Risk assessment of "other substances"
- L-lysine

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety
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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 limited to the use of L-lysine in food supplements. Risks related to lysine added to food and drinks, protein hydrolysates or high dietary protein intake are outside the scope of the opinion. The report is based on previous risk assessments of lysine and scientific papers retrieved from a comprehensive literature search.

According to information from the NFSA, L-lysine is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of 1000, 2000, 2500, 2750 and 3000 mg/day of L-lysine from food supplements. Foods rich in L-lysine are generally protein rich foods such as meat, dairy products, eggs, legumes, and some fish. Based on NHANES III (1988-1994), the overall mean intake of L-lysine from food and food supplements in the United States was 5.3 g/day (IOM, 2005).

L-Lysine, an indispensable amino acid, is present in all proteins in the human body. Its catabolisation takes place mainly in the liver. The two nitrogen groups are transferred to alpha-ketoglutarate to form glutamate. The remaining carbon skeleton is broken down to acetoacetyl-CoA. Lysine is exclusively ketogenic i.e. does not enter gluconeogenesis for the production of glucose.

In the first phase of the present evaluation of L-lysine, previous reports evaluating the safety of L-lysine supplementation in humans were identified. In the second phase, two systematic literature searches have been performed to retrieve scientific papers published before 11 May 2016 (human studies literature search) and before 28 September 2016 (animal studies literature search). Based on these searches, we identified two human studies and one study in rats that could be used for risk assessment of L-lysine in food supplement.

According to a report from the Institute of Medicine in the USA (IOM, 2005), several clinical trials of lysine with intakes ranging from 0.6 to 3.0 g/day for 3 to 6 months have not reported any adverse effects. The same was the case for the two human randomised controlled trials (RCTs) included in this report providing 6 g/day L-lysine orally for 8 weeks to
schizophrenic patients. One 90-days subchronic toxicity study with rats was identified, showing a no observed adverse effect level (NOAEL) of 3357 mg/kg bw per day (the highest dose tested), with no functional, biochemical or histological changes in renal function. In the present report, the value of comparison is set to 86 mg/kg bw per day, corresponding to 6000 mg per day in a 70 kg adult; the daily dose provided in the two human RCTs. The calculated margins of exposures (MOE-values) range from 1.2 to 6.0 for the specified supplement doses with 1000-3000 mg/day of L-lysine. MOE-values below 10 (for interindividual differences in humans) is regarded as acceptable since L-lysine is a nutrient that does not cause any known adverse effects. In addition, the overall mean lysine intake according to NHANES III (5.3 g/day) is close to the the doses considered in the present risk assessment. The requirement for lysine, 30 mg/kg bw per day, corresponding to 2.1 g/day in a 70 kg adult, is close to the doses considered in the present risk assessment. The NOAEL suggested in the 90 days subchronic rat study supports the suggestion that these doses are well tolerated in humans even with somewhat low MOE-values.

VKM concludes that:

- In adults (≥18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine 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 specified doses of L-lysine in food supplements. VKM concludes that:

- In adults (≥18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.
**Key words:** L-lysine, 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.


I denne rapporten har VKM vurdert helserisiko ved L-lysin som kosttilskudd. Vurderingen er basert på andre tidligere risikovurderinger av aminosyren og vitenskapelige artikler som er funnet i systematiske litteratursøk.


L-lysin er en essensiell aminosyre som finnes i alle proteiner i menneskekroppen. Nedbrytningen foregår hovedsakelig i leveren der de to nitrogengruppene overføres til alfa-ketoglutarat og danner glutamat. Det resterende karbonskjelettet brytes ned til acetoacetil-CoA. Lysin er ketogent og går ikke inn i glukoneogenesen for dannelse av glukose.

I den første fasen av evaluering av "andre stoffer" ble tidligere rapporter som har risikovurdert tilskudd med L-lysin hos mennesker kartlagt. I denne risikovurderingen er det i tillegg gjennomført systematiske litteratursøk der vitenskapelige artikler publisert før 11. mai 2016 (for humanstudier) og før 28. september 2016 (for dyrestudier) ble identifisert. Basert på disse søkene fant vi to studier på mennesker og en studie på rotter som kunne brukes i denne risikovurderingen av L-lysin i kosttilskudd.

