch, 1996). Also the presence of polar metabolites in the tissues of rats has been shown (Zaripheh et al., 2003). Furthermore, in a rabbit preliminary study provided by the petitioner, which included 14C-radiolabelled lycopene (dosed by oral gavage as a single dose of 6 mg/kg bw) and also normal lycopene (doses by oral gavage at 131 mg/kg bw/day for up to 21 days) chemical and radioactivity analyses of plasma revealed the presence of metabolites (Edwards et al., 2002)."*

2.4 Toxicological data/Adverse effects

2.4.1 Genotoxicity

Several genotoxicity studies were described in (JECFA, 2006). The studies followed OECD test guidelines 471, 473, 474, 476 or 486. The *in vitro* studies included tests for gene

mutation in bacteria (*Salmonella typhimurium*, *Escherichia coli*), the *in vivo* studies included a test for micronucleus formation in mouse peripheral blood, tests for DNA damage in human lymphocytes and a test for spontaneous mutation in LacZ mouse DNA. All the results were negative, which means that lycopene was not genotoxic, based on these tests.

2.4.2 Human studies

An overview of the included studies investigating adverse health effects of lycopene in humans is given in Table 2.4.2-1.

Table 2.4.2-1 An overview of human studies investigating adverse health effects of lycopene.

Reference	Study design/ participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Length of study	Adverse effect
			Lycopene	Control/ Placebo				
Banerjee et al. (2009)	A prospective randomized double blind placebo-controlled study. A total of 159 primigravidas at gestational ages between 12 and 20 weeks, with singleton pregnancy and without any medical disorders were enrolled	India	n = 77	n = 82 (edible oil)	2 mg lycopene/day	The efficacy of lycopene in preventing pre-eclampsia in healthy primigravidas	The women were followed up until delivery for the development of pre-eclampsia and maternal, fetal and neonatal outcomes	There was a significantly higher incidence of adverse effects like preterm labor (10.39% with lycopene vs. 1.22% with placebo, P value = 0.02) and incidence of low birth weight (<2.5 kg) babies (22.08% with lycopene vs 9.76% with placebo, P value = 0.05)
Shao and Hathcock (2006)	Risk assessment of lycopene, including 16 randomized, placebo-controlled intervention trials	Several countries (16 included studies)	n = 8 - 52		12 mg/day - 150 mg/day	Adverse health effects	From 7 days to 20 weeks	No adverse effects were reported

A prospective randomized double-blind placebo-controlled study was performed by Banerjee et al. (2009) to evaluate the efficacy of lycopene in preventing pre-eclampsia in healthy primigravidas. A total of 159 primigravidas at gestational ages between 12 and 20 weeks, with singleton pregnancy and without any medical disorders, were enrolled. Seventy-seven received 2 mg oral lycopene daily until delivery, and 82 (controls) received placebo daily until delivery. The two study groups were not significantly different in terms of blood pressure, mean maternal age or mean gestational age at the start of the therapy. The women were followed up until delivery for the development of pre-eclampsia and maternal, fetal and neonatal outcomes. The results showed no significant difference between the two groups in developing pre-eclampsia (18.18% with lycopene vs. 18.29% with placebo, P value = 0.99). On the contrary, there was a significantly higher incidence of adverse effects like preterm labour (10.39% with lycopene vs. 1.22% with placebo, P value = 0.02). The mean birth weight of the babies were not significantly different between the groups, however, there was a significantly higher incidence of low birth weight (<2.5 kg) babies in the lycopene group (22.08% with lycopene vs. 9.76% with placebo, P value = 0.05). The results indicated that an oral intake of lycopene increased the incidence of preterm labour and low birth weight babies. To evaluate the impact of the results presented in this publication, a more detailed reporting is necessary. Preterm labor was only reported as preterm or no, however, the degree of preterm should also be reported. In addition, the data on low birth weight should have been more detailed. Due to the weaknesses in the reporting, VKM cannot use the results from this study in the risk characterisation.

A risk assessment of lycopene was performed by Shao and Hathcock (2006). The inclusion criteria were: study duration; at least 1 week, lycopene dose; not less than 8 mg/day, and study design; only randomized, placebo-controlled intervention trials. Studies that were uncontrolled and unblended and studies investigating acute bioavailability, pharmacokinetics or post-prandial responses from single bolus doses were excluded. Studies that did not quantify the administered dose of lycopene (such as certain feeding studies) were also excluded. In total, 16 human safety studies were included, in which the highest lycopene dose was 150 mg/day (for 7 days) and the longest study duration was 20 weeks (the lycopene dose was 13.3 mg/day). No observed adverse effects were reported in any of these studies.

2.4.2.1 Interactions

There was no information concerning interactions in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of interactions.

