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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 vitamnier og mineraler kan kosttilskudd også inneholde «andre stoffer» som har en ernæringsmesig 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 kosttilskud 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 excisting 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.

	Substance	**CAS Number**
Fatty acids	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; 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
Amino acids and related substances	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

	Substance	CAS Number
	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
Substances in the body	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; 55128-59-1; 8002-43-5; 97281-47-5
	Phosphatidylinositol	97281-52-2
	Taurine	107-35-7
Plant substances	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-Caffeylquinic 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 *Citrus paradisi*)	10236-47-2
	Piperine (from *Piper nigrum)*	94-62-2
	Polyphenols (green coffee bean extract)	
	Polyphenols (cranberry and blueberry extracts)	
	Polyphenols (green tea extract)	
	Rosavin (*Rhodiola rosea* extract)	84954-92-7
	Zeaxanthin (E161h)	144-68-3
Fiber and prebiotics	Beta-glucan	9051-97-2; 9041-22-9
	Konjac glucomannan (E425)	37220-17-0
	Inulin	9005-80-5

	Substance	CAS Number
Enzymes	Amylase	9000-92-4
	Cellulase	9012-54-8
	Lactase	9031-11-2
	Lipase	9001-62-1
	Peptidase	9031-96-3
Others	Bee pollen	
	Colostrum	146897-68-9
	Propolis	9009-62-5
	Royal jelly	8031-67-2
Probiotics	*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	
	Streptococcus thermophilus	

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 Administartion. These assessments are included in the Select Committee on GRAS Substances (SCOGS) Database http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=&sortColumn=&rpt=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
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, 2013	The use as food supplement was assessed - 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
Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements (1)	AESAN, 2012	The use as fodd supplement was assessed - Alpha-linoleic 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. - EPA and DHA; a maximum amount of 3 g/day of the combination of EPA and DHA is acceptable.

Title	Prepared by, publication year	Information on safety and established use limits
OPINION of the French Food Safety Agency on the update of French population reference intakes (ANCs) for fatty acids	AFSSA, 2010	Docosahexaenoic acid and eicosapentaenoic acid; no risk identified.
Health risks and benefits of trans fatty acids in food - Recommendations	AFSSA, 2005	Information on safety and established use limits was not available in an abstract/summary. (The version in english starts at page 201)
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, 2011	Information on safety and established use limits was not available in an abstract/summary.
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, 2011	Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).
Höhe der derzeitigen *trans*-Fettsäureaufnahme in Deutschland ist gesundheitlich unbedenklich	BfR, 2013	Information on safety and established use limits was not available in an abstract/summary.
BfR recommends the setting of maximum levels for the fortification of foods with omega-3 fatty acids	BfR, 2009	Information on safety and established use limits was not available in an abstract/summary.
Müssen Fischverzehrer ihre Ernährung durch Fischöl-Kapseln ergänzen?	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
Scientific Opinion on the extension of use for DHA and EPA-rich algal oil from Schizochytrium sp. as a Novel Food ingredient	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.
Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA)	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.
SCIENTIFIC OPINION. Statement on the safety of the "conjugated linoleic acid (CLA)-rich oils" Clarinol® and Tonalin® TG 80 as Novel Food ingredients	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 3and 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.
Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol	EFSA, 2010	- Total fat; there are not sufficient data to define a Lower Threshold Intake (LTI) or Tolerable Upper Intake Level (UL) for total fat. - 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. - Alpha-linoleic acid; the Panel proposes not to set a Tolerable Upper Intake Level for alpha-linolenic acid.

Title	Prepared by, publication year	Information on safety and established use limits
Scientific Opinion on the safety of "conjugated linoleic acid (CLA)-rich oil" (Clarinol®) as a Novel Food ingredient	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.
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, 2004	Information on safety and established use limits was not available in an abstract/summary.
Baltic herring as nutrition; risk-benefit analysis	Finnish food safety authority Evira, ongoing project	DHA and EPA; includes docosahexaenoic acid and eicosapentaenoic acid.
Linoleic acid	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.
Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids	IOM, 2005	- 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. - n-6 polyunsaturated fatty acids; there is insufficient evidence to set a UL for n-6 polyunsaturated fatty acids. - n-3 fatty acids; there is insufficient evidence to set a UL for n-3 fatty acids.

