Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2016: 59

Risk assessment of "other substances" – L-serine

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2016: 59
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Risk assessment of "other substances" - L-serine

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Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM). Per Ole Iversen (chair), Livar Frøyland, Margaretha Haugen, Sigrun Henjum, Kristin Holvik, Martinus Løvik, Bjørn S. Skålhegg, Tonje H. Stea, Tor A. Strand and Grethe S. Tell.

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

Acknowledgment

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Competence of VKM experts

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

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Summary

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

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

The present report is a risk assessment of specified doses of L-serine in food supplements, and it is based on previously published risk assessments and scientific papers retrieved from a comprehensive literature search.

L-serine is a non-essential amino acid which is produced endogenously and is supplied from the diet. In addition to its role in protein synthesis, L-serine has an important role as a major contributor to the one-carbon pool and is involved in the metabolism of several key compounds, including glycine, cysteine, taurine, and phospholipids and of D-serine.

According to information from NFSA, L-serine is an ingredient in food supplements sold in Norway. NSFA has requested a risk assessment of 50, 500, 1000, 1250, 1500 and 1750 mg/day of L-serine from food supplements. Most dietary proteins contain about 4-5% L-serine. Rich sources of proteins are meat, dairy products, legumes, fish, nuts, seeds, eggs and whole grains. Dietary intake of L-serine in Norway is not known, but results show an overall mean intake of L-serine from food and food supplements of 3.5 g/day in the United States (NHANES III, USA).

In the first phase of the present evaluation of "other substances", previous reports that have assessed the safety of L-serine supplementation in humans were identified. In the second phase, a systematic literature search was performed to retrieve scientific papers published before 11 May 2016 (human studies literature search) and before 28 July 2016 (animal studies literature search). Based on this search, we did not identify any long-term studies in healthy individuals that could be used for safety evaluations. On the other hand, three relevant animal studies were included in this report.

The animal studies revealed no adverse health effects as a result of the tested doses of L-serine (840-3000 mg/kg bw per day). For the risk characterisation of L-serine, in the absence of long-term studies in healthy individuals, VKM based the value of comparison on the no

observed adverse effect level (NOAEL), 3000 mg/kg bw per day which was the highest dose tested in a 90-days toxicological study in rats. This value was used to calculate the Margin of Exposure (MOE) values for daily intake of 50, 500, 1000, 1250, 1500 and 1750 mg L-serine in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). The MOE-values ranged from 74 to 4200, which were considered acceptable since L-serine is a nutrient that does not cause any well documented adverse effects and because studies indicate a high endogenous production (Snell, 1986) and a high dietary intake of L-serine (NHANES III, USA) compared to the doses considered in the present risk assessment.

Thus, VKM concludes that:

- In adults (≥18 years), the specified doses 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements are unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements are unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 50, 500, 1000, 1500 and 1800 mg/day L-serine in food supplements are unlikely to cause adverse health effects.

Children younger than 10 years were not within the scope of the present risk assessment.

Short summary

At the request of the Norwegian Food Safety Authority, the Norwegian Scientific Committee for Food Safety (VKM) has characterised the risk of daily doses of 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements. In the absence of long-term studies in healthy individuals, VKM used a NOAEL of 3000 mg/kg bw per day from a 90-days toxicological study in rodents.

- In adults (≥18 years), the specified doses 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements are unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements are unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 50, 500, 1000, 1500 and 1800 mg/day L-serine in food supplements are unlikely to cause adverse health effects.

Key words: Serine, food supplement, adverse health effect, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, VKM.

Sammendrag på norsk

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

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

I denne rapporten har VKM vurdert helserisiko ved L-serin som kosttilskudd. Vurderingen er basert på tidligere publiserte risikovurderinger av aminosyren og vitenskapelige artikler som er identifisert gjennom et omfattende systematisk litteratursøk.

For mennesker er L-serin en ikke-essensiell aminosyre som produseres endogent og inntas gjennom kosten. I tillegg til å bidra i proteinsyntesen, har L-serin en avgjørende rolle i en-karbonmetabolismen og inngår i metabolismen av flere næringsstoffer, blant annet glysin, cystein, taurin, fosfolipider og D-serin.

Ifølge informasjon fra Mattilsynet er L-serin en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere følgende doser av L-serin i kosttilskudd: 50, 500, 1250, 1000, 1500 og 1750 mg/dag. Rike proteinkilder er kjøtt, meieriprodukter, belgfrukter, fisk, nøtter, frø, egg og fullkornsprodukter og protein fra kosten inneholder omtrent 4-5 % L-serin. Inntaket av L-serin i norsk kosthold er ikke kjent, men gjennomsnittlig inntak av L-serin fra kosten i USA i alle aldersgrupper, inkludert både kvinner og menn, er 3.5 g/dag (NHANES III, USA).

I første fase av denne evalueringen av "andre stoffer" ble tidligere rapporter som har risikovurdert tilskudd med L-serin hos mennesker identifisert. I andre fase ble det gjennomført et systematisk litteratursøk hvor vitenskapelige artikler publisert før 11. mai 2016 (humanstudier) og før 28. juli 2016 (dyrestudier) ble kartlagt. Resultatet fra litteratursøket viste ingen langtidsstudier blant friske individer som var egnet som grunnlag for risikovurderingen av L-serin. Tre relevante dyrestudier ble imidlertid identifisert og er inkludert i denne rappporten.

Resultatene fra dyrestudiene viste ingen negative helseeffekter for noen av dosene med L-serin som ble testet (840-3000 mg/kg kroppsvekt per dag). I mangel på langtidsstudier blant friske individer har VKM derfor basert risikovurdering av L-serin på den høyeste testet dose (NOAEL (no observed adverse effect level), 3000 mg/kg kroppsvekt per dag) i en 90-dagers toksikologisk studie blant rotter. Denne verdien ble videre brukt som grunnlag for å beregne Margin of Exposure- (MOE) -verdier ved et daglig inntak av 50, 500, 1000, 1250, 1500 and

1750 mg L-serin blant barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år). MOE-verdiene varierte fra 74 til 4200, hvilket i dette tilfellet ble ansett som akseptabelt ettersom L-serin er et næringsstoff som ikke er forbundet med kjente negative helseeffekter. I tillegg viser en amerikansk studie et relativt høyt inntak av L-serin fra kosten (NHANES III, USA) og en eksperiementell studie indikerer høy endogen produksjon av L-serin (Snell, 1986).

