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# An overview of previous risk assessments of “other substances”

**Report from the Secretariat of the Norwegian Scientific Committee for Food Safety**

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2014: 14  
An overview of previous risk assessments of «other substances»

Report from the Secretariat of the Norwegian Scientific Committee for Food Safety

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# Summary

Food supplements are foods intended to supplement the normal diet. In addition to vitamins and minerals, food supplements may also consist of “other substances” with nutritional or physiological effects. “Other substances” may also be added to e.g. sports products and energy drinks. “Other substances” are added to a product to have a positive health effect, but can also have harmful effects. The Norwegian Food Safety Authority (NFSA) has compiled a list of «other substances» used in food supplements and other foods in Norway. The secretariat of the Norwegian Scientific Committee for Food Safety (VKM) has at the request of the Norwegian Food Safety Authority (NFSA) prepared an overview of existing risk/safety assessments of these substances.

**Key words:** VKM, Norwegian Scientific Committee for Food Safety, other substances, food supplements

# Sammendrag på norsk

Kosttilskudd er mat som brukes som supplement til den normale kosten. I tillegg til vitaminer og mineraler kan kosttilskudd også inneholde «andre stoffer» som har en ernæringsmessig eller fysiologisk effekt. «Andre stoffer» kan også bli tilsatt til sportsprodukter, energidrikker og andre næringsmidler for at de skal ha en positiv helseeffekt hos personen som inntar dem. Vi vet imidlertid at «andre stoffer» kan ha helseskadelige effekter. Mattilsynet har utarbeidet en liste over «andre stoffer» som brukes i kosttilskudd og annen mat i Norge. Sekretariatet til Vitenskapskomiteen for mattrygghet har på oppdrag fra Mattilsynet utarbeidet en oversikt over allerede eksisterende risikovurderinger av andre stoffer.

# Abbreviations

ADI - acceptable daily intake

AESAN - Spanish Agency for Food Safety and Nutrition

AFSSA - French Food Safety Agency

ALA - alpha-linolenic acid

ANSES - French Agency for Food, Environmental and Occupational Health & Safety

BfR - Bundesinstitut für Risikobewertung

CLA - conjugated linoleic acid

COT - Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

DHA - docosahexaenoic acid

DPA - docosapentaenoic acid

EFSA - European Food Safety Authority

EMA - European Medicines Agency

EPA - eicosapentaenoic acid

GLA - gamma-linolenic acid

GMP - good manufacturing practice

GRAS - Generally Recognized As Safe

IOM - Institute of Medicine

LOAEL - lowest observed adverse effect level

LOEL - lowest observed effect level

MDI - maximum daily intake

NFSA - Norwegian Food Safety Authority

NOAEL - no observed adverse effect level

NOEL - no observed effect level

OSL - observed safe level

SACN - Scientific Advisory Committee on Nutrition

TDI - tolerable daily intake

TWI - tolerable weekly intake

UL - tolerable upper intake level

VKM - Norwegian Scientific Committee for Food Safety

# Background as provided by the Norwegian Food Safety Authority

Food supplements are foods intended to supplement the normal diet. In addition to vitamins and minerals, food supplements may also consist of “other substances” with nutritional or physiological effects. “Other substances” may also be added to e.g. sports products and energy drinks. “Other substances” are added to a product to have a positive health effect, but can also have harmful effects. Type and extent of the negative health effect is dependent on the substance and the quantity consumed.

The Norwegian Food Safety Authority (NFSA) aims to develop a national regulation of “other substances”. In Denmark, a positive list with usage conditions and specifications for 35 substances on the Danish market has been established. The Norwegian Food Safety Authority has recommended the use of the Danish legislation as a model for a national legislation. The intention is therefore to develop a positive list for substances found in the Norwegian market.

# Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) has compiled a list of «other substances» used in food supplements and other foods in Norway. NFSA has requested the Norwegian Scientific Committee for Food Safety (VKM) for assistance with analysing the safety of the enlisted substances.

The assignment will be divided in several phases.

Risk/safety assessments for some of the substances on the list have already been carried out by competent authorities. In phase 1 of the assignment, VKM has been requested to find/search for existing risk/safety assessments for “other substances” enlisted by NFSA, prepared by a competent risk assessment authority. VKM is also requested to describe data on upper limits (UL), guidance limits (GL) or other safe limits established in these assessments.

# Report

## 1 Introduction

Food supplements may, in addition to vitamins and minerals, also consist of “other substances” with nutritional or physiological effects. “Other substances” may also be added to e.g. sports products and energy drinks. The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to prepare an overview of existing relevant risk/safety assessments of “other substances” listed in Table 1-1, prepared by competent authorities.

**Table 1-1.** “Other substances” used in food supplements and other foods in Norway, as reported to NFSA by the industry.

|   | <b>Substance</b>               | <b>CAS Number</b>                    |
|---|--------------------------------|--------------------------------------|
| <b>Fatty acids</b>                        | Linoleic acid                  | 60-33-3                              |
|   | Alpha-linolenic acid (ALA)     | 463-40-1                             |
|   | Conjugated linoleic acid (CLA) | 2420-56-6; 121250-47-3               |
|   | Gamma-linolenic acid (GLA)     | 506-26-3                             |
|   | Docosahexaenoic acid (DHA)     | 6217-54-5; 25167-62-8                |
|   | Docosapentaenoic acid (DPA)    | 24880-45-3; 25448-00-4               |
|   | Eicosapentaenoic acid (EPA)    | 10417-94-4; 1553-41-9;<br>25378-27-2 |
|   | Oleic acid                     | 112-80-1                             |
|   | Palmitoleic acid               | 373-49-9; 2091-29-4                  |
|   | Phospholipids                  |                                      |
|   | Vaccenic acid                  | 143-25-9; 506-17-2; 693-72-1         |
| <b>Amino acids and related substances</b> | L-Alanine                      | 56-41-7                              |
|   | L-Arginine                     | 74-79-3                              |
|   | L-Aspartic acid                | 56-84-8                              |
|   | Beta-Alanine                   | 107-95-9                             |
|   | L-Citrulline                   | 372-75-8                             |
|   | L-Cysteine (E920)              | 52-90-4                              |
|   | L-Cystine (E920)               | 56-89-3                              |
|   | L-Glutamine                    | 56-85-9                              |
|   | L-Glutamic acid (E620)         | 56-86-0                              |
|   | Glycine (E640)                 | 56-40-6                              |
|   | L-Histidine                    | 71-00-1                              |
|   | L-Isoleucine                   | 7004-09-3; 73-32-5                   |
|   | L-Leucine (E641)               | 61-90-5                              |
|   | L-Lysine                       | 56-87-1                              |
|   | L-Methionine                   | 63-68-3                              |



|                               | <b>Substance</b>                               | <b>CAS Number</b>   |
|-------------------------------|--|---|
|                               | DL-Phenylalanine                               | 150-30-1  |
|                               | L-Phenylalanine                                | 63-91-2   |
|                               | L-Proline                                      | 147-85-3  |
|                               | L-Serine                                       | 56-45-1   |
|                               | L-Threonine                                    | 72-19-5   |
|                               | L-Tryptophan                                   | 73-22-3   |
|                               | L-Tyrosine                                     | 60-18-4   |
|                               | L-Valine                                       | 72-18-4   |
| <b>Substances in the body</b> | L-Arginine-alpha-ketoglutarate                 | 16856-18-1; 556834-44-7                                       |
|                               | L-Carnitine                                    | 541-15-1 406-76-8   |
|                               | L-Carnitine-L-tartrate                         | 36687-82-8  |
|                               | Choline  | 62-49-7   |
|                               | Coenzyme Q10                                   | 303-98-0  |
|                               | Collagen                                       | 9007-34-5   |
|                               | Creatine                                       | 57-00-1   |
|                               | D-Ribose                                       | 50-69-1   |
|                               | Glucuronolactone                               | 32449-92-6  |
|                               | Inositol                                       | 87-89-9   |
|                               | Phosphatidylcholine/ Lecithin (E322)           | 8052-43-5; 8030-76-0;<br>55128-59-1; 8002-43-5;<br>97281-47-5 |
|                               | Phosphatidylinositol                           | 97281-52-2  |
|                               | Taurine  | 107-35-7  |
| <b>Plant substances</b>       | Anthocyanins (blueberry) (E163)                | 11029-12-2  |
|                               | Astaxanthin                                    | 472-61-7  |
|                               | Bioflavonoids                                  | 61788-55-4  |
|                               | Caffeine                                       | 58-08-2   |
|                               | Curcumin (E100)                                | 458-37-7  |
|                               | Chlorogenic acid                               | 327-97-9  |
|                               | 5-Caffeoylquinic acid                          | 906-33-2  |
|                               | Catechins (green tea extract)                  | 7295-85-4   |
|                               | Isoflavones (soy bean)                         | 574-12-9  |
|                               | Lutein (E161b)                                 | 127-40-2  |
|                               | Lycopene (E160d)                               | 502-65-8  |
|                               | Naringin (from <i>Citrus paradisi</i> )        | 10236-47-2  |
|                               | Piperine (from <i>Piper nigrum</i> )           | 94-62-2   |
|                               | Polyphenols (green coffee bean extract)        |   |
|                               | Polyphenols (cranberry and blueberry extracts) |   |
|                               | Polyphenols (green tea extract)                |   |
|                               | Rosavin ( <i>Rhodiola rosea</i> extract)       | 84954-92-7  |
|                               | Zeaxanthin (E161h)                             | 144-68-3  |
| <b>Fiber and prebiotics</b>   | Beta-glucan                                    | 9051-97-2; 9041-22-9  |
|                               | Konjac glucomannan (E425)                      | 37220-17-0  |
|                               | Inulin   | 9005-80-5   |

|                                   | <b>Substance</b>                      | <b>CAS Number</b> |
|-----------------------------------|---------------------------------------|-------------------|
| <b>Enzymes</b>                    | Amylase                               | 9000-92-4         |
|                                   | Cellulase                             | 9012-54-8         |
|                                   | Lactase                               | 9031-11-2         |
|                                   | Lipase                                | 9001-62-1         |
|                                   | Peptidase                             | 9031-96-3         |
| <b>Others</b>                     | Bee pollen                            |                   |
|                                   | Colostrum                             | 146897-68-9       |
|                                   | Propolis                              | 9009-62-5         |
|                                   | Royal jelly                           | 8031-67-2         |
| <b>Probiotics</b>                 | <i>Bacillus coagulans GBI 30 6086</i> |                   |
|                                   | <i>Bifidus breve</i>                  |                   |
|                                   | <i>Bifidus infantis</i>               |                   |
|                                   | <i>Bifidobacterium bifidum</i>        |                   |
|                                   | <i>Bifidobacterium lactis</i>         |                   |
|                                   | <i>Bifidobacter longum</i>            |                   |
|                                   | <i>Enterococcus faecium</i>           |                   |
|                                   | <i>Lactobacillus acidophilus</i>      |                   |
|                                   | <i>Lactobacillus bulgaricus</i>       |                   |
|                                   | <i>Lactobacillus casei</i>            |                   |
|                                   | <i>Lactobacillus coagulans</i>        |                   |
|                                   | <i>Lactobacillus helveticus</i>       |                   |
|                                   | <i>Lactobacillus paracasei</i>        |                   |
|                                   | <i>Lactobacillus plantarum</i>        |                   |
|                                   | <i>Lactobacillus rhamnosus</i>        |                   |
|                                   | <i>Lactobacillus salivarius</i>       |                   |
|                                   | <i>Lactococcus lactis</i>             |                   |
| <i>Streptococcus thermophilus</i> |                                       |                   |

The risk and/or safety assessments included in the present report were prepared by the following risk assessment bodies.

- The Norwegian Scientific Committee for Food Safety.
- The European Food Safety Authority (EFSA).
- National risk assessment bodies in the member states of The European Food Safety Authority. EFSA has initiated national Focal Points in the member states to act as an interface between EFSA and the different national food safety authorities, research institutes, consumers and other EFSA related stakeholders. To get an overview of assessments of "other substances" listed in table 1 prepared by EFSA member states, a request was sent from the Norwegian EFSA's point of contact.
- The Select Committee, US Food and Drug Administration. These assessments are included in the Select Committee on GRAS Substances (SCOGS) Database <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=&sortColumn=&pt=scogsListing>. This database allows access to opinions and conclusions from 115

SCOGS reports published between 1972-1980 on the safety of over 370 Generally Recognized As Safe (GRAS) food substances. The GRAS ingredient reviews were conducted by the Select Committee in response to a 1969 White House directive by President Richard M. Nixon.

- Other competent bodies (e.g. the European Medicines Agency, the Institute of Medicine and the Nordic Council of Ministers).

## 2 Relevant risk and/or safety assessments of fatty acids

Fatty acids used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes linoleic acid, alpha-linolenic acid (ALA), conjugated linoleic acid (CLA), gamma-linolenic acid (GLA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), eicosapentaenoic acid (EPA), oleic acid, palmitoleic acid, phospholipids and vaccenic acid. An overview of risk and/or safety assessments of these substances is given in table 2-1.