Title	Prepared by, publication year	Information on safety and established use limits
Update on trans fatty acids and health	SACN, 2007	Information on safety and established use limits was not available in an abstract/summary.
Evaluation of negative and positive health effects of n-3 fatty acids as constituents of food supplements and fortified foods	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

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

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

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

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

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

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
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, 2013	The use as a food supplement was assessed - L-histidine; a maximum daily quantity of 1.12 g of L-histidine is acceptable. - L-glutamine; a maximum daily quantity of 5 g of L-glutamine is acceptable.

Title	Prepared by, publication year	Information on safety and established use limits
Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements (1)	AESAN, 2012	The use as a food supplement was assessed - 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. - L-glutamic acid; a maximum amount of 1 g/day is acceptable. - Beta-alanine; high doses of beta-alanine may produce paresthesia. - L-arginine; an OSL of 20 g/day for supplementation with L-arginine has been established. - 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; - 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. - L-histidine; a maximum daily amount of 750 mg of L-histidine is of the order of the requirement established by the WHO. - L-isoleucine; there is a high tolerance level to L-isoleucine. - L-leucine; it has not been possible to establish a NOAEL or LOAEL for the oral intake of L-leucine. - L-lysine; a maximum daily amount of 2,250 mg of L-lysine is acceptable. - L-methionine + L-cysteine; a maximum daily amount of 300 mg of Lcysteine is lower than the requirements of L-methionine + L-cysteine established by the WHO. - L-tyrosine + L-phenylalanine; a maximum daily amount of 1,900 mg for the sum of L-tyrosine and L-phenylalanine is acceptable. - L-threonine; a maximum daily amount of 1,150 mg is in line with the L-threonine requirement established by the WHO. - L-tryptophan (obtained by protein hydrolysis); a maximum daily amount of 300 mg of L-tryptophan is acceptable. - L-valine; a maximum amount of 1,950 mg/day of L-valine is acceptable.

Title	Prepared by, publication year	Information on safety and established use limits
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, 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
Apport en protéines : consommation, qualité, besoins et recommandations **Protein intake: dietary intake, quality, requirements and recommendations**	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 highorvery high, are proposed.
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, 2011	Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).
COT Statement on Tryptophan and the Eosinophilia-Myalgia Syndrome	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.
Scientific Opinion on Dietary Reference Values for protein	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
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, 2008	Glycine, L-lysine, L-arginine, L-cysteine, cysteine; LD_{50} values derived from acute toxicity studies (Annex IV). 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). L-lysine monohydrate, L-cysteine; NOAEL values derived from developmental and reproductive toxicity studies. 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; *in vitro* genotoxicity studies (Annex IV).
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, 2006	Information on safety and established use limits was not available in an abstract/summary.
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, 2003	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
L-glutamic acid	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.
Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids	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.
Risk assessment of histidine, methionine, S-adenosylmethionine and tryptophan	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.
Risikogruppering av aminosyrer	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

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 appved 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