VKM konkluderer derfor som følger:

- For voksne (≥18 år) er det usannsynlig at de spesifiserte dosene på 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskud vil forårsake negative helseeffekter.
- For ungdom (14 til <18 år) er det usannsynlig at de spesifiserte dosene på 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskud vil forårsake negative helseeffekter.
- For barn (10 til <14 år) er det usannsynlig at de spesifiserte dosene på 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskud vil forårsake negative helseeffekter.

Barn under 10 år inngår ikke i dette oppdraget.

Kort sammendrag

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag for Mattilsynet vurdert risiko ved daglig inntak av 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskudd. I mangel på langtidsstudier blant friske individer har VKM tatt utgangspunkt i en 90 dagers toksikologisk studie blant gnagere som resulterte i en NOAEL på 3000 mg/kg kroppsvekt.

VKM konkluderer derfor som følger:

- For voksne (≥18 år) er det usannsynlig at de spesifiserte dosene på 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskud vil forårsake negative helseeffekter.
- For ungdom (14 til <18 år) er det usannsynlig at de spesifiserte dosene på 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskud vil forårsake negative helseeffekter.
- For barn (10 til <14 år) er det usannsynlig at de spesifiserte dosene på 50, 500, 1000, 1250, 1500 and 1750 mg L-serin fra kosttilskud vil forårsake negative helseeffekter.

Abbreviations and glossary

Abbreviations

AESAN - Spanish Agency for Food Safety and Nutrition
ASC - alanine/serine/ cysteine
ASCT1 - alanine/serine/cysteine transporter 1 / SLC1A4
ATA2 - alanine/serine/cysteine transporter 1 / SLC1A4
BAT (rBAT) - brown adipose tissue (recruitable BAT)
bw - body weight
EFSA - European Food Safety Authority
IOM - Institute of Medicine, USA
LAT2 - L-type amino acid transporter 2
MOE - Margin of exposure
NAS - N-acetyl serine
NFSA - Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NOAEL - no observed adverse effect level
OECD - Organisation for Economic Co-operation and Development
PepT1 and 2 - hydrogen ion/peptide cotransporter 1 and 2
PGDH - phosphoglycerate-dehydrogenase
PS - phosphatidyl serine
UL - tolerable upper intake level
VKM - Norwegian Scientific Committee for Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet]
WHO - World Health Organization

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (European Regulation (EC) No. 1925/2006, Article 2; http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1925&from=en).

"Negative health effect" and "adverse health effect" are broad terms. The World Health Organization (WHO) has established the following definition of "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

An adverse event is considered serious if it results in death, is life-threatening, requires or prolongs hospitalisation, is a congenital anomaly or birth defect, is a persistent or significant disability/incapacity, or is another serious or important medical event.

Background as provided by the Norwegian Food Safety Authority

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

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

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

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

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of L-serine in food supplements at the following doses: 50, 500, 1000, 1250, 1500 and 1750 mg/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance with the guidance document developed in Phase 2) for the specified doses (Phase 3).

The safety assessments for "other substances" present in food supplements shall be carried out for the general population, age 10 years and older.

1 Introduction

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

This risk assessment concerns the substance L-serine per se, and no specific products.

In this series of risk assessments of "other substances" the VKM has not evaluated any claimed beneficial effects from these substances, but merely possible adverse effects at specified doses found on the Norwegian market.

According to information from the Norwegian Food Safety Authority (NFSA), L-serine is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of an intake of 50, 500, 1000, 1250, 1500 and 1750 mg L-serine per day from food supplements. The total serine exposure from other sources than food supplements is not included in the risk assessment. According to NHANES III (1988-1994), the overall mean intake of L-serine from food and food supplements in the United States was 3.5 g/day, while men 31 through 50 years of age had the highest intakes at the 99th percentile of 7.9 g/day (NHANES III, USA). Information on habitual dietary intake of L-serine in Norway is not available.

L-serine is characterised as a non-essential amino acid and is available from a wide range of protein-rich foods in the diet. Most dietary proteins contain about 4-5% L-serine (Kohlmeier, 2015). In addition to being derived from diet, L-serine is produced endogenously, and the *de novo* biosynthetic pathway has been identified as the major source of L-serine (van der Crabben et al., 2013). Content of serine in a 70 kg man is about 300-400 g (Bikker et al., 1994).There is a lack of studies reporting the *in vivo* significance of its biosynthesis, but a study in rodents have estimated the *de novo* synthesis of L-serine to be ~370 mg/100 g bw per day (Snell, 1986).

2 Hazard identification and characterisation

2.1 Literature

This present risk assessment is based on previous risk assessments of L-serine, as well as scientific papers retrieved from a systematic search in literature published before 11 May 2016 (human studies literature search) and before 28 July 2016 (animal studies literature search). The literature searches aimed at retrieving human and animal studies on adverse effects caused by L-serine.

2.1.1 Previous risk assessments

Risks related to L-serine have previously been evaluated by the Institute of Medicine (IOM), USA, 2005; the Norwegian Scientific Committee for Food Safety (VKM), Norway, 2011; and the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (ASEAN), Spain, 2015.

Of the reports mentioned above, the literature searches underlying these reports have only been described in the report from VKM (2011).

Table 2.1.1-1: Overview of previous risk assessments of L-serine

Risk assessment body, country, publication year	Objective	Conclusion	Suggested doses
IOM, USA, 2005	To establish dietary reference intakes and identify potential adverse effects of L-serine and other nutrients	Data were not available for dose-response assessment and derivation of a UL for L-serine in apparently healthy humans	Not established
VKM, Norway, 2011	To qualitatively rank 30 amino acids according to high, moderate or low risk	L-serine was grouped "moderate risk"	Not established
ASEAN, Spain, 2015	To assess the use of L-serine as a food supplement	A maximum daily quantity of 200 mg of L-serine is acceptable from the safety point of view for use as a food supplement	Acceptable dose: 200 mg/day

Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids from Institute of Medicine (IOM). USA, 2005

According to the IOM (2005), there were no studies in humans that would permit an evaluation of possible adverse effects of L-serine and animal studies pertaining to the toxicity of supplemental serine are limited. Concerning human data, one study is cited. In four healthy adults given a single oral dose of 15 g of serine, no adverse effects were reported (Pepplinkhuizen et al., 1980). Further, IOM (2005) states that there are no studies in humans that would permit an evaluation of the possible adverse effects of repeated administration, thus the safety of repeated dose oral administration of supplemental serine cannot be assessed. Concerning animal data, the report cited a study by (Artom et al., 1945) in which rats were given 100 mg/day of L-serine via stomach tube for 14 days. In this study, there was a decrease in food consumption but no other effects were noted. In addition, the IOM (2005) refers to other studies (Morehead et al., 1945; Wachstein, 1947) which have shown that supplemental L-serine at levels as low as 10 mg/day resulted in decreased appetite, increased mortality, and renal necrosis in rats.