Ifølge en rapport fra Institute of Medicine i USA (IOM 2005), har kliniske studier med lysininntak fra 0,6 til 3,0 g/dag i 3 til 6 måneder ikke rapportert funn av negative helseeffekter. Det samme var tilfellet for de to randomiserte kontrollerte studiene (RCT) i mennesker som er inkludert i denne rapporten. I begge studiene ble det gitt 6 g L-lysin per dag i 8 uker til pasienter med schizofreni. En 90-dagers subkronisk toksisitetstudie med rotter viste en NOAEL (no observed adverse effect level) på 3357 mg/kg kroppsvekt per dag. Dette var den høyeste testede dosen og det var ingen funksjonelle, biokjemiske eller
histologiske forandringer eller endringer i nyrefunksjon. I denne VKM-rapporten settes "value for comparison" i risikovurderingen av L-lysin til 86 mg/kg kroppsvekt per dag, svarende til 6000 mg L-lysin per dag i en 70 kg voksen som var dosen som ble gitt i de to RCTene.

De beregnede verdiene for "margins of exposures" (MOE-verdiene) er i området 1,2 til 6,0 for de spesifiserte dosene i kosttilskudd på 1000 til 3000 mg/dag av L-lysin. MOE-verdier under 10 (for interindividuelle forskjeller mellom mennesker) ble ansett som akseptabt ettersom L-lysin er et næringsstoff og ikke har gitt noen kjente negative helseeffekter. Videre er det totale gjennomsnittlige inntaket av lysin fra kosten på 5,3 g/dag (NHANES III) nært opptil de dosene som er vurdert i denne risikovurderingen. Anbefalt inntak av lysin er 30 mg/kg per kg kroppsvekt per dag, som svarer til 2,1 g/dag som er nært opp til de dosene som er vurdert. En NOAEL fra røttestudien på 3357 mg/kg kroppsvekt per dag understøtter at disse dosene vil tolereres godt hos mennesker, selv med noe lave MOE-verdier.

Vitenskapskomiteen for mattrygghet (VKM) konkluderer med at:

- For voksne (≥18 år) er det usannsynlig at de spesifiserte dosene på 1000, 2000, 2500, 2750 og 3000 mg/dag L-lysin i kosttilskudd vil forårsake negative helseeffekter.
- For ungdom (14 til <18 år) er det usannsynlig at de spesifiserte dosene på 1000, 2000, 2500, 2750 og 3000 mg/dag L-lysin i kosttilskudd vil forårsake negative helseeffekter.
- For barn (10 til <14 år) er det usannsynlig at de spesifiserte dosene på 1000, 2000, 2500, 2750 og 3000 mg/dag L-lysin i kosttilskudd 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 inntak spesifikke doser av L-lysin i kosttilskudd. VKM konkluderer med at:

- For voksne (≥18 år) er det usannsynlig at de spesifiserte dosene på 1000, 2000, 2500, 2750 og 3000 mg/dag L-lysin i kosttilskudd vil forårsake negative helseeffekter.
- For ungdom (14 til <18 år) er det usannsynlig at de spesifiserte dosene på 1000, 2000, 2500, 2750 og 3000 mg/dag L-lysin i kosttilskudd vil forårsake negative helseeffekter.
- For barn (10 til <14 år) er det usannsynlig at de spesifiserte dosene på 1000, 2000, 2500, 2750 og 3000 mg/dag L-lysin i kosttilskudd vil forårsake negative helseeffekter.
Abbreviations and glossary

Abbreviations

AE - adverse event
AESAN - Spanish Agency for Food Safety and Nutrition
BAT - brown adipose tissue (recruitable BAT)
bw - body weight
CAT - cationic amino acid transporter
EFSA - European Food Safety Authority
IOM - Institute of Medicine, USA
LAT - L-type amino acid transporter
NFSA - Norwegian Food Safety Authority [Norw.: Mattilsynet]
NO - nitrogen oxid
NOAEL - no observed adverse effect level
PANSS - positive and negative syndrome scale
RCT - randomised controlled trial
SCL - solute carrier 7 family
UL - tolerable upper intake level
VKM - Norwegian Scientific Committee for Food Safety [Norw.: Vitenskapkomiteen 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.
"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-lysine in food supplements at the following doses: 1000, 2000, 2500, 2750 and 3000 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-lysine 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 used in Norway.

According to information from the Norwegian Food Safety Authority (NFSA), L-lysine is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of the intake of 1000, 2000, 2500, 2750 and 3000 mg L-lysine per day from food supplements. The total L-lysine 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-lysine from food and food supplements in the United States was 5.3 g/day. The median dietary intake of lysine by adult women during 1988-1994 ranged from 3.4 to 4.6 g/day, and by adult men from 4.7 to 7.5 g/day (IOM, 2005).

L-lysine is an essential amino acid used as a building block for all proteins in the human body. L-lysine is a limiting amino acid in cereal diets (WHO, 2007). L-lysine plays a major role in calcium absorption, carnitine production, growth, building muscle protein, recovering from surgery or sport injuries and the body's production of hormones, enzymes and antibodies (Singh et al., 2011).