**Table 2-1.** Risk and/or safety assessments of fatty acids including linoleic acid, alpha-linolenic acid (ALA), conjugated linoleic acid (CLA), gamma-linolenic acid (GLA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), eicosapentaenoic acid (EPA), oleic acid, palmitoleic acid, phospholipids and vaccenic acid.

| Title   | Prepared by, publication year | Information on safety and established use limits  |
|---|-------------------------------|---|
| <b>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 (2)</b> | AESAN, 2013                   | The use as food supplement was assessed <ul style="list-style-type: none"> <li>- ALA; the proposal of a maximum quantity of 2 g/day of ALA, with an LA/ALA ratio of a maximum of 5 presented by the AESAN, is acceptable</li> </ul>   |
| <b>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)</b> | AESAN, 2012                   | The use as food supplement was assessed <ul style="list-style-type: none"> <li>- Alpha-linolenic acid; a maximum quantity of 1 g/day of alpha-linolenic acid with a linoleic acid/alpha-linolenic acid ratio of a maximum of 5 presented by the AESAN, is acceptable.</li> <li>- EPA and DHA; a maximum amount of 3 g/day of the combination of EPA and DHA is acceptable.</li> </ul> |

| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <b>OPINION of the French Food Safety Agency on the update of French population reference intakes (ANCs) for fatty acids</b>  | AFSSA, 2010                   | Docosahexaenoic acid and eicosapentaenoic acid; no risk identified.  |
| <b>Health risks and benefits of trans fatty acids in food - Recommendations</b>  | AFSSA, 2005                   | Information on safety and established use limits was not available in an abstract/summary. (The version in english starts at page 201) |
| <b>OPINION of the French Agency for Food, Environmental and Occupational Health &amp; Safety on a "safety assessment of the use of an oil enriched with Conjugated Linoleic Acid (CLA)"</b>  | ANSES, 2011                   | Information on safety and established use limits was not available in an abstract/summary.   |
| <b>OPINION of the French Agency for Food, Environmental and Occupational Health &amp; Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs</b> | ANSES, 2011                   | Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).  |
| <b>Höhe der derzeitigen <i>trans</i>-Fettsäureaufnahme in Deutschland ist gesundheitlich unbedenklich</b>  | BfR, 2013                     | Information on safety and established use limits was not available in an abstract/summary.   |
| <b>BfR recommends the setting of maximum levels for the fortification of foods with omega-3 fatty acids</b>  | BfR, 2009                     | Information on safety and established use limits was not available in an abstract/summary.   |
| <b>Müssen Fischverzehrer ihre Ernährung durch Fischöl-Kapseln ergänzen?</b>  | BfR, 2006                     | Information on safety and established use limits was not available in an abstract/summary.   |

| Title   | Prepared by, publication year | Information on safety and established use limits   |
|---|-------------------------------|--|
| <b>Scientific Opinion on the extension of use for DHA and EPA-rich algal oil from Schizochytrium sp. as a Novel Food ingredient</b>   | EFSA, 2014                    | EPA, DHA and DPA; in a previous opinion on the Tolerable Upper Intake Level of EPA, DHA and docosapentaenoic acid (DPA), the Panel concluded that supplemental intake of EPA and DHA combined at doses up to 5 g/day, does not give rise to safety concerns for adults. Based on estimations of high intake of DHA and EPA from the NFI which are considered to be conservative, the Panel considers that this level will not be exceeded by the use of the NFI. The conclusion that there are no safety concerns for the NFI is supported by a 90-day study in which no adverse effect was observed at the highest dose tested of 5 %, equivalent to 3.149 and 3.343 g NFI/kg body weight per day for male and female rats. |
| <b>Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA)</b>                                      | EFSA, 2012                    | EPA, DHA and DPA; no tolerable upper intake level (UL) for EPA, DHA or DPA has been set by any authoritative body. The Panel concludes that the available data are not sufficient to establish a tolerable upper intake level for n-3 LCPUFA (DHA, EPA, and DPA, individually or combined) for any population group.   |
| <b>SCIENTIFIC OPINION. Statement on the safety of the “conjugated linoleic acid (CLA)-rich oils” Clarinol® and Tonalin® TG 80 as Novel Food ingredients</b>                                   | EFSA, 2012                    | CLA; the Panel concludes that the safety of Clarinol® and Tonalin® TG 80 has been established for the proposed uses and daily doses (3.75 g Clarinol® and 4.5 g Tonalin® TG 80 corresponding to approximately 3 and 3.5g of CLA, respectively) for up to six months. The safety of CLA consumption for periods longer than six months has not been established under the proposed conditions of use. The safety of CLA consumption by type-2 diabetic subjects has not been established.   |
| <b>Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol</b> | EFSA, 2010                    | <ul style="list-style-type: none"> <li>- Total fat; there are not sufficient data to define a Lower Threshold Intake (LTI) or Tolerable Upper Intake Level (UL) for total fat.</li> <li>- n-6 polyunsaturated fatty acids; the Panel proposes not to set a Tolerable Upper Intake Level (UL) for total or any of the n-6 polyunsaturated fatty acids.</li> <li>- Alpha-linolenic acid; the Panel proposes not to set a Tolerable Upper Intake Level for alpha-linolenic acid.</li> </ul>   |

| Title  | Prepared by, publication year                                       | Information on safety and established use limits   |
|--|---|--|
| <b>Scientific Opinion on the safety of "conjugated linoleic acid (CLA)-rich oil" (Clarinol®) as a Novel Food ingredient</b>  | EFSA, 2010  | CLA; the Panel concludes that the safety of Clarinol®, an oil with approximately 80 % CLA 1:1 mixture of t9,c11 and t10,c12 isomers, has been established for the proposed uses at intakes of 3.75 g Clarinol® per day (corresponding to 3 g CLA), for up to six months. The safety of CLA consumption for periods longer than six months has not been established under the proposed conditions of use. The safety of CLA consumption by type-2 diabetic subjects has not been established. |
| <b>Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the presence of trans fatty acids in foods and the effect on human health of the consumption of trans fatty acids</b> | EFSA, 2004  | Information on safety and established use limits was not available in an abstract/summary.   |
| <b>Baltic herring as nutrition; risk-benefit analysis</b>  | Finnish food safety authority Evira, ongoing project                | DHA and EPA; includes docosahexaenoic acid and eicosapentaenoic acid.  |
| <b>Linoleic acid</b>   | FDA; The Select Committee on GRAS Substances (SCOGS) Database, 1975 | Linoleic acid; there is no evidence in the available information on linoleic acid that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used as a nutrient or dietary supplement at levels now current or that might reasonably be expected in the future.   |

| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids</b>            | IOM, 2005                     | <ul style="list-style-type: none"> <li>- Total fat; a Tolerable Upper Intake Level (UL) is not set for total fat because there is no defined intake level of fat at which an adverse effect occurs.</li> <li>- n-6 polyunsaturated fatty acids; there is insufficient evidence to set a UL for n-6 polyunsaturated fatty acids.</li> <li>- n-3 fatty acids; there is insufficient evidence to set a UL for n-3 fatty acids.</li> </ul>  |
| <b>Update on trans fatty acids and health</b>  | SACN, 2007                    | Information on safety and established use limits was not available in an abstract/summary.  |
| <b>Evaluation of negative and positive health effects of n-3 fatty acids as constituents of food supplements and fortified foods</b> | VKM, 2011                     | EPA and/or DHA; it is not possible to identify clear adverse effects from EPA and/or DHA, which can be used for setting tolerable upper intake levels. In the studies investigating ALA, no negative health effects have been observed. Intake of ALA from linseed oil and margarine up to 8 g/day in addition to the contribution from a Western diet has not shown any negative health effects and it is therefore no rationale to set an upper tolerable intake level for ALA. |

## **2.1 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 (2)**

AESAN (the Spanish Agency for Food Safety and Nutrition), 2013

Reference number: AESAN-2013-004

Report approved by the Scientific Committee on plenary session November 20th, 2013

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS\\_2.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS_2.pdf)



## **2.2 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 (the Spanish Agency for Food Safety and Nutrition), 2012

Reference number: AESAN-2012-008

Report approved by the Scientific Committee on plenary session November 28th, 2012

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS.pdf)

## **2.3 OPINION of the French Food Safety Agency on the update of French population reference intakes (ANCs) for fatty acids**

AFSSA (French Food Safety Agency), 2010

<https://www.anses.fr/sites/default/files/documents/NUT2006sa0359EN.pdf>

## **2.4 Health risks and benefits of trans fatty acids in food – Recommendations**

AFSSA (French Food Safety Agency), 2005

<https://www.anses.fr/sites/default/files/documents/NUT-Ra-AGtransEN.pdf>

## **2.5 OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on a “safety assessment of the use of an oil enriched with Conjugated Linoleic Acid (CLA)”**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2011

<https://www.anses.fr/sites/default/files/documents/NUT2011sa0185EN.pdf>

## **2.6 OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2011

<https://www.anses.fr/sites/default/files/documents/NUT2007sa0314EN.pdf>

## **2.7 Höhe der derzeitigen *trans*-Fettsäureaufnahme in Deutschland ist gesundheitlich unbedenklich**

BfR (Bundesinstitut für Risikobewertung), 2013

Stellungnahme 028/2013 des BfR vom 6. Juni 2013

<http://www.bfr.bund.de/cm/343/hoehe-der-derzeitigen-trans-fettsaeureaufnahme-in-deutschland-ist-gesundheitlich-unbedenklich.pdf>

## **2.8 BfR recommends the setting of maximum levels for the fortification of foods with omega-3 fatty acids**

BfR (Bundesinstitut für Risikobewertung), 2009

[http://www.bfr.bund.de/cm/349/bfr\\_recommends\\_the\\_setting\\_of\\_maximum\\_levels\\_for\\_the\\_fortification\\_of\\_foods\\_with\\_omega\\_3\\_fatty\\_acids.pdf](http://www.bfr.bund.de/cm/349/bfr_recommends_the_setting_of_maximum_levels_for_the_fortification_of_foods_with_omega_3_fatty_acids.pdf)

## **2.9 Müssen Fischverzehrer ihre Ernährung durch Fischöl-Kapseln ergänzen?**

BfR (Bundesinstitut für Risikobewertung), 2006

Information Nr. 034/2006 des BfR vom 19. Juli 2006

[http://www.bfr.bund.de/cm/343/muessen\\_fischverzehrer\\_ihre\\_ernaehrung\\_durch\\_fischoel\\_kapseln\\_ergaenzen.pdf](http://www.bfr.bund.de/cm/343/muessen_fischverzehrer_ihre_ernaehrung_durch_fischoel_kapseln_ergaenzen.pdf)

## **2.10 Scientific Opinion on the extension of use for DHA and EPA-rich algal oil from Schizochytrium sp. as a Novel Food ingredient**

EFSA (European Food Safety Authority), 2014  
EFSA Journal 2014; 12(10):3843  
EFSA Panel on Dietetic Products, Nutrition and Allergies  
<http://www.efsa.europa.eu/fr/efsajournal/doc/3843.pdf>

## **2.11 Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA)**

EFSA, (European Food Safety Authority), 2012  
EFSA Journal 2012; 10(7):2815  
EFSA Panel on Dietetic Products, Nutrition and Allergies  
<http://www.efsa.europa.eu/en/efsajournal/doc/2815.pdf>

## **2.12 SCIENTIFIC OPINION. Statement on the safety of the “conjugated linoleic acid (CLA)-rich oils” Clarinol® and Tonalin® TG 80 as Novel Food ingredients**

EFSA, (European Food Safety Authority), 2012  
EFSA Journal 2012; 10(5):2700  
EFSA Panel on Dietetic Products, Nutrition and Allergies  
<http://www.efsa.europa.eu/en/efsajournal/doc/2700.pdf>

## **2.13 Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol**

EFSA (European Food Safety Authority), 2010

EFSA Journal 2010; 8(3):1461  
EFSA Panel on Dietetic Products, Nutrition and Allergies  
<http://www.efsa.europa.eu/de/efsajournal/doc/1461.pdf>

## **2.14 Scientific Opinion on the safety of "conjugated linoleic acid (CLA)-rich oil" (Clarinol®) as a Novel Food ingredient**

EFSA (European Food Safety Authority), 2010  
EFSA Journal 2010; 8(5):1601  
EFSA Panel on Dietetic Products, Nutrition and Allergies  
<http://www.efsa.europa.eu/en/efsajournal/doc/1601.pdf>

## **2.15 Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the presence of trans fatty acids in foods and the effect on human health of the consumption of trans fatty acids**

EFSA (European Food Safety Authority), 2004  
The EFSA Journal 2004; 81, 1-49  
EFSA Panel on Dietetic Products, Nutrition and Allergies  
<http://www.efsa.europa.eu/en/efsajournal/doc/81.pdf>

## **2.16 Baltic herring as nutrition; risk-benefit analysis**

Evira (Finnish Food Safety Authority, National Institute for Health and Welfare, and Game and Fisheries Research), ongoing project

## **2.17 The Select Committee on GRAS Substances (SCOGS) Database**

FDA (U.S. Food and Drug Administration), 1975

Report No.: 65

ID Code: 60-33-3

<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogslisting&id=190>

## **2.18 Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids**

IOM (Institute of Medicine), 2005

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes.

