Vitenskapskomiteen for mattrygghet
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# Risk assessment of "other substances in food supplements - L-methionine

**Statement from 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: 57
Risk assessment of "other substances" – L-methionine

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# Risk assessment of "other substances" - methionine

## Authors preparing the draft statement

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## Assessed and approved

The statement 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 Steen Skålhegg, Tonje Holte Stea, Tor A. Strand and Grethe S. Tell.

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

## Acknowledgment

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou.

## 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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# Abbreviations and/or glossary

IOM - Institute of Medicine, USA
LOAEL - lowest observed adverse effect level
NFSA - Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
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 Helath 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/ Norwegian Environment Agency

"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/ Norwegian Environment Agency

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of L-methionine in food supplements at the following doses: 200, 300, 500, 600 and 700 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.

# 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.

In the 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 used in Norway.

This statement regards the substance L-methionine per se, and no specific products.

According to information from the Norwegian Food Safety Authority (NFSA), L-methionine is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of the intake of 200, 300, 500, 600 and 700 mg L-methionine per day from food supplements. The total L-methionine exposure from other sources than food supplements is not included in the risk assessment.

This statement is based on a previous risk assessment from VKM of L-methionine, as well as scientific papers retrieved from a systematic search in literature published from 2012 up till 19 February 2016. The literature search aimed at retrieving human studies on adverse effects caused by L-methionine.

# Previous reports

## Risk assessment of L-methionine (VKM, 2013)

In 2013, VKM summarised the risk assessment of L-methionine as follows (In: Risk assessment of histidine, methionine, S-adenosylmethionine and tryptophan, ISBN: 978-82-8259-079-2):

"In 2005, Institute of Medicine, US (IOM) concluded that it was insufficient data to establish a tolerable upper intake level (UL) for methionine. One relevant new animal and four human studies with methionine were identified after 2002. Two of the new studies in humans reported on methionine-loading tests. One study in infants showed serious adverse health effects in infants given a protein hydrolysate with L-methionine equivalent to 8800 mg/L.

There are indications that intake of methionine during the so called acute methionine-loading test is associated with adverse health effects such as dizziness, nausea, sleepiness and decreased or increased blood pressure. In the loading test, 100 mg methionine per kg body weight is given after a 12-hour fast. This intake (100 mg/kg body weight) of L-methionine may be regarded as the lowest observed adverse effect level (LOAEL).

Although IOM has concluded that no UL could be established for methionine it has been reported that use of methionine as a single amino acid may have adverse health effects. An intake at 100 mg/kg body weight of L-methionine may be regarded as a LOAEL. With a conservative approach and the use of an uncertainty factor of 10 for between people variations and a factor of 3 for the uncertainty of LOAEL, a tentative guidance level (GL) of 100/30 ~ 3 mg of L-methionine per kg body weight can be suggested. In a 70 kg man this is equivalent to an intake of 210 mg per daily dosage".

# Literature search

The systematic literature search for published literature from 2012 to 2016 was performed using MEDLINE and EMBASE in order to retrieve any recent human studies identifying potential adverse effects caused by L-methionine published after the search included in the latest VKM (2013) report. Both databases were searched to ensure comprehensive study retrieval. The literature search was conducted 19 February 2016, and included human studies.

## Search strategy human studies

Database: Embase <1974 to 2016 February 19>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1. methionine*.ti. (22860)
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. (9673918)
3. 1 and 2 (3608)
4. (conference abstract* or letter* or editorial*).pt. (4875670)
5. 3 not 4 (3427)
6. limit 5 to (danish or english or norwegian or swedish) (3297)
7. limit 6 to human (1244)
8. limit 7 to yr="2012 -Current" (290)
9. remove duplicates from 8 (176)

## Publication selection

The literature search identified 176 articles. In the primary screening, titles and abstracts of all unique publications retrieved were screened against the inclusion criteria.

- An adverse effect/adverse effects in relation to L-methionine alone is addressed
- Route of exposure for humans is oral
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal L-methionine absorption and metabolism

In vitro studies were not included.

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 by one member of the committee.

No studies from this literature search fulfilled the inclusion criteria or were considered relevant for the purpose of risk assessment of L-methionine. No new evidence has thus been identified which could alter the conclusion in the VKM (2013) opinion.

No specific vulnerable groups were identified in the reviewed literature.

# Conclusion

VKM maintains the guidance level from 2013 at 210 mg methione per day.