IOM (2005) concludes that data on the adverse effects of L-serine intake from supplements were not available for a dose-response assessment and derivation of a UL in apparently healthy humans.

VKM report on risk categorisation of amino acids. Norway, 2011

In 2011, VKM conducted a risk categorisation of about 30 amino acids and amino acid compounds based on potential health risks related to high intakes of the amino acids (VKM, 2011). It was emphasised that the report had several limitations and could only be regarded as an initial screening and not as risk assessment of the many amino acids. The task was to qualitatively rank 30 amino acids according to high, moderate or low risk for adverse health effects. In this report, L-serine was grouped among the amino acids possessing a moderate potential risk for adverce health effects. Due to lack of scientific evidence, this categorisation was merely based on the general knowledge of amino acids as potent bioactive compounds.

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. Spain, 2015

To provide scientific evidence for authorisation of certain nutrients in the manufacture of food supplements, AESAN (2015) conducted a safety assessment of 15 substances in 2015.

In line with IOM (2005), this report referred to a study of Pepplinkhuizen et al. (1980) which showed no adverse effects after providing a single oral dose of 15 g serine (200 mg/kg bw of serine) to four healthy adults. The AESAN report also referred to a study among pregnant women diagnosed with a deficiency of the 3-phosphoglycerate-dehydrogenase (3-PGDH)

enzyme in the foetus (de Koning et al., 2003). 3-PGDH deficiency is an L-serine biosynthesis disorder, characterised by congenital microcephaly, severe psychomotor retardation, and intractable seizures. In this latter mentioned study, no adverse effects were observed in the women, the foetus or the newborn child after receiving treatment with 190 mg/kg bw of serine 3 times per day for the last 20 weeks of pregnancy.

Further, the AESAN report evaluated the safety of phosphatidylserine (PS), where two studies concluded that the observed safe level of PS as a food supplement would be up to doses of 200 mg, three times a day (Jorissen et al., 2001; Jorissen et al., 2002). Other studies have indicated that the consumption of PS at doses of 300 mg PS per day for 15 weeks did not produce any adverse effects (Vakhapova et al., 2011).

In addition, this report referred to animal studies (rats), examining the safety level of L-serine, the acetylated derivative of L-serine (NAS) and phosphatidylserine. Kaneko et al. (2009) reported no adverse effects after male and female rats were orally exposed to 500, 1500 and 3000 mg L-serine/kg bw per day, and concluded that a NOAEL could be established at 3000 mg/kg bw per day. Further, van de Mortel et al. (2010) assessed the acute oral toxicity of 2000 mg/kg bw of NAS, without observing any adverse effects. In addition, the latter mentioned study assessed the subchronic oral toxicity for doses of NAS, over 28 days, of 100, 500 and 1000 mg/kg bw per day. In this part of the study, the authors observed a NOAEL for systemic toxicity of 839.7 mg/kg bw and of 893.6 mg/kg bw for males and females, respectively. A study by Lifshitz et al. (2015) assessed the toxicity in rats orally exposed to 1100, 2200 and 3400 mg/kg bw per day of fish phospholipids (49% PS) for 90 days. Doses of 1100 and 2200 mg/kg bw per day did not cause adverse effects, however, the highest dose (3400 mg/kg bw per day equivalent to 1666 mg/kg bw per day of PS), caused histopathological changes, classified as minimal-mild and female rats also displayed focal miniralisation. The results generated in this study resulted in a NOAEL of 2100 mg/kg/day, equivalent to 1029 mg/kg bw per day of PS. Based on these studies, the AESAN report concluded that a maximum daily quantity of 200 mg of L-serine is acceptable for use as a food supplement from the safety point of view.

2.1.2 Literature search

A literature search was performed in MEDLINE and EMBASE in order to retrieve publications on adverse effects caused by L-serine. Both databases were searched to ensure comprehensive study retrieval. The human studies literature search was conducted 11 May 2016. Studies on experimental animals were identified in a separate search in the same databases 28 July 2016.

The strategies for the searches are outlined in Appendix 1.

2.1.2.1 Publication selection and data extraction

The literature search for human studies identified 1558 articles, whereas the search for animal studies identified 1424 articles. In the primary screening, titles and abstracts of all unique publications retrieved were independently screened against the inclusion criteria.

Inclusion criteria:

- An adverse effect/adverse effects in relation to L-serine alone is addressed
- Route of exposure for humans is oral
- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetics are similar to oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of L-serine
- No co-administration of other substances that potentially might mimic or confound an effect of L-serine
- Animal model studies were included if they reported results from chronic or sub-chronic toxicity or feeding studies and addressed adverse effects relevant to human health

In vitro studies were not included, but were in some cases read in order to provide background information regarding potential toxic properties of L-serine.

Studies focusing on various metabolites derived from L-serine, including acetyl-serine, phosphatidylserine were excluded.

Papers in languages other than English, Norwegian, Danish or Swedish were excluded.

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

The papers that passed the primary screening were reviewed in full text against the same inclusion criteria by the author of this report. The search for human studies resulted in 1 full text article reporting effect of a single oral dose of serine. No long-term human studies were found relevant for safety evaluations of L-serine.The search for relevant animal studies resulted in three full text articles. All three articles are included in the results of this report (Figure 2.1.2.1-1).