Food and Nutrition Board

[http://www.nal.usda.gov/fnic/DRI/DRI\\_Energy/energy\\_full\\_report.pdf](http://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf)

## **2.19 Update on trans fatty acids and health**

SACN (The Scientific Advisory Committee on Nutrition), 2007

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/339359/SACN Update on Trans Fatty Acids 2007.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/339359/SACN_Update_on_Trans_Fatty_Acids_2007.pdf)

## **2.20 Evaluation of negative and positive health effects of n-3 fatty acids as constituents of food supplements and fortified foods**

VKM (The Norwegian Scientific Committee for Food Safety), 2011

The Scientific Steering Committee

Doc. no.: 08-707-final

ISBN: 978-82-8082-365-6

<http://www.vkm.no/dav/c7a41adb79.pdf>



### 3 Relevant risk and/or safety assessments of amino acids and related substances

Amino acids and related substances used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes L-arginine, L-aspartic acid, beta-alanine, L-citrulline, L-cysteine, L-cystine, L-glutamine, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, DL Phenylalanine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine. An overview of risk and/or safety assessments of these substances is given in table 3-1.

**Table 3-1.** Risk and/or safety assessments of amino acids and related substances including L-arginine, L-aspartic acid, beta-alanine, L-citrulline, L-cysteine, L-cystine, L-glutamine, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, DL Phenylalanine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine .

| Title   | Prepared by, publication year | Information on safety and established use limits  |
|---|-------------------------------|---|
| <b>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 (2)</b> | AESAN, 2013                   | The use as a food supplement was assessed <ul style="list-style-type: none"> <li>- L-histidine; a maximum daily quantity of 1.12 g of L-histidine is acceptable.</li> <li>- L-glutamine; a maximum daily quantity of 5 g of L-glutamine is acceptable.</li> </ul> |

|  |                    |   |
|--|--------------------|---|
| <p><b>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)</b></p> | <p>AESAN, 2012</p> | <p>The use as a food supplement was assessed</p> <ul style="list-style-type: none"> <li>- L-isoleucine + L-leucine + L-valine; a maximum daily amount of 5 g of the sum of L-isoleucine, L-leucine and L-valine is acceptable.</li> <li>- L-glutamic acid; a maximum amount of 1 g/day is acceptable.</li> <li>- Beta-alanine; high doses of beta-alanine may produce paresthesia.</li> <li>- L-arginine; an OSL of 20 g/day for supplementation with L-arginine has been established.</li> <li>- L-cysteine; a maximum daily amount of 300 mg of L-cysteine is lower than the requirements of L-methionine + L-cysteine established by the WHO;</li> <li>- L-glutamine; no adverse effects have been observed in either the safety studies conducted with L-glutamine or in its use at high doses in clinical nutrition.</li> <li>- L-histidine; a maximum daily amount of 750 mg of L-histidine is of the order of the requirement established by the WHO.</li> <li>- L-isoleucine; there is a high tolerance level to L-isoleucine.</li> <li>- L-leucine; it has not been possible to establish a NOAEL or LOAEL for the oral intake of L-leucine.</li> <li>- L-lysine; a maximum daily amount of 2,250 mg of L-lysine is acceptable.</li> <li>- L-methionine + L-cysteine; a maximum daily amount of 300 mg of L-cysteine is lower than the requirements of L-methionine + L-cysteine established by the WHO.</li> <li>- L-tyrosine + L-phenylalanine; a maximum daily amount of 1,900 mg for the sum of L-tyrosine and L-phenylalanine is acceptable.</li> <li>- L-threonine; a maximum daily amount of 1,150 mg is in line with the L-threonine requirement established by the WHO.</li> <li>- L-tryptophan (obtained by protein hydrolysis); a maximum daily amount of 300 mg of L-tryptophan is acceptable.</li> <li>- L-valine; a maximum amount of 1,950 mg/day of L-valine is acceptable.</li> </ul> |
|--|--------------------|---|



| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>AVIS de l'Agence française de sécurité sanitaire des aliments du 16 juin 2009 relatif à l'emploi de tryptophane à hauteur de 1000 mg dans les compléments alimentaires AFSSA (French Food Safety Agency)</b>  | AFSSA, 2009                   | Tryptophan; AFSSA recommends to reject the proposed threshold of 1000 mg/day and to maintain the limit of 220 mg/day for tryptophan in food supplements. This limit is proposed by the COT in 2004 and reaffirmed in 2005   |
| <b>Apport en protéines : consommation, qualité, besoins et recommandations</b><br><b>Protein intake: dietary intake, quality, requirements and recommendations</b>   | AFSSA, 2007                   | In this report, a tolerable upper intake level, defined as being the limit beyond which there is a risk related to excessive nutrient intake, is not proposed for either nitrogen or amino acids, due to a lack of experimental and epidemiological data. However, two upper protein intake levels, beyond which intakes are considered to be high or very high, are proposed.                  |
| <b>OPINION of the French Agency for Food, Environmental and Occupational Health &amp; Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs</b> | ANSES, 2011                   | Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).   |
| <b>COT Statement on Tryptophan and the Eosinophilia-Myalgia Syndrome</b>   | COT, 2004                     | Tryptophan; applying an uncertainty factor of 10 to the mean therapeutic dose of 2228 mg tryptophan per day, to allow for uncertainty with respect to the actual cause of EMS, indicates that a dose of 220 mg tryptophan per day as a dietary supplement would not present an appreciable risk to health, providing that it meets the purity criteria specified in the European Pharmacopoeia. |
| <b>Scientific Opinion on Dietary Reference Values for protein</b>  | EFSA, 2012                    | Protein; the available data are not sufficient to establish a Tolerable Upper Intake Level (UL) for protein.  |

| Title   | Prepared by, publication year | Information on safety and established use limits  |
|---|-------------------------------|---|
| <p><b>Amino acids from chemical group 34. Flavouring Group Evaluation 26, Revision 1. Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food</b></p>                                    | <p>EFSA, 2008</p>             | <p>Glycine, L-lysine, L-arginine, L-cysteine, cysteine; LD<sub>50</sub> values derived from acute toxicity studies (Annex IV).</p> <p>Glycine, D,L-alanine, beta-alanine, D,L-valine, L-leucine, D,L-isoleucine, L-phenylalanine, L-glutamine, L-lysine monochlorhydrate, L-arginine, L-proline, L-cysteine, D,L-methionine, taurine, cystine; NOAEL values derived from subacute/subchronic/chronic/carcinogenicity studies (Annex IV).</p> <p>L-lysine monohydrate, L-cysteine; NOAEL values derived from developmental and reproductive toxicity studies.</p> <p>Glycine, D,L-alanine, D,L-valine, L-leucine, D,L-isoleucine, L-phenylalanine, L-tyrosine, threonine, L-aspartic acid, L-glutamine, L-lysine, L-lysine monochlorhydrate, L-arginine, L-proline, L-histidine, L-cysteine, D,L-methionine, taurine, cysteine; <i>in vitro</i> genotoxicity studies (Annex IV).</p> |
| <p><b>Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to the use of L-cysteine in foods intended for infants and young children</b></p> | <p>EFSA, 2006</p>             | <p>Information on safety and established use limits was not available in an abstract/summary.</p>   |

| Title  | Prepared by, publication year                                       | Information on safety and established use limits   |
|--|---|--|
| <b>Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to N-Acetyl-L-cysteine for use in foods for particular nutritional uses and in foods for special medical purposes</b> | EFSA, 2003  | Information on safety and established use limits was not available in an abstract/summary.   |
| <b>L-glutamic acid</b>   | FDA; The Select Committee on GRAS Substances (SCOGS) Database, 1980 | L-glutamic acid; (report No.: 37a) there is no evidence in the available information on L-glutamic acid, L-glutamic acid hydrochloride, monosodium L-glutamate, monoammonium L-glutamate, and monopotassium L-glutamate that demonstrates, or suggests reasonable grounds to suspects, a hazard to the public when they are used at levels that are now current and in the manner now practices. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard. |
| <b>Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids</b>  | IOM, 2005   | Total protein and amino acids; there were insufficient data to provide dose–response relationships to establish a Tolerable Upper Intake Level (UL) for total protein or for any of the amino acids. However, the absence of a UL means that caution is warranted in using any single amino acid at levels significantly above that normally found in food.  |
| <b>Risk assessment of histidine, methionine, S-adenosylmethionine and tryptophan</b>   | VKM, 2013   | Histidine, methionine, S-adenosylmethionine and tryptophan; because no dose-response studies or adverse health effects related to dose were found, UL for these four amino acids could not be established. However, in this assessment a tentative guidance level (GL) at 210 mg/day is suggested for methionine, and 220 mg/day is suggested as a tentative daily GL for tryptophan.  |
| <b>Risikogruppering av aminosyrer</b>  | VKM, 2011   | Individual amino acids; no tolerable upper intake levels are established for the individual amino acids.   |

### **3.1 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 (2)**

AESAN (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition, 2013

Reference number: AESAN-2013-004

Report approved by the Scientific Committee on plenary session November 20th, 2013

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS\\_2.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS_2.pdf)

### **3.2 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, (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2012

Reference number: AESAN-2012-008

Report approved by the Scientific Committee on plenary session November 28th, 2012

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS.pdf)

### **3.3 AVIS de l'Agence française de sécurité sanitaire des aliments du 16 juin 2009 relatif à l'emploi de tryptophane à hauteur de 1000 mg dans les compléments alimentaires AFSSA (French Food Safety Agency)**

AFSSA (French Food Safety Agency), 2009

<http://www.anses.fr/sites/default/files/documents/NUT2009sa0057.pdf>

### **3.4 Apport en protéines : consommation, qualité, besoins et recommandations / Protein intake: dietary intake, quality, requirements and recommendations**

AFSSA (French Food Safety Agency), 2007

<https://www.anses.fr/sites/default/files/documents/NUT-Sy-ProteinesEN.pdf>

### **3.5 OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2011

<https://www.anses.fr/sites/default/files/documents/NUT2007sa0314EN.pdf>

### **3.6 COT Statement on Tryptophan and the Eosinophilia-Myalgia Syndrome**

COT (Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment), 2004

<http://cot.food.gov.uk/pdfs/tryptophanamend200401.pdf>

### **3.7 Scientific Opinion on Dietary Reference Values for protein**

EFSA (European Food Safety Authority), 2012

EFSA Journal 2012; 10(2):2557

EFSA Panel on Dietetic Products, Nutrition and Allergies

<http://www.efsa.europa.eu/en/efsajournal/doc/2557.pdf>

### **3.8 Amino acids from chemical group 34. Flavouring Group Evaluation 26, Revision 1. Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food**

EFSA (European Food Safety Authority) 2008

The EFSA Journal (2008) 790, 1-51

Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food

<http://www.efsa.europa.eu/en/efsajournal/doc/790.pdf>

### **3.9 Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to the use of L-cysteine in foods intended for infants and young children**

EFSA (European Food Safety Authority), 2006

The EFSA Journal 2006; 390, 1-7

Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

<http://www.efsa.europa.eu/en/efsajournal/doc/390.pdf>

### **3.10 Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to N-Acetyl-L-cysteine for use in foods for particular nutritional uses and in foods for special medical purposes**

EFSA, (European Food Safety Authority), 2003

The EFSA Journal 2003; 21, 1-8

Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

<http://www.efsa.europa.eu/en/efsajournal/doc/22.pdf>

### **3.11 The Select Committee on GRAS Substances (SCOGS) Database**

FDA (U.S. Food and Drug Administration), 1980

Report No.: 37a

ID Code: 56-86-0

<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogslisting&id=187>

### **3.12 Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids**

IOM (Institute of Medicine), 2005

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes.

Food and Nutrition Board

[http://www.nal.usda.gov/fnic/DRI/DRI\\_Energy/energy\\_full\\_report.pdf](http://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf)

### **3.13 Risk assessment of histidine, methionine, S-adenosylmethionine and tryptophan**

VKM (The Norwegian Scientific Committee for Food Safety), 2013

Panel on nutrition, dietetic products, novel food and allergy

Doc. no.: 12-704-final

ISBN: 978-82-8259-079-2

<http://www.vkm.no/dav/ba7a85274a.pdf>

### **3.14 Risikogruppering av aminosyrer**

VKM (The Norwegian Scientific Committee for Food Safety), 2011

Panel on nutrition, dietetic products, novel food and allergy

Dok. nr.: 09-703-endelig

ISBN: 978-82-8259-031-0

<http://www.vkm.no/dav/fcf209d537.pdf>



## 4 Relevant risk and/or safety assessments of substances in the body

Substances in the body used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes L-arginine-alpha-ketoglutarate, L-carnitine, L-carnitine-L-tartrate, choline, coenzyme Q10, collagen, creatine, D-ribose, glucuronolactone, inositol, phosphatidylcholine, lecithin, phosphatidylinositol, and taurine. An overview of risk and/or safety assessments of these substances is given in table 4-1.