Foods rich in L-lysine are generally protein rich foods such as meat, dairy products, legumes, fish, nuts, seeds, eggs and whole grains. The requirements for adults of L-lysine are 30 mg/kg bw per day (WHO, 2007), corresponding to 2100 mg/day for a 70 kg adult.
2 Hazard identification and characterisation

2.1 Literature

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

2.1.1 Previous risk assessments

Risks related to L-lysine have previously been evaluated by: the Institute of Medicine (IOM), USA, 2005; the Norwegian Scientific Committee for Food Safety (VKM), Norway, 2011; the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (ASEAN), Spain, 2012 and 2015. Of the reports mentioned above, the literature search underlying the report was only described in the report from VKM (2011).

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

<table>
<thead>
<tr>
<th>Risk assessment body, country, publication year</th>
<th>Objective</th>
<th>Conclusion</th>
<th>Suggested doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOM, USA, 2005</td>
<td>To establish dietary reference intakes and identify potential adverse effects of L-lysine and other nutrients</td>
<td>Data were not available for dose-response assessment and derivation of a UL for L-lysine in apparently healthy humans</td>
<td>Not established</td>
</tr>
<tr>
<td>VKM, Norway, 2011</td>
<td>To qualitatively rank 30 amino acids according to high, moderate or low risk</td>
<td>L-lysine was grouped &quot;moderate risk&quot;</td>
<td>Not established</td>
</tr>
<tr>
<td>ASEAN, Spain, 2012</td>
<td>To assess the use of L-lysine as a food supplement</td>
<td>A maximum daily quantity of 2250 mg of L-lysine is acceptable from the safety point of view for use as a food supplement.</td>
<td>Acceptable doses: 2250 mg/day</td>
</tr>
</tbody>
</table>
Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids from Institute of Medicine (IOM). USA, 2005

According to IOM (2005): "Acute intake of high levels of lysine in humans interferes with dietary protein metabolism and competes with the transport of arginine, suggesting that adverse effects from high levels of lysine are more likely to occur if protein intake or dietary arginine intake is low. Intravenous L-lysine (16.5 to 41.3 g/day in young men) has been shown to inhibit renal tubular protein reabsorption (Mogensen and Solling, 1977). L-Lysine shares an intestinal transport system with L-arginine (McCarthy et al., 1964; Rosenberg et al., 1966), and competes with L-arginine for reabsorption from renal tubules (Kamin and Handler, 1951; Webber et al., 1961). Higher plasma and urinary concentrations of carnitine were found in six healthy adult males given a single 5 g oral dose of lysine (Vijayasarathy et al., 1987). In another study of eight healthy males (15 to 20 years of age) given a single oral dose of 1.2 g of L-lysine hydrochloride, growth hormone release was not significantly stimulated and no side effects were reported (Isidori et al., 1981). Increased liver total lipids, triacylglycerol, and cholesterol concentrations were found in rats fed 5 percent L-lysine and 15 percent casein for 2 weeks (Hevia et al., 1980a), an effect that can be reversed by feeding arginine (Hevia et al., 1980b)".

IOM (2005) states that "several clinical trials of lysine intakes from 0.6 to 3.0 g/day for 3 to 6 months in people with herpes infections have, in general, not found or reported any adverse effects and that few adverse effects of L-lysine have been observed in humans or animals after high, mostly acute, doses. The one adverse effect was an upset stomach in 3 of 27 patients given 3 g/day of L-lysine hydrochloride for 6 months and in 1 of the 25 controls (Griffith et al., 1987)".

The data on the adverse effects of L-lysine from supplements were considered not sufficient for a dose–response assessment and derivation of a UL for healthy humans.

VKM report on risk categorisation of amino acids, 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 VKM report from 2011 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-lysine was grouped among the amino acids possessing a moderate potential risk for adverse health effects. Due to lack of scientific evidence, this categorisation was merely based on the general knowledge of amino acids as potent bioactive compounds.

Supplementation with a dose of between 1.0 and 3.0 g L-lysine/day for 6 months did not have any adverse effects on healthy individuals (Flodin, 1997). The use of daily doses of between 0.4 and 1.5 g/day of L-lysine for up to 3 years to treat the herpes simplex virus did not have secondary effects (Griffith et al., 1987). The AESAN (2012) proposed that, based on the information available to date and taking into account the considerations reflected in their report, a maximum daily amount of 2250 mg of L-lysine is acceptable from the safety point of view for use as a food supplement.

2.1.2 Literature search

Systematic literature searches were performed in MEDLINE and EMBASE in order to retrieve publications on adverse effects caused by L-lysine. Both databases were searched to ensure comprehensive study retrieval. The literature search was conducted 11 May 2016, and included human studies. A search for animal studies was conducted on 28 September 2016. The strategies for the searches are outlined in Appendix 1.