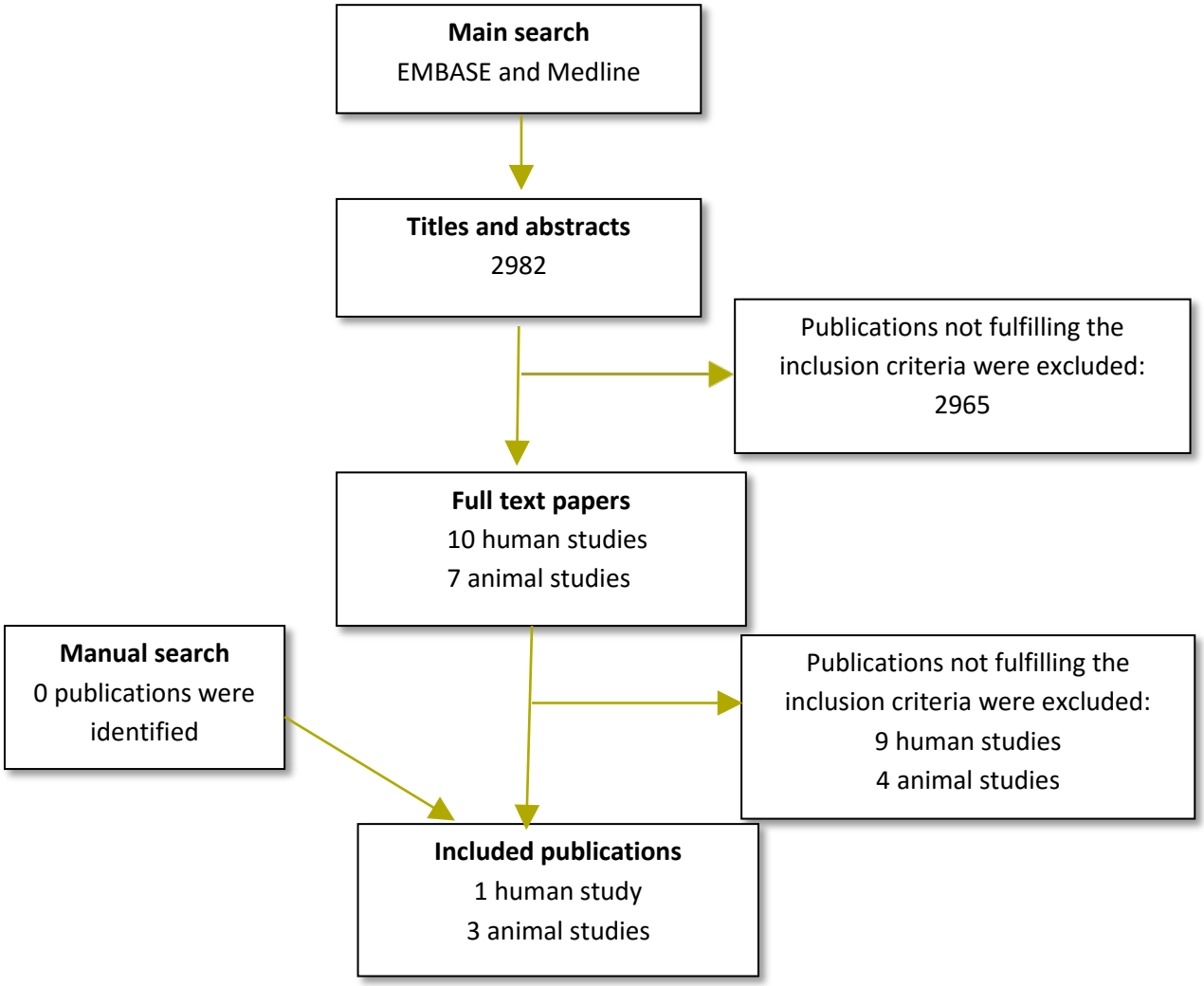

Figure 2.1.2.1-1: Flowchart for publication selection for L-serine.

2.2 General information

2.2.1 Chemistry

L-serine ((S)-2-amino-3-hydroxypropanoic acid; L-Ser) [CAS No. 56-45-1] is a non-essential amino acid with a molecular weight of 105.09 g/mol and a chemical structure shown in Figure 2.2.1-1.

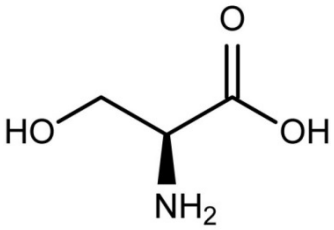

Figure 2.2.1-1: Structural formula of L-serine.

2.2.2 Occurrence

L-serine is released with the breakdown of proteins, and most dietary proteins contain about 4-5% L-serine. Moderately rich sources are eggs (7.4%), beans (5.5%), milk (5.4%), and rice (5.3%); chicken meat contains a slightly smaller percentage (3.4%) (Kohlmeier, 2015). L-serine is also available in food supplements, and adequate amounts are consumed when total protein intake meets recommendations (Kohlmeier, 2015). Heat treatment of foods, however, decreases the amount of bioavailable L-serine (Dworschak, 1980).

Allthough L-serine also is supplied from the diet and degradation of protein and phospholipids and also synthesised directly from glycine, the *de novo* biosynthetic pathway is the major source of serine (van der Crabben et al., 2013). Kohlmeier (2015) has described that L-serine synthesis does not depend on dietary intake so long as total protein consumption provides amino group for endogenous synthesis of L-serine. In a 70 kg male with moderate lipid stores body protein level is about 15% of which 3-4% is serine, i.e. 10.5 kg protein containing 300-400 g serine (Bikker et al., 1994).

2.3 Absorption, distribution, metabolism and excretion

2.3.1 Absorption and distribution

Various enzymes from the stomach, pancreas, and intestinal wall break down proteins containing L-serine, none of them with particular preference for L-serine residues (Kohlmeier, 2015). Various routes of absorption have been described: filtered di- and tripeptides containing L-serine are taken up from the lumen of the proximal tubulus via the hydrogen ion/peptide cotransporter 1 and 2 (PepT1 and PepT2). Rodent studies indicate that L-serine is taken up across the brush border membrane, a process mediated by sodium-amino acid cotransport system B^0, and the other half by transport system ASC (Avissar et al., 2001; Munck and Munck, 1999). The sodium-independent rBAT glycoprotein-anchored transporter $BAT1/b^{0,+}$ uses L-serine in most situations as a counter molecule in exchange for the transport of other neutral amino acid and usually effects net serine transport into lumen. After uptake, some of the L-serine is used for the enterocyte's own protein synthesis, and significant amounts are converted to glycine. L-serine export across the basolateral membrane uses mainly the sodium-amino acid cotransporter systems A (ATA2) and ASC (ASCT1). LAT2 can transport L-serine in either direction across the basolateral membrane in

exchange for another neutral amino acid. Depending on the difference between intracellular and interstitial concentration, a net export of L-serine can also be achieved.

The plasma concentration of L-serine (typically around 120 µmol/l) increases significantly after meals (Tsai and Huang, 1999). Uptake from the blood into tissues occurs via an array of transporters, many of them identical or similar to those described for intestinal absorption (Kohlmeier, 2015).