**Table 4-1.** Risk and/or safety assessments of substances in the body including L-arginine-alpha-ketoglutarate, L-carnitine, L-carnitine-L-tartrate, choline, coenzyme Q10, collagen, creatine, D-ribose, glucuronolactone, inositol, phosphatidylcholine (lecithin), phosphatidylinositol, and taurine.

| Title   | Prepared by, publication year | Information on safety and established use limits  |
|---|-------------------------------|---|
| <b>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 (2)</b> | AESAN, 2013                   | The use as a food supplement was assessed.<br>Myo-inositol; a maximum quantity of 2 g/day of myo-inositol is acceptable from the safety point of view for use as a food supplement. |

| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <b>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)</b>                              | AESAN, 2012                   | <p>The use as a food supplement was assessed</p> <ul style="list-style-type: none"> <li>- L-carnitine; a maximum daily amount of 2 g of L-carnitine, using L-carnitine or L-carnitine hydrochloride as sources and of 3 g if L-carnitine tartrate is used is acceptable</li> <li>- Taurine; a maximum daily amount of 1,000 mg of taurine is acceptable.</li> <li>- Coenzyme Q10; considering that an OSL of 1,200 mg/day has been established, the Scientific Committee concludes that, based on the information available to date and taking into account the general considerations reflected in this report, the AESAN proposal of a maximum amount of 200 mg/day of the coenzyme Q10 is acceptable.</li> <li>- Choline; a maximum amount of 1,500 mg/day of choline is acceptable.</li> <li>- Creatine monohydrate; a maximum amount of 3,000 mg/day of creatine monohydrate is acceptable.</li> <li>- Inositol (hexaphosphate); a maximum amount of 2,000 mg/day of inositol (hexaphosphate) is acceptable.</li> </ul> |
| <b>OPINION of the French Food Safety Agency on the assessment of risk from consumption of an "energy" drink containing substances other than technological additives: taurine, D-glucuronolactone, inositol, vitamins B2, B3, B5, B6 and B12</b> | AFSSA, 2006                   | Information on safety and established use limits was not available in an abstract/summary.   |

| Title   | Prepared by, publication year | Information on safety and established use limits   |
|---|-------------------------------|--|
| <b>AVIS de l'Agence française de sécurité sanitaire des aliments relatif à l'évaluation de à l'emploi de taurine, D-glucuronolactone, de diverses vitamines et de caféine (à une dose supérieure à celle actuellement admise dans les boissons) dans une boisson dite « énergétique »</b>                         | AFSSA, 2003                   | Includes taurine and D-glucuronolactone  |
| <b>Avis de l'Agence française de sécurité sanitaire des aliments du 23 janvier 2001 relatif à l'évaluation des risques présentés par la créatine pour le consommateur et de la véracité des allégations relatives à la performance sportive ou à l'augmentation de la masse musculaire (mandate 2000-SA-0086)</b> | AFSSA, 2001                   | Information on safety and established use limits was not available in an abstract/summary. |
| <b>Opinion of the French Agency for Food, Environmental and Occupational Health and Safety on the assessment of risk concerning the consumption of so-called "energy drinks"</b>  |                               |  |
| <b>Opinion of the French Agency for Food, Environmental and Occupational Health &amp; Safety on the assessment of risks concerning the consumption of so-called "energy drinks"</b>   | ANSES, 2013                   | Information on safety and established use limits was not available in an abstract/summary. |

| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>Scientific Opinion on the safety and efficacy of L-carnitine and L-carnitine-L-tartrate as feed additives for all animal species based on a dossier submitted by Lonza Benelux BV</b>                           | EFSA; 2012                    | The FEEDAP Panel considers that the use of L-carnitine and L-carnitine L-tartrate as additives in animal nutrition is safe for the consumer.  |
| <b>The use of taurine and D-glucurono-γ-lactone as constituents of the so-called “energy” drinks</b>   | EFSA, 2009                    | <ul style="list-style-type: none"> <li>- Taurine; it can be concluded that the NOAEL derived from a new 13-week oral neurotoxicity study in male and female rats including functional observational battery and locomotor activity tests, confirmed the NOAEL established in the prior 13-week study, described already by the SCF in 2003, of 1000 mg taurine/kg bw/day, and provided evidence for a NOAEL of 1500 mg taurine/kg bw/day for behavioural effects.</li> <li>- D-glucurono-γ-lactone; based on the results of this study, the NOAEL for daily oral administration of D-glucurono-γ-lactone in rats was 1000 mg/kg bw/day, the highest dose tested.</li> </ul> |
| <b>Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to L-Carnitine-L-tartrate for use in foods for particular nutritional uses</b> | EFSA, 2003                    | Tartaric acid; the ADI for tartaric acid and its salts is 0 - 30 mg/kg bw.  |

| Title   | Prepared by, publication year  | Information on safety and established use limits   |
|---|--|--|
| <b>Inositol</b><br><br><b>Choline chloride and choline bitartrate</b><br><br><b>Lecithin</b>    | FDA; The Select Committee on GRAS Substances (SCOGS) Database, 1975 and 1979 | <ul style="list-style-type: none"> <li>- Inositol; (report No. 51, ID Code: 87-89-8) there is no evidence in the available information on inositol that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.</li> <li>- Choline chloride and choline bitartrate (Report No. 42, ID Code: 87-67-242) there is no evidence in the available information on choline chloride and choline bitartrate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.</li> <li>- Choline chloride and choline bitartrate; (Report No.: 42, ID Code: 67-48-1) there is no evidence in the available information on choline chloride and choline bitartrate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.</li> <li>- Lecithin; (report no.: 106, ID Code: 8002-43-5) the Select Committee concludes that there is no evidence in the available information on lecithin and lecithin bleached with hydrogen peroxide that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.</li> </ul> |
| <b>Dietary Reference Intakes: Vitamins</b>  | IOM, 1998  | Choline; UL for adults (19 and older) is 3.5 g/day.<br>UL for other life stage groups at<br><a href="http://www.iom.edu/~media/Files/Activity%20Files/Nutrition/DRI/DRI_Vitamins.pdf">http://www.iom.edu/~media/Files/Activity%20Files/Nutrition/DRI/DRI_Vitamins.pdf</a>  |
| <b>Opinion of the Scientific Committee on Food on Additional information on "energy" drinks</b> | SCF, 2003  | Glucuronolactone; Further studies would be required to establish upper safe levels for daily intake<br>Taurine; Further studies would be required to establish upper safe levels for daily intake of taurine and glucuronolactone  |

| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>Opinion on Caffeine, Taurine and D-Glucurono - g -Lactone as constituents of so-called "energy" drinks (expressed on 21 January 1999)</b>   | SCF, 1999                     | For taurine and glucuronolactone, the Committee is unable to conclude that the safety-in-use of taurine and glucuronolactone in the concentration ranges reported for these constituents in "energy" drinks has been adequately established. Further studies would be required to establish upper safe levels for daily intake of taurine and glucuronolactone  |
| <b>Assessment of creatine in sports products</b>   | VKM, 2010                     | Creatine; VKM Panel on nutrition, dietetic products, novel food and allergy supports the EFSA conclusion that supplementation of creatine in doses below 3 g/day is unlikely to pose any risks if the purity of the creatine compound is adequate. Scientific long-term studies with doses up to 5-10 g/day in adult athletes have shown no harmful effects, but there are no dose-response studies indicating a safe upper limit for creatine.         |
| <b>New information on ingredients in so-called "energy drinks"</b>   | VKM, 2009                     | Taurine and D-glucurono-γ-lactone; based on new studies presenting NOAELs for taurine and D-glucurono-γ-lactone, both of 1000 mg/kg bw/day, the EFSA ANS Panel concludes that exposure to taurine and D-glucurono-γ-lactone as individual ingredients at the levels presently used in "energy drinks", and at the intake levels presented are of no safety concern. The VKM Panel 4 endorses this conclusion and considers it as valid also for Norway. |
| <b>Risikovurdering av "energidrikker" med koffein, taurin, glukuronolakton, inositol og vitaminer</b>  | VKM, 2005                     | Inositol; det finnes, ut fra dagens kunnskap, ikke grunnlag for å si noe om hvor mye inositol som kan inntas uten at det kan gi uheldige virkninger.  |
| <b>Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO FOOD ADDITIVES SERIES NO. 5</b> | WHO, 1974                     | Estimate of acceptable daily intake for man: Not limited.*  |

#### **4.1 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 (2)**

AESAN (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2013

Reference number: AESAN-2013-004

Report approved by the Scientific Committee on plenary session November 20th, 2013

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS\\_2.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS_2.pdf)

#### **4.2 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 (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2012

Reference number: AESAN-2012-008

Report approved by the Scientific Committee on plenary session November 28th, 2012

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS.pdf)

#### **4.3 OPINION of the French Food Safety Agency on the assessment of risk from consumption of an “energy” drink containing substances other than technological additives: taurine, D-glucuronolactone, inositol, vitamins B2, B3, B5, B6 and B12**

AFSSA (French Food Safety Agency), 2006

<http://www.anses.fr/sites/default/files/documents/NUT2006sa0236EN.pdf>

#### **4.4 AVIS de l'Agence française de sécurité sanitaire des aliments relatif à l'évaluation de à l'emploi de taurine, D-glucuronolactone, de diverses vitamines et de caféine (à une dose supérieure à celle actuellement admise dans les boissons) dans une boisson dite « énergétique »**

AFSSA (French Food Safety Agency, 2003)

<https://www.anses.fr/sites/default/files/documents/NUT2002sa0260.pdf>

#### **4.5 Avis de l'Agence française de sécurité sanitaire des aliments du 23 janvier 2001 relatif à l'évaluation des risques présentés par la créatine pour le consommateur et de la véracité des allégations relatives à la performance sportive ou à l'augmentation de la masse musculaire (mandate 2000-SA-0086)**

AFSSA (French Food Safety Agency, 2001)

<http://www.anses.fr/sites/default/files/documents/NUT2000sa0086.pdf>

#### **4.6 Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of risks concerning the consumption of so-called "energy drinks"**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety) 2012

Request no. 2012-SA-0212

<https://www.anses.fr/sites/default/files/documents/NUT2012sa0212EN.pdf>

#### **4.7 Scientific Opinion on the safety and efficacy of L-carnitine and L-carnitine L-tartrate as feed additives for all animal species based on a dossier submitted by Lonza Benelux BV1**

EFSA (European Food Safety Authority), 2012

The EFSA Journal 2012; 10(5), 2676

<http://www.efsa.europa.eu/en/efsajournal/doc/2676.pdf>



#### **4.8 The use of taurine and D-glucurono- $\gamma$ -lactone as constituents of the so-called “energy” drinks**

EFSA (European Food Safety Authority), 2009

The EFSA Journal 2009; 935, 1-31

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

<http://www.efsa.europa.eu/en/efsajournal/doc/935.pdf>

#### **4.9 Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to L-Carnitine-L-tartrate for use in foods for particular nutritional uses**

EFSA (European Food Safety Authority), 2003

The EFSA Journal 2003; 19, 1-13

EFSA Panel on Food additives, flavourings, processing aids and materials in contact with food

<http://www.efsa.europa.eu/en/efsajournal/doc/19.pdf>

#### **4.10 The Select Committee on GRAS Substances (SCOGS) Database**

FDA (U.S. Food and Drug Administration), 1975

Report No.: 51

ID Code: 87-89-8

<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogslisting&id=162>

FDA (U.S. Food and Drug Administration), 1979

Report No.: 106

ID Code: 8002-43-5

<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogslisting&id=185>

#### **4.11 Dietary Reference Intakes: Vitamins**

Institute of medicine (IOM), 1998

[http://www.iom.edu/~media/Files/Activity%20Files/Nutrition/DRI/DRI\\_Vitamins.pdf](http://www.iom.edu/~media/Files/Activity%20Files/Nutrition/DRI/DRI_Vitamins.pdf)

#### **4.12 Opinion of the Scientific Committee on Food on Additional information on "energy" drinks**

SCF (Scientific committee on Food), 2003

SCF/CS/PLEN/ENDRINKS/16 Final

[http://ec.europa.eu/food/fs/sc/scf/out169\\_en.pdf](http://ec.europa.eu/food/fs/sc/scf/out169_en.pdf)

#### **4.13 Opinion on Caffeine, Taurine and D-Glucurono - g -Lactone as constituents of so-called "energy" drinks (expressed on 21 January 1999)**

SCF (Scientific committee on Food), 1999

[http://ec.europa.eu/food/fs/sc/scf/out22\\_en.html](http://ec.europa.eu/food/fs/sc/scf/out22_en.html)

#### **4.14 Assessment of creatine in sports products**

VKM (The Norwegian Scientific Committee for Food Safety), 2010

Panel on on Nutrition, Dietetic Products, Novel Food and Allergy

Doc. no.: 09-702

ISBN: 978-82-8259-006-8

<http://www.vkm.no/dav/3178aba783.pdf>

#### **4.15 New information on ingredients in so-called "energy drinks"**

VKM (The Norwegian Scientific Committee for Food Safety), 2009

Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics

09-404-4 final

<http://www.vkm.no/dav/a8859a2195.pdf>

#### **4.16 Risikovurdering av "energidrikker" med koffein, taurin, glukuronolakton, inositol og vitaminer**

VKM (The Norwegian Scientific Committee for Food Safety), 2005

The Scientific Steering Committee

04/701-1-endelig

<http://www.vkm.no/dav/59955595ba.pdf>

#### **4.17 Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO FOOD ADDITIVES SERIES NO. 5**

WHO (World Health Organization), 1974

<http://www.inchem.org/documents/jecfa/jecmono/v05je42.htm>

# 5 Relevant risk and/or safety assessments of plant substances

Plant substances used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes anthocyanins (blueberry), astaxanthin, bioflavonoids, caffeine, curcumin, chlorogenic acid, isoflavone (soy bean), 5-caffeoylquinic acid, catechins (green tea), isoflavones (soy bean), lutein, lycopene, naringin (from *Citrus paradisi*), piperine (from *Piper nigrum*), polyphenols (green coffee bean extract), polyphenols (cranberry and blueberry extracts), polyphenols (green tea extract), Rosavin (*Rhodiola rosea* extract), and zeaxanthin. An overview of risk and/or safety assessments of these substances is given in table 5-1.