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

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
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, 2013	The use as a food supplement was assessed. 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
Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements (1)	AESAN, 2012	The use as a food supplement was assessed - 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 - Taurine; a maximum daily amount of 1,000 mg of taurine is acceptable. - 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. - Choline; a maximum amount of 1,500 mg/day of choline is acceptable. - Creatine monohydrate; a maximum amount of 3,000 mg/day of creatine monohydrate is acceptable. - Inositol (hexaphosphate); a maximum amount of 2,000 mg/day of inositol (hexaphosphate) is acceptable.
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, 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
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, 2003	Includes taurine and D-glucuronolactone
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, 2001	Information on safety and established use limits was not available in an abstract/summary.
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"		
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, 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
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	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.
The use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks	EFSA, 2009	- 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. - 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.
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, 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
Inositol **Choline chloride and choline bitartrate** **Lecithin**	FDA; The Select Committee on GRAS Substances (SCOGS) Database, 1975 and 1979	- Inositiol; (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. - 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. - 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. - 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.
Dietary Reference Intakes: Vitamins	IOM, 1998	Choline; UL for adults (19 and older) is 3.5 mg/day. UL for other life stage groups at http://www.iom.edu/~/media/Files/Activity%20Files/Nutrition/DRIs/DRI_Vitamins.pdf
Opinion of the Scientific Committee on Food on Additional information on "energy" drinks	SCF, 2003	Glucuronolactone; Further studies would be required to establish upper safe levels for daily intake 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
Opinion on Caffeine, Taurine and D-Glucurono - g -Lactone as constituents of so-called "energy" drinks (expressed on 21 January 1999)	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
Assessment of creatine in sports products	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.
New information on ingredients in so-called "energy drinks"	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.
Risikovurdering av "energidrikker" med koffein, taurin, glukuronolakton, inositol og vitaminer	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.
Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO FOOD ADDITIVES SERIES NO. 5	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

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

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-γ-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/DRIs/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

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

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 paradis*), 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 paradis*), 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

Title	Prepared by, publication year	Information on safety and established use limits
Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements (1)	AESAN, 2012	The use as a food supplement was assessed. - 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. - Lycopene; a maximum amount of 15 mg/day of lycopene is acceptable from the safety point of view for use as a food supplement. - All trans lutein/zeaxanthin; although there are other sources for obtaining lutein, to date safety studies have been carried out with *trans* lutein associated to *trans* zeaxanthin from *Tagetes erecta*, 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 *trans* lutein, associated with *trans* 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.

Title	Prepared by, publication year	Information on safety and established use limits
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, 2006	Information on safety and established use limits was not available in an abstract/summary.
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, 2005	Information on safety and established use limits was not available in an abstract/summary.
Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation - Recommandations	AFSSA, 2005	Information on safety and established use limits was not available in an abstract/summary.
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, 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
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, 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 isoflavonerich soy extract and vitamin C.
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, 2013	Includes caffeine, taurine and glucuronolactone
AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail	ANSES, 2012	Includes lutein
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, 2011	Includes green tea

Title	Prepared by, publication year	Information on safety and established use limits
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, 2011	Includes a list of substances that have been the subject of AFSSA Opinions (Annex 1).
Risikobewertung von Pflanzen und pflanzlichen Zubereitungen	BfR, 2013	Includes Rhodiola rosea (L.) SCOP. (Rosenwurz)
Gesundheitliche Bewertung von synephrin- und koffeinhaltigen Sportlerpro-dukten und Schlankheitsmitteln	BfR, 2013	Information on safety and established use limits was not available in an abstract/summary.
Isolated isoflavones are not without risk	BfR, 2007	Information on safety and established use limits was not available in an abstract/summary.
Säuglingsnahrung aus Sojaeiweiß ist kein Ersatz für Kuhmilchprodukte	BfR, 2007	Information on safety and established use limits was not available in an abstract/summary.
Statement on the reproductive effects of caffeine	COT, 2008	Caffeine; no specific ADI set but risk of foetal growth retardation less than 2% at caffeine intakes ≤200 mg/day.
Scientific Opinion on the safety of astaxanthin-rich ingredients (AstaREAL A1010 and AstaREAL L10) as novel food ingredients	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.

Title	Prepared by, publication year	Information on safety and established use limits
Scientific Opinion on the re-evaluation of anthocyanins (E 163) as a food additive	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.
SCIENTIFIC OPINION Statement on the safety assessment of the exposure to lutein preparations based on new data on the use levels of lutein	EFSA, 2012	Lutein; the ADI of 1 mg/kg bw/day.
Statement on the safety of synthetic zeaxanthin as an ingredient in food supplements	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.
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, 2011	Lutein; The ANS Panel established an ADI of 1 mg/kg bw/day and noted that this ADI refers to lutein derived from *Tagetes erecta* containing at least 80% carotenoids.