2.3.2 Metabolism, physiological function and excretion

In addition to being derived from the diet and protein and phospholipid turnover, L-serine is synthesised *de novo* from 3-phosphoglycerate, an intermediate in the glycolytic pathway, directly from glycine via the freely reversible serine hydroxymethyltransferase reaction and indirectly from hydroxyproline in the kidneys (Kohlmeier, 2015; Lowry et al., 1985; van der Crabben et al., 2013). Normally synthesised almost entirely in the liver, a limitation in the availability of dietary protein causes a marked induction of serine synthesis in the liver (Kalhan and Hanson, 2012). The amount of L-serine synthesised *de novo* is estimated to be ~370 mg/100 g bw per day in rat (Snell, 1986), and a review study report that the clinical phenotype and the therapeutic response to exogenous serine in serine deficiency syndromes, suggest that the *de novo* synthesis of serine is critical and that dietary serine is insufficient to meet the demands of whole body serine homeostasis (Tabatabaie et al., 2010).

The main function of L-serine is being a substrate for protein synthesis. Surplus serine will be oxidised yielding energy. Furthermore, the metabolic role of serine is underscored by its important role as a major contributor to the one-carbon pool; L-serine is a major source of methyl group donation in the one carbon metabolism that involves the folate and methionine cycle and is hence involved in the biosynthesis of choline, nucleotides and proteins as well as the maintenance of redox status (Anderson et al., 2012). Recent genetic and functional evidence suggests that hyperactivation of the serine-dependent one carbon pathway is a possible driver of oncogenesis and establishes links to cellular epigenetic status, such as genetic imprinting. Based on the number of clinically available agents that target one carbon metabolism, it has been suggested that targeting glycine-dependent one-carbon metabolism can be applied in precision cancer medicine (Locasale, 2013).

L-serine is also a precursor for the synthesis of a number of key compounds, including glycine, cysteine, taurine, and phospholipids and of D-serine; the latter plays a critical role as a neuromodulator in the brain (Kalhan and Hanson, 2012; Wolosker et al., 1999). In addition, L-serine participates indirectly in the biosynthesis of purines and pyrimidines by transferring a methylene group (C3-serine) to tetrahydrofolate.

Very little L-serine is lost via urine in healthy people and losses of L-serine via feces are negligible in humans with normal gastrointestinal function (Kohlmeier, 2015).

2.4 Toxicological data / adverse effects

2.4.1 Human studies

In the human studies search, no relevant long-term studies were identified in children, adolescents or adults.

A study by Pepplinkhuizen et al. (1980), cited in previous reports, investigated whether disturbance in the serine-glycine metabolism may have a key role in certain schizophreniform psychotic syndroms. This study evaluated possible effects of a single oral dose of 210 mg/kg serine given to four patients and four healthy control subjects. In patients, a serine induced psychosis occurred about 5 hours after ingestion of the amino acid and lasted 3-6 hours. None of the controls reacted to serine loading. The results, however, will not be used for safety evaluations in the present report due to limitations in the study design which only allowed investigation of possible acute effects of L-serine.

2.4.1.1 Interactions

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

2.4.1.2 Allergic sensitisation (including adjuvant effects)

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

2.4.2 Animal studies

Three relevant studies were identified from the animal studies literature search and included in the present report (Table 2.4.2-1).

Table 2.4.2-1: An overview of included animal studies investigating possible adverse health effects of L-serine.

Reference	Animals	Substance	Doses	Main endpoints[1]	Duration of exposure	Adverse effects	NOAEL[2] (mg/kg bw per day)
Tada et al. (2010)	Fisher 344 rats, 10/sex/group	L-serine	Powder diet containing 0, 0.06, 0.5, 1.5 and 5.0% L-serine	Urinalysis, hematology, serum biochemistry, organ weights, gross- and histopathological examination	90 days	None	M: 2765 F: 2905
Kaneko et al. (2009)	Sprague-Dawley rats, 10/sex/group	L-serine	Oral administration of 0, 500, 1500, and 3000 mg/kg bw per day	Urinalysis, hematology, serum biochemistry, organ weights, gross- and histopathological examination	13 weeks	None	M: 3000 F: 3000
van de Mortel et al. (2010) (Two sub-studies are included)	Sprague-Dawley rats 1. 5/sex/group 2. 10/sex/group	N-acetyl-L-serine (NAS) L-serine (control)	1. Oral administration of 2000 mg NAS kg bw per day and 2000 mg L-serine kg bw per day 2. Oral administration of 100, 500, and 1000 mg NAS/kg bw per day and 1000 mg L-serine/kg bw per day	Hematology, serum biochemistry, organ weights, gross and histopathological examination	1. acute dose 2. 28 days	None	M: 840 F: 894

[1] All endpoints are described and specified in more detail below.

[2] All values represent the highest dose tested.

A 90-day feeding toxicity study of L-serine in male and female Fischer 344 rats. Tada et al., 2010

The purpose of this study was to conduct a subchronical feeding study of L-serine with 10 male and 10 female Fischer 344 rats fed a powder diet containing 0, 0.06, 0.5, 1.5 or 5.0% concentrations of L-serine for 90 days (Tada et al., 2010). The powder used in this study was a purified 20% casein diet in order to exclude possible influence and interference due to the presence of other amino acids. This study was conducted in compliance with the guidelines of the Japanese Ministry of Health, Labour and Welfare; MHLW (Guidelines for designation of food additives and for revision of standards for use of food additives, MHLW, Japan).

There were no toxicological significant, treatment-related changes in body weight, food intake, water-intake or urinalysis data. In several of the hematology-, serum biochemistry- and organ weight parameters, significant changes were observed between some of the treated groups and the controls. All these changes, however, were subtle and lacked any corresponding pathological findings. In addition, the increased or decreased values remained within the range of the historical control values and the histopathological assessment revealed only sporadic and/or spontaneous lesions.

The authors of this study concluded that the NOAEL for L-serine was determined to be at least a dietary dose of 5.0%, i.e. 2765 mg/kg bw per day for male rats and 2905 mg/kg bw per day for female rats (highest dose tested).

A 13-week subchronic oral toxicity study of L-serine in rats. Kaneko et al., 2009

The purpose of this study was to conduct a subchronical oral toxicity study to evaluate the safety of L-serine in male and female Sprague-Dawley rats (Kaneko et al., 2009). The supplement was administred once daily by gavage in rats at dose levels of 0, 500, 1500, and 3000 mg/kg bw per day for 13 weeks. This study was conducted in compliance with the OECD guidelines.

Daily clinical signs, body weight, and food consumption were not affected by ingestion of the test article. There were no treatment-related adverse effects on urinalysis, hematology, serum biochemistry, organ weights, gross and histopathological examination.

The authors concluded that the NOAEL for L-serine was 3000 mg/kg bw per day for both animal sexes (highest dose tested).