**Table 5-1.** Risk and/or safety assessments of plant substances including anthocyanins (blueberry), astaxanthin, bioflavonoids, caffeine, curcumin, chlorogenic acid, isoflavone (soy bean), 5-caffeoylquinic acid, catechins (green tea), isoflavones (soy bean), lutein, lycopene, naringin (from *Citrus paradisi*), piperine (from *Piper nigrum*), polyphenols (green coffee bean extract), polyphenols (cranberry and blueberry extracts), polyphenols (green tea extract), Rosavin (*Rhodiola rosea* extract), and zeaxanthin.

| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <p><b>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)</b></p> | <p>AESAN, 2012</p>            | <p>The use as a food supplement was assessed.</p> <ul style="list-style-type: none"> <li>- Astaxanthin; (from shellfish and fish) the maximum daily amount of 4 mg of astaxanthin in food supplements proposed by the AESAN may be considered within the safety limits for medium-term intake as, taking a maximum intake value of astaxanthin through seafood estimated at 1.95 mg/day, the upper exposure level, including the food supplements, would be less than 6 mg/day. Due to the chemical characteristics and to assess the potential risk of its long-term intake, carcinogenicity studies must be conducted using models that include exposure to environmental contaminants. Although studies in humans have not shown any adverse effects, the threshold dose from which it may interfere with the metabolism of certain medicines is not known. Due to the absence of studies on teratogenic effects, food supplements of astaxanthin are not recommended for pregnant women. In addition, due to the lack of scientific information, the intake is not recommended for children and nursing mothers.</li> <li>- Lycopene; a maximum amount of 15 mg/day of lycopene is acceptable from the safety point of view for use as a food supplement.</li> <li>- All trans lutein/zeaxanthin; although there are other sources for obtaining lutein, to date safety studies have been carried out with <i>trans</i> lutein associated to <i>trans</i> zeaxanthin from <i>Tagetes erecta</i>, with the appearance of safety problems when other sources are used. The Scientific Committee concludes that, based on the information available to date and taking into account the general considerations reflected in this report, the proposal of a maximum amount of 20 mg/day of <i>trans</i> lutein, associated with <i>trans</i> zeaxanthin, is acceptable from the safety point of view for use as a food supplement. However it should be noted that this estimate only refers to its intake as a supplement in adults.</li> </ul> |

| Title   | Prepared by, publication year | Information on safety and established use limits   |
|---|-------------------------------|--|
| <b>OPINION of the French Food Safety Agency on the assessment of risk from consumption of an “energy” drink containing substances other than technological additives: taurine, D-glucuronolactone, inositol, vitamins B2, B3, B5, B6 and B12.</b> | AFSSA, 2006                   | Information on safety and established use limits was not available in an abstract/summary. |
| <b>Avis de l’Agence française de sécurité sanitaire des aliments du 25 juillet 2005 relatif à l’évaluation des risques éventuels liés à l’emploi de lycopène en tant qu’ingrédient alimentaire</b>  | AFSSA, 2005                   | Information on safety and established use limits was not available in an abstract/summary. |
| <b>Sécurité et bénéfices des phytoestrogènes apportés par l’alimentation - Recommandations</b>  | AFSSA, 2005                   | Information on safety and established use limits was not available in an abstract/summary. |
| <b>OPINION of the French Food Safety Agency (AFSSA) regarding the assessment of additional information on the stability of vitamin D and the phytoestrogen content of soy milk.</b>   | AFSSA, 2005                   | Information on safety and established use limits was not available in an abstract/summary. |

| Title   | Prepared by, publication year | Information on safety and established use limits  |
|---|-------------------------------|---|
| <b>OPINION of the French Food Safety Agency regarding the assessment of the safety in use of a food supplement combining three active compounds: "lacto-lycopene" (a lycopene-rich tomato extract combined with lacto-proteins), an isoflavone-rich soy extract and vitamin C</b> | AFSSA, 2004                   | The French Food Safety Agency (AFSSA) assess the safety in use of a food supplement combining three active compounds: a lycopene-rich tomato extract combined with lactoproteins called "lacto-lycopene", an isoflavone-rich soy extract and vitamin C. |
| <b>Opinion of the French Agency for Food, Environmental and Occupational Health &amp; Safety on the assessment of risks concerning the consumption of so-called "energy drinks"</b>   | ANSES, 2013                   | Includes caffeine, taurine and glucuronolactone   |
| <b>AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail</b>   | ANSES, 2012                   | Includes lutein   |
| <b>AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif au risque de toxidermie induit par la consommation de lutéine et de zéaxanthine dans les compléments alimentaires</b>   | ANSES, 2011                   | Includes green tea  |

| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>OPINION of the French Agency for Food, Environmental and Occupational Health &amp; Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs</b> | ANSES, 2011                   | Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).                                   |
| <b>Risikobewertung von Pflanzen und pflanzlichen Zubereitungen</b>   | BfR, 2013                     | Includes Rhodiola rosea (L.) SCOP. (Rosenwurz)  |
| <b>Gesundheitliche Bewertung von synephrin- und koffeinhaltigen Sportlerprodukten und Schlankheitsmitteln</b>  | BfR, 2013                     | Information on safety and established use limits was not available in an abstract/summary.                              |
| <b>Isolated isoflavones are not without risk</b>   | BfR, 2007                     | Information on safety and established use limits was not available in an abstract/summary.                              |
| <b>Säuglingsnahrung aus Sojaweiß ist kein Ersatz für Kuhmilchprodukte</b>  | BfR, 2007                     | Information on safety and established use limits was not available in an abstract/summary.                              |
| <b>Statement on the reproductive effects of caffeine</b>   | COT, 2008                     | Caffeine; no specific ADI set but risk of foetal growth retardation less than 2% at caffeine intakes $\leq 200$ mg/day. |



| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <b>Scientific opinion. Risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones</b> | EFSA, 2015                    | The human data did not support the hypothesis of an increased risk of breast cancer from observational studies nor of an effect on mammographic density nor on proliferation marker Ki-67 expression in interventional studies. No effect was found on endometrial thickness and histopathological changes in the uterus up to 30 months of supplementation with 150 mg/day of soy isoflavones. After 60 months some non-malignant histopathological changes were reported. Thyroid hormones levels were not changed following intake of isoflavones from food supplements. The background exposure from the diet in the general European population was estimated to be lower than 1 mg/day, whereas in consumers of soy-based foods it could be higher. The Panel concluded that it was not possible to derive a single health-based guidance value for the different preparations in post-menopausal women. However the doses used in the intervention studies and their duration could serve as guidance for the intake of food supplements. |
| <b>Scientific Opinion on the safety of astaxanthin-rich ingredients (AstaREAL A1010 and AstaREAL L10) as novel food ingredients</b>    | EFSA, 2014                    | Astaxanthin; the Panel bases the evaluation of the NFIs on the acceptable daily intake (ADI) of 0.034 mg/kg bw for astaxanthin derived by the FEEDAP Panel.  |
| <b>Scientific Opinion on the re-evaluation of anthocyanins (E 163) as a food additive</b>  | EFSA, 2013                    | Anthocyanins have been previously evaluated by JECFA in 1982 and the SCF in 1975. JECFA has established an ADI of 2.5 mg/kg bw/day for anthocyanins from grape skin, while the SCF has not derived an ADI for anthocyanins. Studies on the toxicokinetics and toxicological properties of anthocyanins have mainly used fruit extracts, which contain several anthocyanins. Therefore, based on these studies, conclusions cannot be drawn for specific anthocyanins, but may be made for anthocyanins in general. Since anthocyanins used as the food additive E 163 are poorly defined, it is not clear whether the substances used in the various studies are relevant for assessment of the specific E 163 anthocyanins. The Panel concluded that the currently available toxicological database was inadequate to establish a numerical ADI for anthocyanins.   |

| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>SCIENTIFIC OPINION Statement on the safety assessment of the exposure to lutein preparations based on new data on the use levels of lutein</b>                          | EFSA, 2012                    | Lutein; the ADI of 1 mg/kg bw/day.  |
| <b>Statement on the safety of synthetic zeaxanthin as an ingredient in food supplements</b>  | EFSA, 2012                    | Zeaxanthin; the Panel identifies a NOAEL at 150 mg/kg bw per day in the two-generation reproduction toxicity study and has no concerns with regard to genotoxicity. Given the absence of a chronic toxicity/carcinogenicity study, the Panel applies an uncertainty factor of 200 on the NOAEL in the two-generation study. This results in 0.75 mg/kg bw per day for synthetic zeaxanthin corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg. The Panel concludes that based on the available data, intakes of 0.75 mg/kg bw per day for synthetic zeaxanthin, corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg, do not raise safety concerns. |
| <b>Scientific Opinion on the re-evaluation of lutein preparations other than lutein with high concentrations of total saponified carotenoids at levels of at least 80%</b> | EFSA, 2011                    | Lutein; The ANS Panel established an ADI of 1 mg/kg bw/day and noted that this ADI refers to lutein derived from <i>Tagetes erecta</i> containing at least 80% carotenoids.   |
| <b>Statement on the divergence between the risk assessment of lycopene by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA)</b>                        | EFSA, 2010                    | Lycopene; A statement on the divergence between the risk assessment of lycopene by the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The AFC Panel derived an ADI of 0.5 mg/kg bw/day   |

| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <b>Scientific Opinion on the re-evaluation of lutein (E 161b) as a food additive</b>   | EFSA, 2010                    | <p>Lutein; has been previously evaluated by the EU Scientific Committee for Food (SCF) in 1975 and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2006. JECFA established a group Acceptable Daily Intake (ADI) of 0-2 mg/kg body weight (bw) for lutein from <i>Tagetes erecta</i> and zeaxanthin. The SCF could not establish an ADI.</p> <p>The Panel concluded, based on the NOAEL of 200 mg/kg bw/day (the highest dose level tested) in a 90-day rat study, the absence of developmental toxicity at dose levels up to 1000 mg/kg bw/day (the highest dose level tested), the fact that lutein is not genotoxic, the fact that in 90-day studies no effects on reproductive organs were observed, and the fact that lutein is a normal constituent of the diet, that an ADI can be derived. Given the absence of a multigeneration reproductive toxicity study and of chronic toxicity/carcinogenicity studies the Panel applies an uncertainty factor of 200 and establishes an ADI of 1 mg/kg bw/day. The Panel noted that this ADI refers to lutein derived from <i>Tagetes erecta</i> containing at least 80% carotenoids consisting of lutein and zeaxanthin (79 and 5% respectively).</p> |
| <b>Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive</b>  | EFSA, 2010                    | <p>Curcumin; has been previously evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the EU Scientific Committee on Food (SCF). In 2004 JECFA allocated an ADI of 0-3 mg/kg bw/day.</p> <p>The Panel concluded that the present database supports an ADI of 3 mg/kg bw/day based on the NOAEL of 250-320 mg/kg bw/day from the reproductive toxicity study for a decreased body weight gain in the F2 generation observed at the highest dose level, and an uncertainty factor of 100.</p>   |
| <b>Use of Lycopene as a food colour - Scientific Opinion of the Panel on Food additives, Flavourings, Processing Aids and Materials in Contact with Food</b> | EFSA, 2008                    | <p>Lycopene; the Panel derives an ADI of 0.5 mg/kg bw/day using a safety factor of 100 based on a NOAEL of 50 mg/kg bw/day from a one year rat study and a non-reversible increase in alanine transaminase (ALT). This ADI refers to lycopene from all sources.</p>  |

| Title   | Prepared by, publication year   | Information on safety and established use limits  |
|---|---|---|
| <b>Opinion of the safety of 'synthetic Zeaxanthin as an ingredient in food supplements'</b>                 | EFSA, 2008  | Lutein and synthetic zeaxanthin; these intake levels are within the range of the group ADI 0-2 mg/kg body weight for lutein and synthetic zeaxanthin as established by JECFA. However, in the opinion of the Panel, the toxicological data on synthetic zeaxanthin are not sufficient to derive an acceptable daily intake. |
| <b>ESCO working group on isoflavones</b>  | ESCO, ongoing work  | Information on safety and established use limits was not available in an abstract/summary.  |
| <b>Assessment report on <i>Camellia sinensis</i> (L.) Kuntze, non fermentatum folium</b>                    | EMA, 2013   | Information on safety and established use limits was not available in an abstract/summary.  |
| <b>Assessment report on <i>Rhodiola rosea</i> L., rhizoma et radix</b>                                      | EMA, 2012   | Information on safety and established use limits was not available in an abstract/summary.  |
| <b>ASSESSMENT REPORT ON <i>CURCUMA LONGA</i> L. RHIZOMA</b>   | EMA, 2009   | Information on safety and established use limits was not available in an abstract/summary.  |
| <b>PlantLIBRA: Plant food supplements. Levels of intake, benefit and risk assessment (EU –project, WP1)</b> | Finnish Food Safety Authority Evira (FI), Fundacion para la Investigacion Nutricional (ES), Institute of Food Research (UK) | Includes bioflavonoids, caffeine, catechins (green tea extract), lutein, and polyphenols (green tea extract).   |
| <b>Exposure of Finnish consumers to food additives</b>  | Finnish Food Safety Authority Evira, ongoing project  | Includes lutein, lycopene, and curcumin   |

| Title   | Prepared by, publication year                                       | Information on safety and established use limits   |
|---|---|--|
| <b>Caffeine</b>   | FDA; The Select Committee on GRAS Substances (SCOGS) Database, 1978 | Caffeine; (report No.: 89, ID Code: 58-08-2) in light of these considerations, the Select Committee concludes that: A. While no evidence in the available information on caffeine demonstrates a hazard to the public when it is used in cola type beverages at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies be conducted. B. It is inappropriate to include caffeine among the substances generally recognized as safe (GRAS). At current levels of consumption of cola-type beverages, the dose of caffeine can approximate that known to induce such pharmacological effects as central nervous system stimulation.   |
| <b>Risk assessment of caffeine among children and adolescents in the Nordic countries</b>   | Nordic Council of Ministers, 2008                                   | Caffeine; international scientific institutions, such as the World Health Organisation (WHO), the Scientific Committee for Food (SCF) and the European Food Safety Authority (EFSA) have not determined an acceptable daily intake (ADI) or upper tolerable intake level for caffeine. Children/adolescents with any type of anxiety problem, with headaches, or with sleep problems, should be checked out for caffeine consumption. Although there is a striking lack of quantitative data on the effect of caffeine in children and adolescents, the project group identified, through literature studies, several biological effects of low level caffeine exposure, such as tolerance development, withdrawal symptoms and anxiety and jitteriness. For tolerance development NOEL- and LOEL-values of 0.3 and 1.0–1.3 mg/kg bw respectively, were identified, whereas a LOAEL for anxiety and jitteriness was identified at an intake of 2.5 mg/kg bw. |
| <b>PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8736. Novel food ingredients: oils rich in conjugated linoleic acid in food</b> | Superior Health Council, 2011                                       | Information on safety and established use limits was not available in an abstract/summary.   |
| <b>New information on ingredients in so-called "energy drinks"</b>  | VKM, 2009   | Caffeine; the intake of caffeine in pregnant women should not exceed 100 - 200 mg/day  |