2.4.2.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature reviewed in the present risk assessment. The absence of information in the

selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

2.4.3 Animal studies

In a study by Jian et al. (2008), the subacute oral toxicity of lycopene produced by recombinant *Escherichia coli* was tested. Doses of 0, 200, 500 and 2000 mg/kg bw per day were administered daily by gavage to 10 rats/sex/group for 28 days. Sterile water was used as control. No statistically significant, dose-related effects on body weight gain, clinical signs or ophthalmoscopic parameters were observed in any treatment group. Likewise, no treatment-related or dose-related toxic effect was found in hematology, clinical chemistry, urinalysis, blood coagulation, organ weights, gross observation or histopathology. A NOAEL of 2000 mg/kg bw per day was derived for lycopene produced by recombinant *E. coli*.

2.4.3.1 Interactions

There was no information concerning interactions in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of interactions.

2.4.3.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

2.4.4 Vulnerable groups

The results from one study indicated that lycopene increased the incidence of preterm labor and low birthweight babies (see 2.4.2) (Banerjee et al., 2009).

2.5 Summary of hazard identification and characterisation

Lycopene belongs to a large group of naturally-occurring pigments known as carotenoids. Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. The major sources of natural lycopene in the human diet are tomatoes and tomato-based products.

Several previous risk assessments have summarized safety studies of lycopene. An ADI of 0.5 mg/kg bw per day was established by EFSA (2008). The ADI was derived from the NOAEL of 50 mg/kg bw per day from a 52-week toxicity study in rats, based on a partly reversible increased level of the liver enzyme alanine transaminase (ALT), however, a dose level where the effects on the enzymes were considered not toxicologically significant. The

ADI was established for lycopene from all sources (lycopene from tomatoes, synthetic lycopene and lycopene from the fungus *B. trispora*). For an adult of 70 kg body weight, this value corresponds to an intake of 35 mg/day.

In 2009, JECFA concluded that, based on lycopene's low toxicity, there was no need to establish a numerical ADI. Thus, a group ADI "not specified" for lycopene from all sources (tomatoes, synthetic lycopene and lycopene from *B. trispora*) was established (JECFA, 2009).

EFSA concluded that the divergence of the scientific opinions, EFSA (2008) and JECFA (2009), was not based on data that were not available to EFSA during its evaluation of lycopene, but rather to diverging interpretation of the results in the study from which the EFSA ADI was established (Smith et al. 2005; unpublished).

There are case reports of yellow-orange skin discoloration and/or gastrointestinal discomfort after prolonged high intakes of lycopene-rich food and supplements, those effects being reversible upon cessation of lycopene ingestion (JECFA, 2006). In addition, one study indicated that lycopene increased the incidence of preterm labor and low birthweight babies. However, due to weaknesses in the reporting, VKM cannot use the results from this study in the risk characterisation.

The value used for comparison with the estimated exposure in the risk characterisation is the ADI of 0.5 mg/kg bw per day established by EFSA (2008).

3 Exposure / Intake

3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 10 mg/day of lycopene as food supplement for children (10 years and above), adolescents and adults. The default body weights (bw) for these age groups determined by EFSA were used to calculate the intake for these age groups (EFSA, 2012): 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults (≥18 years); 70.0 kg.

From a daily dose of 10 mg lycopene, the daily exposure is 0.23 mg/kg bw per day for children (10 to <14 years), 0.16 mg/kg bw per day for adolescents (14 to <18 years), and 0.14 mg/kg bw per day for adults (≥18 years) (Table 3.1-1).

Table 3.1-1 The estimated exposure of children, adolescents and adults from lycopene in food supplements.

Group	**Daily dose (mg)**	**Body weight (kg)**	**Exposure (mg/kg bw per day)**
Children (10 to <14 years)	10	43.4	0.23
Adolescents (14 to <18 years)	10	61.3	0.16
Adults (≥18 years)	10	70.0	0.14

3.2 Other sources

Lycopene belongs to the carotenoid group that is responsible for the red colour in many fruits and vegetables. The major sources of natural lycopene in the human diet are tomatoes and tomato-based products. Fruits like pink grapefruit, water melon, rosehip, papaya and guava are also sources of lycopene (Nguyen and Schwartz, 1999).

According to dietary surveys, regular intakes of lycopene from natural dietary sources in different populations were estimated to be on average between 0.5 and 5 mg/day, with high intakes up to about 8 mg/day (EFSA, 2008). High consumption of fruits and vegetables, especially tomato products, may result in occasional intakes of 20 mg lycopene/day or more (EFSA, 2008). EFSA noted that total daily exposure to lycopene from *B. trispora* as a food colour potentially could range from 2 to 6 mg on the average and go up to 11 to 23 mg at the high level. Thus, EFSA did not exclude an occasionally combined high exposure from both natural dietary sources and food colours up to 43 mg of lycopene per day (EFSA, 2008).