Toxicology studies with N-acetyl-L-serine. Van de Mortel et al., 2010

The purpose of the two studies presented in this paper, was to assess the potential *in vitro* and *in vivo* mutagenicity and genotoxicity of N-acetyl-L-serine (NAS) and the acute and repeated dose oral toxicity of NAS in rodents (van de Mortel et al., 2010). The acute toxicity of NAS and L-serine was evaluated in Sprague Dawley rats (n=5/sex/group), which were administrated the negative control (deionized water), NAS (2000 mg/kg bw), or comparative control (L-serine; 2000 mg/kg bw) one time by oral gavage. The 28-day repeated dose dietary toxicity study was conducted with NAS and L-serine in Sprague Dawley rats (n=10/sex/group), which were assigned to one of five treatment groups: dietary control group, NAS at 100, 500, or 1000 mg/kg bw per day, or L-serine at 1000 mg/kg bw per day. NAS or L-serine was incorporated in rat chow. Both the acute dose study and the repeated dose study were conducted in compliance with the OECD guidelines.

The study evaluating oral acute toxicity of NAS and L-serine observed the animals for clinical signs of toxicity including mortality, signs of illness, injury, or abnormal behavior. In addition, feed consumption values were determined. All animals survived to scheduled sacrifice.

Thereafter, organs were removed and weighted and all animals were given a complete gross pathology examination.

In the repeated dose 28-day oral toxicity study, rats were observed for viability during the pre-exposure and exposure periods. In addition, a functional observation battery was conducted, motor activity, body weights and feed comsumption values were determined and ophthalmological examinations were performed before the first day of exposure and during the exposure period.

No mortality or evidence of adverse effects was observed in Sprague Dawley rats following acute oral administration at a dose of 2000 mg of NAS/kg bw. Similarly, no evidence of adverse effects was observed in Sprague Dawley rats following repeated dose dietary exposure (28-days) to targeted doses of 100, 500, or 1000 mg of NAS/kg bw per day. All rats survived until scheduled sacrifice and no biologically significant differences were observed in any of the response variables in the NAS exposure groups compared with untreated control groups.

Based on these results, the authors concluded that NAS does not represent a risk for mutagenicity or geno-toxicity, it is not acutely toxic, and the NOAEL for systemic toxicity from repeated dose dietary exposure to NAS was determined to be 840 and 894 of NAS/kg bw per day for male and female rats, respectively (highest dose tested).

2.4.3 Mode of action for adverse effects

No specific or definite mechanisms for adverse effects have been reported.

2.4.4 Vulnerable groups

No vulnerable groups to excess doses of L-serine have been reported. There have been no reported studies involving children, elderly, pregnant women or lactating women.

2.4.4.1 Interactions

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

2.4.4.2 Allergic sensitisation (including adjuvant effects)

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

2.5 Summary of hazard identification and characterisation

For the risk evaluation of specified doses of L-serine in food supplements, a literature search including both human and animal studies was conducted. Based on this search, we did not identify any long-term studies in healthy individuals that could be used for safety evaluations. Concerning human data, only one study from from 1980, which showed no adverse effects after providing a single oral dose of 15 g serine (200 mg/kg bw of serine) given to four healthy adults has been identified. The results from this study, however, will not be used for safety evaluations in the present report due to limitations in the study design which only allowed investigation of possible acute effects of L-serine.

On the other hand, three animal studies were included in this report. Although there were consistent and inconsistent changes in several of the assessed parameters, the outcome of the three studies was fundamentically identical. Data from long-term studies in animals and acute dose studies in humans and animals indicate the absence of significant adverse effects with doses in the range studied (840-3000 mg/kg bw per day).

In summary, the following information is considered in the current assessment:

1. No long-term studies on L-serine in healthy children, adolescents or adult humans were found.
2. Two 90-days toxicological studies in rodents identified a NOAEL of 2765 and 3000 mg/kg bw per day for males and 2905 and 3000 mg/kg bw per day for females, respectively (highest doses tested). In addition, a 28-days toxicological study in rodents identified a NOAEL of 840 mg/kg bw per day for males and 894 mg/kg bw per day for females (highest dose tested).
3. Safety evaluation of L-serine as supplement must at present be based on animal studies allowing evaluation of specific doses.

No serious adverse health effects of L-serine were identified at the doses reported in the animal studies included in this opinion. For the risk characterisation of L-serine, in the absence of relevant human studies in healthy individuals, VKM has based the value of comparison on the NOAEL (highest dose tested) in the studies of rodents (3000 mg/kg bw per day).

3 Exposure / Intake

Exposure of L-serine was estimated from the intake of food supplements. For food supplements, the intake was estimated for the age groups 10 to <14 years, 14 to <18 years and adults (≥18 years).

3.1 Food supplements

The Norwegian Food Safety Authority requested VKM to perform a risk assessment of 50, 500, 1000, 1250, 1500 and 1750 mg/day of L-serine in food supplement for children (10 – 17 years) and adults. The default body weights for age groups determined by EFSA were used: 10 to <14 years = 43.4 kg, 14 to <18 years = 61.3 kg and adults = 70.0 kg (EFSA, 2012). The exposures per kg bw to L-serine from food supplements for various age groups are given in Table 3.1-1.

Table 3.1-1: Estimated exposure of L-serine from specified doses in food supplements in children, adolescents and adults.

Groups	Daily doses (mg)	Body weight (kg)	Exposures (mg/kg bw per day)
Children (10 to <14 years)	50, 500, 1000, 1250, 1500 and 1750	43.4	1, 12, 23, 29, 35 and 40
Adolescents (14 to <18 years)	50, 500, 1000, 1250, 1500 and 1750	61.3	1, 8, 16, 20, 25 and 29
Adults (≥18 years)	50, 500, 1000, 1250, 1500 and 1750	70.0	1, 7, 14, 18, 21 and 25

3.2 Other sources

Dietary intake of L-serine in Norway is not known, but results show an overall mean intake of L-serine from food and food supplements of 3.5 g/day in the United States (NHANES III, USA). Men aged 51-70 years had, in the latter mentioned study, the highest intakes at the 99th percentile of 7.9 g/day. In addition to being derived from diet, L-serine is produced endogenously. There is a lack of human studies estimating the *in vivo* biosynthesis, but a study in rodents have estimated the *de novo* synthesis of L-serine to be ~370 mg/100 g bw per day (Snell, 1986).

4 Risk characterisation

NFSA requested VKM to perform a risk assessment of doses of 50, 500, 1000, 1250, 1500, 1500 and 1750 mg/day of L-serine from food supplements for adults, adolescents and children above 10 years.