### **5.1 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 (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2012

Reference number: AESAN-2012-008

Report approved by the Scientific Committee on plenary session November 28th, 2012

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS.pdf)

### **5.2 OPINION of the French Food Safety Agency on the assessment of risk from consumption of an “energy” drink containing substances other than technological additives: taurine, D-glucuronolactone, inositol, vitamins B2, B3, B5, B6 and B12.**

AFSSA (French Food Safety Agency), 2006

<http://www.anses.fr/sites/default/files/documents/NUT2006sa0236EN.pdf>

### **5.3 Avis de l’Agence française de sécurité sanitaire des aliments du 25 juillet 2005 relatif à l’évaluation des risques éventuels liés à l’emploi de lycopène en tant qu’ingrédient alimentaire**

AFSSA (French Food Safety Agency), 2005

<http://www.anses.fr/sites/default/files/documents/NUT2004sa0336.pdf> (in French)

### **5.4 Sécurité et bénéfices des phyto-estrogènes apportés par l’alimentation – Recommandations**

AFSSA (French Food Safety Agency), 2005

<http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/064000580/0000.pdf>

## **5.5 OPINION of the French Food Safety Agency (AFSSA) regarding the assessment of additional information on the stability of vitamin D and the phytoestrogen content of soy milk**

AFSSA (French Food Safety Agency), 2005

<https://www.anses.fr/sites/default/files/documents/NUT2004sa0363ErEN.pdf>

## **5.6 OPINION of the French Food Safety Agency regarding the assessment of the safety in use of a food supplement combining three active compounds: "lacto-lycopene" (a lycopene-rich tomato extract combined with lacto-proteins), an isoflavone-rich soy extract and vitamin C**

AFSSA (French Food Safety Agency), 2004

<https://www.anses.fr/sites/default/files/documents/NUT2003sa0197EN.pdf>

## **5.7 Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of risks concerning the consumption of so-called "energy drinks"**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2013

<https://www.anses.fr/sites/default/files/documents/NUT2012sa0212EN.pdf>

## **5.8 AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif au risque d'hépatotoxicité lié à la consommation de denrées alimentaires contenant notamment du thé vert**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2012

Opinion on the risk of liver toxicity associated with the consumption of foodstuffs containing green tea in particular

<https://www.anses.fr/sites/default/files/documents/NUT2011sa0108.pdf>

## **5.9 AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif au risque de toxidermie induit par la consommation de lutéine et de zéaxanthine dans les compléments alimentaires**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2011

Opinion on the risk of allergic dermatitis induced by the consumption of lutein and zeaxanthin in food supplements

<https://www.anses.fr/sites/default/files/documents/NUT2010sa0242.pdf>

## **5.10 OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2011

<https://www.anses.fr/sites/default/files/documents/NUT2007sa0314EN.pdf>

## **5.11 Risikobewertung von Pflanzen und pflanzlichen Zubereitungen**

BfR (Bundesinstitut für Risikobewertung), 2013

<http://www.bfr.bund.de/cm/350/risikobewertung-von-pflanzen-und-pflanzlichen-zubereitungen.12394745.pdf> (in German)

## **5.12 Gesundheitliche Bewertung von synephrin- und koffeinhaltigen Sportlerprodukten und Schlankheitsmitteln**

BfR (Bundesinstitut für Risikobewertung), 2013

Stellungnahme Nr. 004/2013 des BfR vom 16. November 2012

<http://www.bfr.bund.de/cm/343/gesundheitliche-bewertung-von-synephrin-und-koffeinhaltigen-sportlerprodukten-und-schlankheitsmitteln.pdf>



### **5.13 Isolated isoflavones are not without risk**

BfR (Bundesinstitut für Risikobewertung), 2013

Updated\* BfR Expert Opinion No. 039/2007, 3 April 2007

[http://www.bfr.bund.de/cm/349/isolated\\_isoflavones\\_are\\_not\\_without\\_risk.pdf](http://www.bfr.bund.de/cm/349/isolated_isoflavones_are_not_without_risk.pdf)

### **5.14 Säuglingsnahrung aus Sojaweiß ist kein Ersatz für Kuhmilchprodukte**

BfR (Bundesinstitut für Risikobewertung), 2013

[http://www.bfr.bund.de/cm/343/saeuglingsnahrung\\_aus\\_sojaweiß\\_ist\\_kein\\_ersatz\\_fuer\\_kuhmilchprodukte.pdf](http://www.bfr.bund.de/cm/343/saeuglingsnahrung_aus_sojaweiß_ist_kein_ersatz_fuer_kuhmilchprodukte.pdf)

### **5.15 Statement on the reproductive effects of caffeine**

COT (Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment), 2008

<http://cot.food.gov.uk/pdfs/cotstatementcaffeine200804.pdf>

### **5.16 Scientific Opinion. Risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones**

EFSA (European Food Safety Authority), 2015

The EFSA Journal 2015; 13(10):4246

EFSA Panel on Food Additives and Nutrient Sources added to Food

[http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/4246.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4246.pdf)

Annex A - Protocol for risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones:

[http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/4246ax1.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4246ax1.pdf)

Annex B - List of studies excluded during full text screening for the systematic review

### **5.17 Scientific Opinion on the safety of astaxanthin-rich ingredients (AstaREAL A1010 and AstaREAL L10) as novel food ingredients**

EFSA (European Food Safety Authority), 2014

The EFSA Journal 2014; 12(7):3757

EFSA Panel on Dietetic Products, Nutrition and Allergies

<http://www.efsa.europa.eu/en/efsajournal/doc/3757.pdf>

### **5.18 Scientific Opinion on the re-evaluation of anthocyanins (E 163) as a food additive**

EFSA (European Food Safety Authority), 2013

The EFSA Journal 2013; 11(4):3145

EFSA Panel on Food Additives and Nutrient Sources added to Food

<http://www.efsa.europa.eu/en/efsajournal/doc/3145.pdf>

### **5.19 SCIENTIFIC OPINION Statement on the safety assessment of the exposure to lutein preparations based on new data on the use levels of lutein**

EFSA (European Food Safety Authority), 2013

The EFSA Journal 2012; 10(3):2589

EFSA Panel on Food Additives and Nutrient Sources added to Food

<http://www.efsa.europa.eu/en/efsajournal/doc/2589.pdf>

### **5.20 Statement on the safety of synthetic zeaxanthin as an ingredient in food supplements**

EFSA (European Food Safety Authority), 2012

The EFSA Journal 2012; 10(10):2891

EFSA Panel on Dietetic Products, Nutrition and Allergies

<http://www.efsa.europa.eu/en/efsajournal/doc/2891.pdf>

### **5.21 Scientific Opinion on the re-evaluation of lutein preparations other than lutein with high concentrations of total saponified carotenoids at levels of at least 80%**

EFSA (European Food Safety Authority), 2011  
The EFSA Journal 2011; 9(5):2144  
EFSA Panel on Food Additives and Nutrient Sources added to Food  
<http://www.efsa.europa.eu/en/efsajournal/doc/2144.pdf>

### **5.22 Statement on the divergence between the risk assessment of lycopene by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA)**

EFSA (European Food Safety Authority), 2010  
The EFSA Journal 2010; 8(7):1676  
EFSA Panel on Food Additives and Nutrient Sources added to Food  
<http://www.efsa.europa.eu/en/efsajournal/doc/1676.pdf>

### **5.23 Scientific Opinion on the re-evaluation of lutein (E 161b) as a food additive**

EFSA (European Food Safety Authority), 2010  
The EFSA Journal 2010; 8(7):1678  
EFSA Panel on Food Additives and Nutrient Sources added to Food  
<http://www.efsa.europa.eu/en/efsajournal/doc/1678.pdf>

### **5.24 Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive**

EFSA (European Food Safety Authority), 2010  
The EFSA Journal 2010; 8(9):1679  
EFSA Panel on Food Additives and Nutrient Sources added to Food  
<http://www.efsa.europa.eu/en/efsajournal/doc/1679.pdf>

## **5.25 Use of Lycopene as a food colour - Scientific Opinion of the Panel on Food additives, Flavourings, Processing Aids and Materials in Contact with Food**

EFSA (European Food Safety Authority), 2008

The EFSA Journal (2008) 674, 1-66

EFSA Panel on Food additives, Flavourings, Processing Aids and Materials in Contact with Food

<http://www.efsa.europa.eu/en/efsajournal/doc/674.pdf>

## **5.26 Opinion of the safety of 'synthetic Zeaxanthin as an ingredient in food supplements'**

EFSA (European Food Safety Authority), 2008

The EFSA Journal (2008) 728, 1-27

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

[http://www.bfr.bund.de/cm/343/efsa\\_opinion\\_on\\_the\\_safety\\_of\\_synthetic\\_zeaxanthin.pdf](http://www.bfr.bund.de/cm/343/efsa_opinion_on_the_safety_of_synthetic_zeaxanthin.pdf)

## **5.27 ESCO working group on isoflavones**

<http://www.efsa.europa.eu/en/escoisoflavones/docs/escoisoflavonesmandate.pdf>

## **5.28 Assessment report on *Camellia sinensis* (L.) Kuntze, non fermentatum folium**

EMA (European Medicines Agency), 2013

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Herbal\\_-\\_HMPC\\_assessment\\_report/2014/04/WC500165886.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2014/04/WC500165886.pdf)

## **5.29 Assessment report on *Rhodiola rosea* L., rhizoma et radix**

EMA (European Medicines Agency), 2012

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Herbal\\_-\\_HMPC\\_assessment\\_report/2012/05/WC500127861.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2012/05/WC500127861.pdf)

### **5.30 ASSESSMENT REPORT ON *CURCUMA LONGA* L. RHIZOMA**

EMA (European Medicines Agency), 2009

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Herbal - HMPC assessment report/2010/02/WC500070700.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2010/02/WC500070700.pdf)

### **5.31 PlantLIBRA: Plant food supplements. Levels of intake, benefit and risk assessment (EU – project, WP1)**

EVIRA (Finnish Food Safety Authority), Fundacion para la Investigacion Nutricional, Institute of Food Research

### **5.32 Exposure of Finnish consumers to food additives**

EVIRA (Finnish Food Safety Authority) ongoing project

### **5.33 The Select Committee on GRAS Substances (SCOGS) Database**

FDA (U.S. Food and Drug Administration), 1978

Report No.: 89,

ID Code: 58-08-2

<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=42>

### **5.34 Risk assessment of caffeine among children and adolescents in the Nordic countries**

Nordic Council of Ministers, 2008

ISBN 978-92-893-1731-3

<http://www.diva-portal.org/smash/get/diva2:701839/FULLTEXT01.pdf>

### **5.35 PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8736. Novel food ingredients: oils rich in conjugated linoleic acid in food**

Superior Health Council, 2011

[http://www.gezondheid.belgie.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19070435\\_en.pdf](http://www.gezondheid.belgie.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19070435_en.pdf)

### **5.36 New information on ingredients in so-called “energy drinks”**

VKM (The Norwegian Scientific Committee for Food Safety), 2009

Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics

09-404-4 final

<http://www.vkm.no/dav/a8859a2195.pdf>

## 6 Relevant risk and/or safety assessments of fiber and prebiotics

Fiber and prebiotics used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes beta-glucan, konjac glucomannan, and inulin. An overview of risk and/or safety assessments of these substances is given in table 6-1.