Title	Prepared by, publication year	Information on safety and established use limits
Statement on the divergence between the risk assessment of lycopene by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA)	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
Scientific Opinion on the re-evaluation of lutein (E 161b) as a food additive	EFSA, 2010	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 Tagetes erecta and zeaxanthin. The SCF could not establish an ADI. 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 Tagetes erecta containing at least 80% carotenoids consisting of lutein and zeaxanthin (79 and 5% respectively).
Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive	EFSA, 2010	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. 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.

Title	Prepared by, publication year	Information on safety and established use limits
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, 2008	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.
Opinion of the safety of 'synthetic Zeaxanthin as an ingredient in food supplements'	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.
ESCO working group on isoflavones	ESCO, ongoing work	Information on safety and established use limits was not available in an abstract/summary.
Assessment report on Camellia sinensis (L.) Kuntze, non fermentatum folium	EMA, 2013	Information on safety and established use limits was not available in an abstract/summary.
Assessment report on *Rhodiola rosea* L., rhizoma et radix	EMA, 2012	Information on safety and established use limits was not available in an abstract/summary.
ASSESSMENT REPORT ON *CURCUMA LONGA* L. RHIZOMA	EMA, 2009	Information on safety and established use limits was not available in an abstract/summary.
PlantLIBRA: Plant food supplements. Levels of intake, benefit and risk assessment (EU –project, WP1)	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).
Exposure of Finnish consumers to food additives	Finnish Food Safety Authority Evira, ongoing project	Includes lutein, lycopene, and curcumin

Title	Prepared by, publication year	Information on safety and established use limits
Caffeine	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.
Risk assessment of caffeine among children and adolescents in the Nordic countries	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.
PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8736. Novel food ingredients: oils rich in conjugated linoleic acid in food	Superior Health Council, 2011	Information on safety and established use limits was not available in an abstract/summary.
New information on ingredients in so-called ”energy drinks”	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

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 zeoxanthin 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 Sportlerpro-dukten 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

5.14 Säuglingsnahrung aus Sojaeiweiß ist kein Ersatz für Kuhmilchprodukte

BfR (Bundesinstitut für Risikobewertung), 2013
http://www.bfr.bund.de/cm/343/saeuglingsnahrung_aus_sojaeiweiss_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 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

5.17 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

5.18 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

5.19 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

5.20 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

5.21 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

5.22 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

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

EFSA (European Food Safety Authority), 2010
The EEFSA 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

5.24 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

5.25 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

5.26 ESCO working group on isoflavones

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

5.27 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

5.28 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

5.29 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

5.30 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

5.31 Exposure of Finnish consumers to food additives

EVIRA (Finnish Food Safety Authority) ongoing project

5.32 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

5.33 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

5.34 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

5.35 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
Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements (1)	AESAN, 2012	The use as a food supplement was assessed. - Beta-glucan; a maximum daily amount of 4 g de beta-glucans is acceptable. - Konjac glucomannan; a maximum amount of 4 g/day is acceptable. - Inulin; a maximum amount of 9 g/day of inulin or the sum of inulin plus fructooligosaccharides (FOS) is acceptable.
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, 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
European Commission, Food science and techniques, Reports of the Scientific Committee for Food (forty-first series)	SCF, 1997	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."

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

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

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, cellulose, lactase, lipase, and peptidase.

Title	Prepared by, publication year	Information on safety and established use limits
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, 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

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
Einschätzung von Propolis und Gelée Royale	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

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

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

Title	Prepared by, publication year	Information on safety and established use limits
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	EFSA, 2014	
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	EFSA 2015	
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	EFSA, 2015	
PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8651. Probiotics and their implications for Belgian public health	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

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

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

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

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 Healh 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
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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 bservations 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. Thresholds 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.