The literature search did not reveal any relevant studies in adults, children (10 to <14 years) and adolescents (14 to <18 years), and there were no studies in children 10 years or older included in previous risk assessments. However, there are no data indicating that children and adolescent are more vulnerable than adults to L-serine. Thus, no tolerance level was set for serine specifically for children or adolescents. Assuming similar tolerance for these age groups as for adults, the same value for comparison as for adults was used for children and adolescents. Concerning human data, only one study from from 1980, which showed no adverse effects after providing a single oral dose of 15 g serine (200 mg/kg bw of serine) to four healthy adults has been identified The results from this study, however, will not be used for safety evaluations in the present report due to limitations in the study design which only allowed investigation of possible acute effects of L-serine. Furthermore, the dose is far above the specified doses in the terms of reference for this report.

No adverse health effects were identified at the doses (840-3000 mg/kg bw per day) reported in the animal studies included in this report. Thus, VKM has based the value of comparison on the NOAEL (highest dose tested): 3000 mg/kg bw per day of L-serine from a 90-days toxicological study in rats for comparison with the estimated exposures. This value was used to calculate the Margin of Exposure (MOE); the ratio of the NOAEL to the exposure.

Although a MOE-value of 100 ideally should be used also in relation to feed studies, this will sometimes give values lower than the lowest daily requirements and considerably lower than net endogenous production of the nutrient in question, and in particular when the NOAEL is derived pragmatically from the highest (and sometimes only) dose tested.

The estimated exposures are presented in Table 3.1-1 and the calculated margins between the NOAEL of 3000 mg/kg bw per day from a 90-days study in rats and the exposure of L-serine from food supplements (MOE-values) are presented in Table 4-1.

Table 4-1: The calculated margins between the NOAEL from a rat study and the exposure to L-serine from food supplements (MOE-values) for the various age groups.

Age groups	50 mg/day	500 mg/day	1000 mg/day	1250 mg/day	1500 mg/day	1750 mg/day
Children (10 to <14 years) (43.4 kg)	2604	260	130	104	87	74
Adolescents (14 to <18 years) (61.3 kg)	3678	368	184	147	123	105
Adults (≥18 years) (70 kg)	4200	420	210	168	140	120

The calculated MOE-values ranged from 74 to 4200 for a daily intake of 50 to 1750 mg/day of L-serine.

Taking into consideration a high daily dietary intake and endogenous production of L-serine compared to the doses considered in the present risk assessment, and because L-serine is a nutrient that does not cause any known adverse affects, MOE-values below 100 have been regarded as acceptable.

Based on the calculated MOE-values from a 90-days study in rats, VKM considers that it is unlikely that daily doses of 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements causes adverse effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

5 Uncertainties

- A major uncertainty for the conclusion is the lack of studies in healthy adults, adolescents and children reporting potential adverse health effects of L-serine supplementation.
- There are only a few long-term animal studies adressing potential adverse health effects of L-serine supplementation.
- There is some uncertainty about relevant safety factors for extrapolation to humans from toxicological studies on major nutrient in rodents and interindividual variability in humans.
- The risk assessment is based on default body weights determined by EFSA. When using the default average body weight of an age (population) group, the variance in all individuals in the group will not be covered. Individuals with body weight less than the default estimate in a given age group are not fully covered in the risk estimate.

6 Conclusions with answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements. The present risk assessment is based on previous risk assessments and scientific papers retrieved from a systematic search in literature published before 11 May 2016 (human studies literature search) and before 28 July 2016 (animal studies literature search).

The literature search did not reveal any relevant studies in children (10 to <14 years), adolescents (14 to <18 years) or adults (≥18 years). No evidence was found to assume specific tolerance levels for L-serine for children or adolescents. Therefore, a similar tolerance as for adults relative to body weight is assumed for these age groups. Further, no particular vulnerable groups for L-serine supplements have been identified.

Three animal studies are included in this report, and the results revealed no adverse health effects at the doses of L-serine tested (840-3000 mg/kg bw per day). For the risk characterisation of L-serine and in the absence of relevant human studies in healthy individuals, VKM has based the value of comparison on the NOAEL (highest dose tested) in the studies of rats (3000 mg/kg bw per day). This value was used to calculate MOE-values for daily intake of 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine. The MOE-values range from 74 to 4200, values which are considered acceptable since L-serine is a nutrient that does not cause any known adverse effects and because studies indicate a high endogenous production and a high dietary intake of L-serine compared to the doses considered in the present risk assessment.

Thus, VKM concludes that:

- In adults (≥18 years), the specified doses 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements are unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses 50, 500, 1000, 1250, 1500 and 1750 mg/day L-serine in food supplements are unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 50, 500, 1000, 1500 and 1800 mg/day L-serine in food supplements are unlikely to cause adverse health effects.

Children younger than 10 years were not within the scope of the present risk assessment.

An overview of the conclusions is presented in Table 6-1. Estimated exposures unlikely to cause adverse health effects (below the values for comparison) are shown in green.

Table 6-1: An overview of the conclusions for L-serine in food supplements.
Green: Estimated exposures to L-serine are unlikely to cause adverse health effects.

	L-serine					
Doses Age groups	50 mg/day	500 mg/day	1000 mg/day	1250 mg/day	1500 mg/day	1750 mg/day
Children (10 to <14 years)						
Adolescents (14 to <18 years)						
Adults (≥18 years)						

7 Data gaps

There is a lack of studies on L-serine in healthy children, adolescents and adult humans.

There are few toxicological studies in animals where L-serine is provided as a single supplement and with an appropriate study design to investigate possible long-term adverse effects.

8 References

AESAN. (2015) Report of the Spanish Agency for Food Safety and Nutrition (AESAN)on the condition for use of certain substances other than vitamins, minerals and plants in food supplements - 4, The Spanish Agency for Food Safety and Nutrition (AESAN), Spain.

Anderson O.S., Sant K.E., Dolinoy D.C. (2012) Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. J Nutr Biochem 23:853-9. DOI: 10.1016/j.jnutbio.2012.03.003.

Artom C., Fishman W.H., Morehead R.P. (1945) The relative toxicity of l- and dl-serine in rats. Proc Soc Exp Biol Med 60:284-7.

Avissar N.E., Ryan C.K., Ganapathy V., Sax H.C. (2001) Na(+)-dependent neutral amino acid transporter ATB(0) is a rabbit epithelial cell brush-border protein. Am J Physiol Cell Physiol 281:C963-71.