**Table 6-1.** Risk and/or safety assessments of fiber and prebiotics including beta-glucan, konjac glucomannan, and inulin.

| Title  | Prepared by, publication year | Information on safety and established use limits  |
|--|-------------------------------|---|
| <b>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)</b>  | AESAN, 2012                   | The use as a food supplement was assessed. <ul style="list-style-type: none"> <li>- Beta-glucan; a maximum daily amount of 4 g de beta-glucans is acceptable.</li> <li>- Konjac glucomannan; a maximum amount of 4 g/day is acceptable.</li> <li>- Inulin; a maximum amount of 9 g/day of inulin or the sum of inulin plus fructooligosaccharides (FOS) is acceptable.</li> </ul> |
| <b>OPINION of the French Agency for Food, Environmental and Occupational Health &amp; Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs</b> | ANSES, 2011                   | Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).   |

| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <b>European Commission, Food science and techniques, Reports of the Scientific Committee for Food (forty-first series)</b> | SCF, 1997                     | <p>Including an opinion on the safety in use of konjac glucomannan as a food additive; "Konjac glucomannan was tested adequately in 90-day feeding studies with rats and beagle dogs. These studies did not reveal any relevant toxic effects and a no-observed-effect level of 2.5 % glucomannan in the diet can be derived, corresponding to 1.25 g/kg body weight/day. However, a long-term toxicity/carcinogenicity study is lacking and only gene mutation tests in bacteria were performed with a negative result, In addition, it has not been clarified to what extent the glucomannan is digested in the human intestine. Therefore an AD1 can not be established. On the other hand, the existing experimental data as well as human experience do not give reason for concern. Konjac glucomannan is consumed as a component of Konjac flour in Far East countries where the Konjac materials have a long history as traditional food. Apart from diarrhoea, abdominal pain and an influence on vitamin absorption after ingestion of high doses of Konjac materials, no adverse effects have become known from studies in humans. Therefore, the Committee considers that the use of Konjac glucomannan as an additive up to 1% in food is acceptable provided that the total intake from all sources did not exceed 3 g/d. This upper limit should be taken into account when setting the conditions of use."</p> |



### **6.1 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 (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2012

Reference number: AESAN-2012-008

Report approved by the Scientific Committee on plenary session November 28th, 2012

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS.pdf)

### **6.2 OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs**

ANSES (French Agency for Food, Environmental and Occupational Health & Safety), 2011

<https://www.anses.fr/sites/default/files/documents/NUT2007sa0314EN.pdf>

### **6.3 European Commission, Food science and techniques, Reports of the Scientific Committee for Food (forty-first series)**

SCF (The Scientific Committee for FOOD), 1997

OPINIONS OF THE SCIENTIFIC COMMITTEE FOR FOOD, including an opinion on the safety in use of konjac glucomannan as a food additive

[http://ec.europa.eu/food/fs/sc/scf/reports/scf\\_reports\\_41.pdf](http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_41.pdf)

# 7 Relevant risk and/or safety assessments of enzymes

Fiber and prebiotics used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes amylase, cellulase, lactase, lipase, and peptidase. An overview of risk and/or safety assessments of these substances is given in table 7-1.

**Table 7-1.** Risk and/or safety assessments of enzymes including amylase, cellulase, lactase, lipase, and peptidase.

| Title   | Prepared by, publication year | Information on safety and established use limits   |
|---|-------------------------------|--|
| <b>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 (3)</b> | AESAN, 2014                   | Lactase; is considered by the NDA panel of the EFSA as sufficiently characterised and recommends a dose of 4500 FCC (Food Chemical Codex) with each meal containing lactose although the dose should be adjusted to each individual depending on the meals taken with lactase (EFSA, 2009). From the safety point of view, this consideration could be admitted as scientific evidence does not reveal that it could produce observable adverse effects. As indicated in Regulation (EU) No 432/2012, establishing a list of permitted health claims made on foods, the target population should be informed that lactose tolerance is variable and advice should be sought regarding the role this substance may play in their diet (EU, 2012). |

## **7.1 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 (3)**

AESAN (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2014

Reference number: AECOSAN- 2014-002

Report approved by the Section of Food Safety and Nutrition on plenary session May 21st, 2014

[http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingles/FOOD\\_SUPPLEMENTS-3.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingles/FOOD_SUPPLEMENTS-3.pdf)

## 8 Relevant risk and/or safety assessments of bee pollen, colostrum, propolis and royal jelly

The use of bee pollen, colostrum, propolis and royal jelly in food supplements and other foods in Norway was reported by the industry to NFSA. An overview of risk and/or safety assessments of these substances is given in table 8 -1.

**Table 8-1.** Risk and/or safety assessments of bee pollen, colostrum, propolis and royal jelly.

| Title   | Prepared by, publication year | Information on safety and established use limits   |
|---|-------------------------------|--|
| <b>Einschätzung von Propolis und Gelée Royale</b> | BfR, 2008                     | Information on safety and established use limits was not available in an abstract/summary. |

### 8.1 Einschätzung von Propolis und Gelée Royale

BfR (Bundesinstitut für Risikobewertung), 2008

[http://www.bfr.bund.de/cm/343/einschaetzung\\_von\\_propolis\\_und\\_gelee\\_royal.pdf](http://www.bfr.bund.de/cm/343/einschaetzung_von_propolis_und_gelee_royal.pdf)

## 9 Relevant risk assessments of probiotics

Probiotics used in food supplements and other foods in Norway, as reported to NFSA by the industry, includes *Bacillus coagulans* GBI 30 6086, *Bifidus breve*, *Bifidus infantis*, *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Bifidobacter longum*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus coagulans*, *Lactobacillus helveticus*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus salivarius*, *Lactococcus lactis*, and *Streptococcus thermophiles*. An overview of risk and/or safety assessments of probiotics is given in table 9 -1.

**Table 9-1.** Risk and/or safety assessments of probiotics.

| Title  | Prepared by, publication year | Information on safety and established use limits   |
|--|-------------------------------|--|
| <b>Gesundheitliche Bewertung isolierter Bakterienstämme als konzentrierte probiotische Lebensmittel/Nahrungsergänzungsmittel</b>   | BfR, 2001                     | Information on safety and established use limits was not available in an abstract/summary. |
| <b>Abschlussbericht der Arbeitsgruppe "Probiotische Mikroorganismenkulturen in Lebensmitteln" am BgVV</b>                          | BfR, 1999                     | Information on safety and established use limits was not available in an abstract/summary. |
| <b>Introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA</b> | EFSA, 2007                    |  |
| <b>SCIENTIFIC OPINION The maintenance of the list of QPS microorganisms intentionally added to food or feed</b>                    | EFSA, 2008                    |  |

| Title  | Prepared by, publication year | Information on safety and established use limits |
|--|-------------------------------|--|
| <b>Scientific Opinion on the maintenance of the list of QPS microorganisms intentionally added to food or feed (2009 update)</b>     | EFSA, 2009                    |  |
| <b>Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2010 update)</b> | EFSA, 2010                    |  |
| <b>Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2011 update)</b> | EFSA, 2011                    |  |
| <b>Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2012 update)</b> | EFSA2012                      |  |
| <b>Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2013 update)</b> | EFSA2013                      |  |

| Title  | Prepared by, publication year | Information on safety and established use limits |
|--|-------------------------------|--|
| <b>SCIENTIFIC OPINION Statement on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 1: Suitability of taxonomic units notified to EFSA until October 2014</b>   | EFSA, 2014                    |  |
| <b>SCIENTIFIC OPINION Statement on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA. 2: Suitability of taxonomic units notified to EFSA until March 2015</b>    | EFSA 2015                     |  |
| <b>SCIENTIFIC OPINION Statement on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 3: Suitability of taxonomic units notified to EFSA until September 2015</b> | EFSA, 2015                    |  |
| <b>PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8651. Probiotics and their implications for Belgian public health</b>  | Superior Health Council, 2012 |  |

## **9.1 Gesundheitliche Bewertung isolierter Bakterienstämme als konzentrierte probiotische Lebensmittel/Nahrungsergänzungsmittel**

BfR (Bundesinstitut für Risikobewertung), 2001

Stellungnahme vom Februar 2001

[http://www.bfr.bund.de/cm/343/gesundheitliche\\_bewertung\\_isolierter\\_bakterienst\\_mme\\_als\\_konzentrierte\\_probiotische.pdf](http://www.bfr.bund.de/cm/343/gesundheitliche_bewertung_isolierter_bakterienst_mme_als_konzentrierte_probiotische.pdf)

## **9.2 Abschlussbericht der Arbeitsgruppe "Probiotische Mikroorganismenkulturen in Lebensmitteln" am BgVV**

BfR (Bundesinstitut für Risikobewertung), 1999

<http://www.bfr.bund.de/cm/343/probiot.pdf>

## **9.3 Introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA**

European Food Safety Authority (EFSA)

The EFSA Journal 2007; 587, 1-16

EFSA Scientific Committee

<http://www.efsa.europa.eu/en/efsajournal/doc/587.pdf>

## **9.4 SCIENTIFIC OPINION The maintenance of the list of QPS microorganisms intentionally added to food or feed**

European Food Safety Authority (EFSA)

The EFSA Journal 2008; 923, 1-48

EFSA Panel on Biological Hazards

<http://www.efsa.europa.eu/en/efsajournal/doc/923.pdf>



## **9.5 Scientific Opinion on the maintenance of the list of QPS microorganisms intentionally added to food or feed (2009 update)**

European Food Safety Authority (EFSA)

The EFSA Journal 2009; 7(12):1431

EFSA Panel on Biological Hazards

<http://www.efsa.europa.eu/en/efsajournal/doc/1431.pdf>

## **9.6 Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2010 update)**

European Food Safety Authority (EFSA)

The EFSA Journal 2010; 8(12):1944

EFSA Panel on Biological Hazards

<http://www.efsa.europa.eu/en/efsajournal/doc/1944.pdf>

## **9.7 Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2011 update)**

European Food Safety Authority (EFSA)

The EFSA Journal 2011; 9(12):2497

EFSA Panel on Biological Hazards

<http://www.efsa.europa.eu/en/efsajournal/doc/2497.pdf>

## **9.8 Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2012 update)**

European Food Safety Authority (EFSA)

The EFSA Journal 2012; 10(12):3020  
EFSA Panel on Biological Hazards  
<http://www.efsa.europa.eu/en/efsajournal/doc/3020.pdf>

### **9.9 Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2013 update)**

European Food Safety Authority (EFSA)  
The EFSA Journal 2013; 1(11):3449  
EFSA Panel on Biological Hazards  
<http://www.efsa.europa.eu/en/efsajournal/doc/3449.pdf>

### **9.10 SCIENTIFIC OPINION Statement on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 1: Suitability of taxonomic units notified to EFSA until October 2014**

European Food Safety Authority (EFSA)  
The EFSA Journal 2014; 12(12):3938  
EFSA Panel on Biological Hazards  
<http://www.efsa.europa.eu/en/efsajournal/doc/3938.pdf>

### **9.11 SCIENTIFIC OPINION Statement on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA. 2: Suitability of taxonomic units notified to EFSA until March 2015**

European Food Safety Authority (EFSA)  
The EFSA Journal 2015; 13(6):4138

EFSA Panel on Biological Hazards

[http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/4138.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4138.pdf)

### **9.12 SCIENTIFIC OPINION Statement on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 3: Suitability of taxonomic units notified to EFSA until September 2015**

European Food Safety Authority (EFSA)

The EFSA Journal 2015; 13(12):4331

EFSA Panel on Biological Hazards

[http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/4331.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4331.pdf)

### **9.13 PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8651. Probiotics and their implications for Belgian public health**

Superior Health Council, 2012

<http://health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19097086.pdf>

# Appendix I

## **The use of substances with nutritional or physiological effect other than vitamins and minerals in food supplements study undertaken for DG SANCO, the European Commission**

Service contract nr SANCO/2006/E4/018

European Advisory Services (EAS)

28 March 2007

[http://ec.europa.eu/food/food/labellingnutrition/supplements/documents/2007\\_A540169\\_study\\_other\\_substances.pdf](http://ec.europa.eu/food/food/labellingnutrition/supplements/documents/2007_A540169_study_other_substances.pdf)

### **EXECUTIVE SUMMARY**

With the implementation of Directive 2002/46/EC, food supplements have been harmonised at the EU level with common rules concerning certain aspects of vitamins and minerals. In view of further harmonisation, article 4.8 of this Directive foresees that the European Commission presents a report to the European Parliament and to the Council on the advisability of establishing specific rules for the use of substances with a nutritional or physiological effect other than vitamins and minerals in food supplements. In order to better understand the potential need for harmonisation of other substances in food supplements, it was considered necessary to analyse the market for such products, the national regulatory and non-regulatory approaches, and the interaction between these other substances and existing EU legislation. By way of comparison, the regulatory and non-regulatory approaches in countries outside Europe were also reviewed.