Lycopene is authorized as a food additive and registered as E160d.

In EU, lycopene can be used in cosmetic products, e.g. as an antioxidant and a cosmetic colourant (CosIng, 2015).

4 Risk characterisation

4.1 Food supplements

NFSA requested VKM to perform a risk assessment of 10 mg/day of lycopene in food supplements for the general population, ages 10 years and above.

The value used for comparison with the estimated exposure in the risk characterisation is the ADI of 0.5 mg/kg bw per day established by EFSA (EFSA, 2008). The ADI was derived from the NOAEL of 50 mg/kg bw per day from a 52-week toxicity study in rats, based on a partly reversible increased level of the liver enzyme ALT. At this dose level, the effects on enzymes were considered not toxicologically significant. An ADI is set to cover the general population, including children. The ADI was set for lycopene from all sources (lycopene from tomatoes, synthetic lycopene and lycopene from the fungus *B. trispora*). For an adult of 70 kg body weight, this value corresponds to an intake of 35 mg/day.

From a daily dose of 10 mg lycopene, the daily exposure is 0.23 mg/kg bw for children (10 to <14 years), 0.16 mg/kg bw for adolescents (14 to <18 years) and 0.14 mg/kg bw for adults (≥18 years) (Table 3.1-1). Thus, the intakes are below the ADI of 0.5 mg/kg bw per day for all age groups. VKM concludes that it is unlikely that daily doses of 3100 mg or 6200 mg D-ribose in food supplements causes adverse effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

5 Uncertainties

5.1 Hazard identification and characterization

The results from one study indicated that lycopene increased the incidence of preterm labor and low birthweight babies (Banerjee et al., 2009). However, due to weaknesses in the reporting, VKM cannot use the results from this study in the risk characterisation.

5.2 Exposure / Intake

With use of the default (mean) body weight of an age (population) group, the variance in all individuals in the group will not be covered.

6 Conclusions with answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of lycopene (10 mg/day) in food supplements. The present risk assessment is based on previous risk assessments and articles retrieved from a literature search.

Lycopene belongs to a large group of naturally-occurring pigments known as carotenoids. Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. The major sources of natural lycopene in the human diet are tomatoes and tomato-based products.

There are case reports of yellow-orange skin discoloration and/or gastrointestinal discomfort after prolonged high intakes of lycopene-rich food and supplements, those effects being reversible upon cessation of lycopene ingestion (JECFA, 2006). In addition, one study indicated that lycopene increased the incidence of preterm labor and low birthweight babies (Banerjee et al., 2009). However, due to weaknesses in the reporting, VKM cannot use the results from this study in the risk characterisation.

An ADI was established by EFSA (2008). An ADI is set to cover the general population, including children. The ADI was derived from the NOAEL of 50 mg/kg bw per day from a 52-week toxicity study in rats, based on a partly reversible increased level of the liver enzyme ALT, however, a level where the effects on the enzymes were considered not toxicologically significant. An ADI is set to cover the general population, including children. The ADI was established for lycopene from all sources (lycopene from tomatoes, synthetic lycopene and lycopene from the fungus *B. trispora*). For an adult of 70 kg body weight, this value corresponds to an intake of 35 mg/day. This ADI was used for comparison with the estimated exposure in the risk characterization.

From a daily dose of 10 mg lycopene, the daily exposure is 0.23 mg/kg bw for children (10 to <14 years), 0.16 mg/kg bw for adolescents (14 to <18 years) and 0.14 mg/kg bw for adults (Table 3.1-1). Thus, the intakes are below the ADI of 0.5 mg/kg bw per day for all age groups.

VKM concludes that it is unlikely that a daily dose of 10 mg lycopene from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions is presented in Table 6.1. Estimated exposures unlikely to cause adverse health effects (below the value for comparison) are shown in green.

Table 6-1 An overview of the conclusions on food supplements. Green: the estimated exposure to lycopene is unlikely to cause adverse health effects.

	Lycopene
Food supplements / **Age groups**	**10 mg/day**
Children (10 to <14 years)	
Adolescents (14 to <18 years)	
Adults (≥18 years)	

7 Data gaps

More studies on lycopene and effects on preterm labor, low birth weight and other related endpoints are needed, as one study reported that an oral intake of lycopene increased the incidence of preterm labour and low birth weight babies.

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Appendix

Search Strategy

Database: Ovid MEDLINE(R) <1946 to June Week 1 2015>, Embase <1974 to 2015 June 16>

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1. lycopene*.ti. (2651)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (8791676)
3. 1 and 2 (871)
4. (conference abstract* or letter* or editorial*).pt. (4464924)
5. 3 not 4 (803)
6. limit 5 to (danish or english or norwegian or swedish) (762)
7. remove duplicates from 6 (414)
8. limit 7 to yr="2008 -Current" (213)