Bikker P., Verstegen M.W., Bosch M.W. (1994) Amino acid composition of growing pigs is affected by protein and energy intake. J Nutr 124:1961-9.

de Koning T.J., Snell K., Duran M., Berger R., Poll-The B.T., Surtees R. (2003) L-serine in disease and development. Biochem J 371:653-61. DOI: 10.1042/BJ20021785.

Dworschak E. (1980) Nonenzyme browning and its effect on protein nutrition. Crit Rev Food Sci Nutr 13:1-40. DOI: 10.1080/10408398009527292.

FVM. (2014) Bekentgørelse om tilsætning af visse andre stoffer end vitaminer og mineraler til fødevarer, Fødevareministeriet (FVM), Fødevarestyrelsen, Denmark.

IOM. (2005) Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids, Institute of Medicine, Washington DC.

Jorissen B.L., Brouns F., Van Boxtel M.P., Ponds R.W., Verhey F.R., Jolles J., Riedel W.J. (2001) The influence of soy-derived phosphatidylserine on cognition in age-associated memory impairment. Nutr Neurosci 4:121-34.

Jorissen B.L., Brouns F., Van Boxtel M.P., Riedel W.J. (2002) Safety of soy-derived phosphatidylserine in elderly people. Nutr Neurosci 5:337-43. DOI: 10.1080/1028415021000033802.

Kalhan S.C., Hanson R.W. (2012) Resurgence of serine: an often neglected but indispensable amino Acid. J Biol Chem 287:19786-91. DOI: 10.1074/jbc.R112.357194.

Kaneko I., Han L., Liu T., Li J., Zhao Y., Li C., Yi Y., Liang A., Hayamizu K. (2009) A 13-week subchronic oral toxicity study of L-serine in rats. Food Chem Toxicol 47:2356-60. DOI: 10.1016/j.fct.2009.06.030.

Kohlmeier M. (2015) Amino Acids and Nitrogen Compounds, Nutrient Metabolism. Structure, Fuction and Genes, Academic Press, USA.

Lifshitz Y., Levi L., Eyal I., Cohen T., Tessler S. (2015) Sub-chronic (13-week) oral toxicity study, preceded by an in utero exposure phase and genotoxicity studies with fish source phosphatidylserine in rats. Food Chem Toxicol 86:234-44. DOI: 10.1016/j.fct.2015.10.008.

Locasale J.W. (2013) Serine, glycine and one-carbon units: cancer metabolism in full circle. Nat Rev Cancer 13:572-83. DOI: 10.1038/nrc3557.

Lowry M., Hall D.E., Brosnan J.T. (1985) Hydroxyproline metabolism by the rat kidney: distribution of renal enzymes of hydroxyproline catabolism and renal conversion of hydroxyproline to glycine and serine. Metabolism 34:955-61.

Morehead R.P., Fishman W.H., Artom C. (1945) Renal Injury in the Rat Following the Administration of Serine by Stomach Tube. Am J Pathol 21:803-15.

Munck B.G., Munck L.K. (1999) Effects of pH changes on systems ASC and B in rabbit ileum. Am J Physiol 276:G173-84.

Pepplinkhuizen L., Bruinvels J., Blom W., Moleman P. (1980) Schizophrenia-like psychosis caused by a metabolic disorder. Lancet 1:454-6.

Snell K. (1986) The duality of pathways for serine biosynthesis is a fallacy. Trend Biochem Sci 11:241-243.

Tabatabaie L., Klomp L.W., Berger R., de Koning T.J. (2010) L-serine synthesis in the central nervous system: a review on serine deficiency disorders. Mol Genet Metab 99:256-62. DOI: 10.1016/j.ymgme.2009.10.012.

Tada Y., Yano N., Takahashi H., Yuzawa K., Ando H., Kubo Y., Nagasawa A., Ohashi N., Ogata A., Nakae D. (2010) Toxicological evaluation of L-proline in a 90-day feeding study with Fischer 344 rats. Regul Toxicol Pharmacol 58:114-20. DOI: 10.1016/j.yrtph.2010.04.011.

Tsai P.J., Huang P.C. (1999) Circadian variations in plasma and erythrocyte concentrations of glutamate, glutamine, and alanine in men on a diet without and with added monosodium glutamate. Metabolism 48:1455-60.

Vakhapova V., Richter Y., Cohen T., Herzog Y., Korczyn A.D. (2011) Safety of phosphatidylserine containing omega-3 fatty acids in non-demented elderly: a double-blind placebo-controlled trial followed by an open-label extension. BMC Neurol 11:79. DOI: 10.1186/1471-2377-11-79.

van de Mortel E.L., Shen Z.A., Barnett J.F., Jr., Krsmanovic L., Myhre A., Delaney B.F. (2010) Toxicology studies with N-acetyl-L-serine. Food Chem Toxicol 48:2193-9. DOI: 10.1016/j.fct.2010.05.045.

van der Crabben S.N., Verhoeven-Duif N.M., Brilstra E.H., Van Maldergem L., Coskun T., Rubio-Gozalbo E., Berger R., de Koning T.J. (2013) An update on serine deficiency disorders. J Inherit Metab Dis 36:613-9. DOI: 10.1007/s10545-013-9592-4.

VKM. (2011) Risk categorisation of amino acids, Vitenskapskomiteen for mattrygghet, Oslo, Norway.

Wachstein M. (1947) Nephrotoxic action of diserine in the rat; the protective action of various amino acids and some other compounds. Arch Pathol (Chic) 43:515-26.

WHO. (1994) Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits, Environmental Health Criteria 170, World Health Organization.

Wolosker H., Sheth K.N., Takahashi M., Mothet J.P., Brady R.O., Jr., Ferris C.D., Snyder S.H. (1999) Purification of serine racemase: biosynthesis of the neuromodulator D-serine. Proc Natl Acad Sci U S A 96:721-5.

Appendix 1

Search strategies for this risk assessment

Search strategy human studies

Database: Embase <1974 to 2016 May 10>, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946 to Present>

1. serine*.ti. (30420)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (9905771)
3. 1 and 2 (6242)
4. (conference abstract* or letter* or editorial*).pt. (4985529)
5. 3 not 4 (5909)
6. limit 5 to (danish or english or norwegian or swedish) (5811)
7. limit 6 to human (2518)
8. remove duplicates from 7 (1558)

Search strategy animal studies

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1. serine*.ti. (30719)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (10138462)
3. 1 and 2 (6339)
4. (conference abstract* or letter* or editorial*).pt. (5127789)
5. 3 not 4 (5996)
6. limit 5 to (danish or english or norwegian or swedish) (5897)
7. limit 6 to animals (2056)
8. remove duplicates from 7 (1471)