### **OTHER SUBSTANCES USED IN FOOD SUPPLEMENTS IN THE EU**

This study takes as a starting point the categorisation and characterisation of substances other than vitamins and minerals. Six categories were identified and 31 substances were chosen in order to review other substances with a nutritional or physiological effect in food supplements on the EU market. The different categories are:

- *amino acids*
- *enzymes*
- *pre- and probiotics*
- *essential fatty acids*
- *botanicals and botanical extracts*
- *miscellaneous bioactive substances*

The substances in each category were chosen based on their significance in the EU food supplement market and/or the extent to which they could illustrate effectively the different regulatory approaches taken by the Member States. Market data from the data collection and analysis company Euromonitor International is used to illustrate the total size of the EU food supplement market and its segments: 50% for vitamin and mineral products, 43% for

supplements containing other substances, and 7% for tonics and bottled nutritive drinks. Growth projections to 2010 provide an indication of the extent to which previous rapid growth cannot be taken as an indicator of future rapid growth with a significant slowdown expected in a number of countries, but the new Member States continuing to record the fastest growth rates. A breakdown of the EU market analyses the most commercially important other substances and variations across the EU region. The regulatory and non-regulatory approaches for botanicals and other bioactive substances in 27 EU Member States are presented based on a questionnaire sent to the Member States, and EAS analysis and experience in reviewing substances and products across the EU. Country overviews include information on positive/negative lists of botanicals and other bioactive substances. Based on the questionnaire completed by the authorities in 26 of the 27 Member States, a review of the regulatory status of a representative sample of substances is provided. This shows that the majority of substances fall within the categories 1-4 below and a minority require either authorisation or are regarded as medicinal substances, falling under categories 5-6 below:

*1. Permitted for use in food supplements either under national law or internal guidelines.*

*2. Permitted for use in food supplements - maximum level established.*

*3. Permitted for use in food supplements under specific conditions.*

*4. Permission may be given on a case by case basis following evaluation.*

*5. Not currently permitted. May be permitted following authorisation.*

*6. Not permitted for use in food supplements, or regarded as medicinal.*

The review of the regulatory status on the use of certain other substances in food supplements and a comparison of the national approaches illustrate the substantial differences across the Member States.

### **BORDERLINE ISSUES AND EUROPEAN COURT JUDGEMENTS**

Despite the overall positive approach of Member States towards mutual recognition, application of this principle appears to be problematic in a number of countries in respect of other substances sold in supplements. Mutual recognition applies to those aspects of food supplements that are not yet harmonised and prohibits quantitative restrictions between Member States. Relevant ECJ cases to mutual recognition issues are highlighted.

Of importance to food supplements is the interpretation of the medicines definition which has very often been the subject of ECJ cases. Several borderline issues have been reported and are seen differently across the Member States.

### **RELEVANT DEVELOPMENTS OF OTHER ORGANISATIONS AND INSTITUTIONS**

The requirements for further legislative work in the field of other substances are considered through reference to the activities of EMEA (European Agency for the Evaluation of Medicinal Products), HMPC (Herbal Medicinal Product Committee), EFSA's (European Food Safety Authority) work on the safety of botanicals, the Council of Europe's Ad Hoc Group on Food Supplements and ILSI's (International Life Sciences Institute) report on the guidance for the safety assessment of botanicals. Additionally, the revision of the novel foods legislation may have an important effect on food supplements, especially when it concerns botanical extracts and isolates.

### **REGULATORY MODELS OUTSIDE THE EU**

Work has also been carried out on the regulatory models that exist outside the EU, and this indicates the existence of approaches as diverse as those present in the EU. Models were reviewed for Australia, Canada, China, Japan and the United States. In Australia, all food supplements fall within the category of '*complementary medicines*' which are evaluated according to their level of risk, and include vitamin, mineral, herbal, aromatherapy and homeopathic products. A positive list of substances that may be used in supplements has been established. Food supplements in Canada are regarded as "Natural Health Products" and may contain a wide range of substances. All products must be registered. A list of acceptable non-medicinal substances that are generally considered to be of minimal toxicological concern is included in the Canadian Natural Health Products Regulations. The State Food and Drug Administration in China regulates supplements as '*health foods*' and maintains positive and negative lists of substances that may be used in health foods/food supplements. In Japan, food supplements containing a broad range of substances are widely sold. Lists clarify which substances are not restricted to medicinal use and can therefore be used in food supplements. In the United States, a wide range of substances is encompassed by the definition of a dietary supplement in the Dietary Supplement Health Education Act.

#### **INTERACTION WITH OTHER EU LEGISLATIVE FRAMEWORKS**

The interaction with other EU legislative frameworks is examined and legal provisions applicable to food supplements are reviewed. Current EU food legislation applies to all food supplement products. Examples of applicable legislation include the general food law requiring safety substantiation and defining traceability rules, and the future list of health claims in the Regulation on nutrition and health claims other than those referring to the reduction of disease risk, and to children's development. Some of these measures can already be seen as providing a level of indirect harmonisation on the use of other substances in food supplements. Provisions set by other legislative frameworks should also be taken into consideration to avoid overlaps and contradictions, for example when it concerns novel foods, or substances already approved for food additive use.

# Appendix II

## **Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the evaluation of allergenic foods for labelling purposes**

The European Food Safety Authority

The EFSA Journal (2004) 32, 1-197

<http://www.efsa.europa.eu/en/efsajournal/doc/32.pdf>

### **SUMMARY**

Amongst adverse reactions to food there are immune-mediated and non-immune mediated reactions. Food allergies comprise immune-mediated reactions to foods mediated either by IgE antibodies or other immunological pathways. Food intolerance comprises non-immunemediated responses that are dependent on enzyme deficiencies, pharmacological reactions, or, as is true in the majority of cases, unknown mechanisms.

EU legislation has recently been modified regarding food labelling in order to ensure derogations to the obligatory declaration of food ingredients are not applicable to those ingredients which may induce food allergies and/or food intolerances (Annex IIIa of Directive 2003/89/EC1). This pertains to cereals containing gluten, crustaceans, eggs, fish, peanuts, soybeans, milk and dairy products including lactose, nuts, sesame seeds, celery, mustard, and sulphite at concentration of 10 mg/kg and above.

In view of the recent scientific developments in this field and the earlier opinion of the Scientific Committee on Food (SCF) on "Adverse reactions to foods and food ingredients" expressed in 1995, the European Food Safety Authority is asked to advise the Commission on: 1) The scientific basis supporting the identification of foods, food components and food ingredients which induce food allergies and food intolerance for foodstuffs labelling purposes; and 2) The possibility of determining thresholds or of identifying other elements (including food processing) which would establish that a food component or a food ingredient is no longer susceptible of inducing adverse reactions.

In general terms, it can be stated that all allergens and products thereof mentioned in the list can cause adverse health effects, and in some cases exposure to these can be fatal. These are the most common food allergens which are generally resistant to food processing and they have the capacity to trigger an allergic reaction in an allergic consumer if they are added to foods. Some of these allergens are very widely distributed all throughout Europe, while others, such as mustard and celery, are more geographically restricted. This list should be kept under review in the light of changing food practices and emergence of new clinical observations and other kind of scientific information.

There is high variability in sensitivity between different sensitised individuals with respect to the dose of allergens required to trigger an adverse effect. In addition, for ethical reasons, highly sensitive individuals are often not tested in an appropriate way to establish thresholds. Hence, the information available is insufficient to draw firm conclusions regarding the highest dose that would not cause an adverse effect. Thus, a system of risk evaluation based on the assessment of no observed adverse effect levels (NOAEL) does not apply currently.

Processing can influence allergenicity of the foods, as does the food matrix in which the allergens are presented to the consumer. In addition, individuals who suffer from allergies to the same food may react to different components of that foodstuff. The data available do not indicate that food processing predictably influences allergenicity, and also the influence of the matrix cannot be predicted.

To minimise the risks to the consumer, analysis of foods for traces of potential food allergens is desirable. However, while sensitive test systems are coming into use and are commercially available for analysis of some allergens in foods, major problems remain with regard to factors such as: insufficient extraction, detection limits outside the range of clinical sensitivity, insufficient specificity due to cross-reaction and insufficient interlaboratory reproducibility.

The possibility that specific derivatives of the food allergens listed in Annex IIIa of the Directive are unlikely to trigger an allergic reaction needs to be evaluated on a case by case basis.

## **Summary assessment of allergenic foods included in Annex IIIa of Directive 2003/89/EC**

### ***Cereals with regard to coeliac disease***

Coeliac disease is an immunologically-based disease caused by gluten. The causal relationship between gluten and its "toxicity" in individuals genetically predisposed to develop coeliac disease is firmly established. Acid hydrolysis may destroy properties of gluten which elicit coeliac disease. However, partial hydrolysis and enzymatic degradation and heat treatment during food processing do not destroy coeliac-triggering peptide units. There are insufficient data to suggest a threshold dose of gluten tolerable for all coeliac patients. The current Codex Alimentarius limit for gluten-free foods of 200 mg gluten/kg food for coeliac patients requires reconsideration. Detection assays for gluten in foods are available.

### ***Cereals with regard to food allergy***

Cereals can cause food allergy. Allergy to cereals in the general population is not very frequent, as few cases are reported in relation to the widespread consumption; in children, however, wheat is a frequent cause of food allergy. Cereal allergens cross-react with pollen allergens. Since wheat is mostly consumed cooked or heat-treated, it is evident that its allergenicity normally survives thermal treatment. Some wheat allergens can be destroyed by heating, while others are thermostable. The lowest reported amount of wheat able to



provoke an allergic reaction is 500 mg. No immunochemical method to analyse foods for non-gluten cereal allergen has been reported.

### ***Fish and crustaceans***

Fish and crustaceans are common food allergens. All major fish allergens cross-react and no fish has been found to be safe in allergic patients. Food processing may affect the allergenicity, but is not a reliable method to reduce allergenicity. Doses of fish provoking an allergic reaction have been reported to be in the milligram range, and for shrimp as a member of crustaceans in the gram range. Threshold doses have not been established. Radioimmunoassays for detection of fish allergens have been described but have not been validated for detection of fish allergens in food. For crustaceans immunochemical detection methods are available but are not sufficiently sensitive to detect the lowest amount demonstrated to elicit an allergic reaction.

### ***Egg***

Egg proteins are frequent triggers of allergic reactions. There are possible clinical crossreactivities between hen eggs and eggs from other species. Heat denaturation and other food processing treatments do not reliably reduce the allergenicity. Doses reported to trigger allergic reactions in clinical studies range from microgram to low milligram levels of orally administered egg proteins. Assays to detect egg allergens in foods are available.

### ***Peanut***

Peanut is a common cause of food allergic reactions, and it is a member of the legume family. It cross-reacts with other members of the legume family, such as soy and lupin. It is the most common cause of reported fatal food-induced anaphylaxis. Peanuts are widely used as ingredients of food. Heat treatment may increase its allergenicity. Reactions can be triggered by doses in the microgram range. It is not possible to determine a reliable threshold dose. Sensitive detection methods for peanut allergens are commercially available but are not appropriate for detection of low levels in processed foods.

### ***Soy***

Soy is a food allergen and soy protein is widely used in processed foods. As a legume, soy may cross-react with other legumes, including peanuts. Cross-reaction with cows' milk allergens has been described. As for many food allergens, heat denaturation and enzymatic digestion of soy affect allergenicity and may reveal new allergenic epitopes. Levels for triggering adverse reaction in soy allergic individuals are variable and are in the low microgram range, although studies that address these questions have not been performed in a satisfactory way. Immunochemical and PCR detection methods for analysis of soy and soy allergens have been described, but seem to be inappropriate for detection in food.

### ***Milk***

Most cows' milk proteins are potential food allergens. Numerous milk allergens have been identified, and some remain active during food preparation and during digestion. Data available show that a substantial proportion of allergic individuals reacts to very low (in the range of micrograms) amounts of allergens, but are insufficient to establish validated threshold doses nor to derive a level of exposure which could protect allergic consumers against a reaction to milk products present in their food in trace amounts. These considerations may be applied to milk of species other than cows, such as buffalos, goats and ewes. Immunochemical detection methods for major milk allergens have been described but may not be appropriate for processed foods. Lactose intolerance is not an allergic or an immune-mediated disease, and does not provoke anaphylactic reactions. It results from a reduced capacity to digest lactose due to a reduced lactase activity in the small intestine. Doses less than 10 g (corresponding to 200 mL of milk) per day are often tolerated by most adults with reduced lactase levels. Residual amounts of cows' milk proteins that can still be present in lactose as contaminants from the production process of lactose might be harmful for milk allergic patients.

### ***Nuts***

Nuts are a common cause of allergic reactions. Multiple nut sensitivities are frequent and often associated with peanut allergies, but cross-reacting allergens have not been identified. Birch pollen sensitised individuals may react to hazelnut allergens. Roasting may reduce but not abolish hazelnut allergenicity. No such data are available for other nuts. A few micrograms may cause reactions in sensitised individuals, but threshold doses have not been established. Several assay systems to detect nut allergens in foods have been developed.

### ***Celery***

Celery is often found in prepacked food as it is widely used in the food industry because of its aromatic flavour. Allergic reactions occur predominantly to raw celery and less frequently to cooked celery, but allergenicity of celery powder is comparable to that of raw celery. Celery allergic patients may react to doses of allergen in the milligram range, but there are insufficient data to determine threshold levels. There is currently no detection assay available.

### ***Mustard***

The major allergens of mustard are resistant to heat and other food processing procedures. Allergen doses causing allergic reactions in mustard allergic patients can be in the high microgram range, although threshold doses have not been established. No specific detection method for mustard allergens has been described.

### ***Sesame seed***

Sesame seeds are widely, and increasingly, used in many processed foods. A few milligrams of sesame protein are able to cause allergic symptoms. Assays for detection of sesame allergens are available.

### ***Sulphites***

Sulphites are used as food additives and may cause severe reactions in sensitive individuals mostly in asthmatic patients. The pathogenesis of adverse reactions to sulphites has not been clearly documented but it is unlikely that sulphite reactions are allergic or immune-mediated or produce anaphylactic reactions. Most sulphite-sensitive individuals will react to ingested metabisulphite in quantities ranging from 20 to 50 mg of sulphites in the food. The smallest concentration of sulphites able to provoke a reaction in sensitive individuals has not been established. Labelling of foods containing sulphiting agents in concentrations of 10 mg/kg or more is required in the EU, though the threshold for sensitivity reactions may be even lower.