2.1.2.1 Publication selection and data extraction

The literature search identified 919 articles in humans (Figure 2.1.2.1-1), whereas the search for animal studies identified 922 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-lysine 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 equal as by 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-lysine
- 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.

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 of both literature searches 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 first screening for relevant human studies resulted in 14 titles and abstracts for full text review. Additionally, a manual search identified 6 potentially relevant studies for full text review. The secondary review resulted in only 2 human studies which were found relevant and included in the results in this report (see Figure 2.1.2.1-1). The first screening for animal studies resulted in 8 full text articles of which only one was relevant and included in this report.

![Flowchart for publication selection for L-lysine.](Image)

**Figure 2.1.2.1-1:** Flowchart for publication selection for L-lysine.
2.2 General information

2.2.1 Chemistry

L-lysine (CAS registry number 56-87-1), chemical formula C6H14N2O2, is an essential α-amino acid in the biosynthesis of proteins, with a molecular weight of 146.19 g/mol and a chemical structure shown in figure 2.2.1-1. It contains an α-amino group (which is in the protonated $-\text{NH}_3^+$ form under biological conditions), α-carboxylic acid group (which is in the deprotonated $-\text{COO}^-$ form under biological conditions), and a side chain lysyl ((CH2)$_4$NH2), classifying it as a charged (at physiological pH), aliphatic amino acid. Lysine is a base and the ε-amino group often participates in hydrogen bonding and as a general base in catalysis. The ε-amino group ($\text{NH}_3^+$) is attached to the fifth carbon from the α-carbon, which is attached to the carboxyl (C=O) group. At physiological pH, the lysine residue bears a positive charge.

![Structural formula of L-lysine.](image)

2.2.2 Occurrence

Rich food sources of L-lysine are e.g. meat, dairy products, egg, legumes (especially soybean), and some fish (especially sardines and cod). In a plant-based diet, lysine is a limiting amino acid. L-lysine is also available in food supplements. In a 70 kg male with moderate lipid stores, body protein level is about 15% (i.e. 10.5 kg protein) of which 7% is estimated to be lysine (based on data from growing pigs (Bikker et al., 1994)), i.e. 700-800 g lysine.

2.3 Absorption, distribution, metabolism and excretion

2.3.1 Absorption and distribution

Intestinal uptake of lysine involves specific transporter proteins. In most tissues, cationic amino acids are transported principally by a Na$^+$-independent system, specific for L-isomers of lysine, arginine, and ornithine. This transport system is known as the Y(+) system and these transporters are members of the SLC7 family of membrane transporters. There are actually at least three transport mechanisms for lysine transport. One is the aforementioned Y(+) system that can be inhibited by leucine with high affinity when Na$^+$ is present, but this affinity is reduced in the absence of sodium. Another mechanism involves a Na$^+$-independent
system that is inhibited by leucine with high affinity only when Na+ is present. An additional transporter is a Na+-dependent transport system that can be inhibited by leucine with high affinity and by alanine (http://themedicalbiochemistrypage.org/ amino-acid-metabolism.php#lysine). While most lysine in blood is part of proteins, the concentration of free lysine in plasma is around 195 µmol/l. Uptake into tissue proceeds mainly via various members of system Y(+). The glucoprotein-anchored heteroexchangers Y(+) LAT1 and Y(+) contribute to a lesser extent to lysine uptake in some tissues. At least one of these transporters is also active in red blood cells. The mitochondrial ornithine transporter 1 can move lysine from cytosol into mitochondria (Kohlmeier, 2015).

2.3.2 Metabolism and excretion

Once taken up by the intestines, dietary lysine can be incorporated into protein or catabolised. Catabolism of lysine occurs almost entirely in the liver. The first step in the major pathway of lysine catabolism is its condensation with ketoglutarate to form saccharopine, which is converted by saccharopine dehydrogenase into a-aminoadipic semialdehyde and glutamate. Oxidation and decarboxylation of the semialdehyde leads to CO₂ and acetoacetyl coenzyme A as final products. There is evidence for an alternate pathway for L-lysine catabolism involving pipecolic acid as an intermediate product but it appears to be of minor importance in normal human metabolism (Flodin, 1997). Losses of intact lysine are minimal due to efficient recovery from both the intestines and kidneys. Nearly 5 g lysine passes across the renal glomeruli, and most of it is reabsorbed from the proximal tubular lumen. Uptake proceeds via the sodium-dependent system B₀, the sodium-independent system Y(+) (CAT-1, SLC7A1) and 2 (CAT-2, SLC7A2), and the transporter heterodimer, consisting of BAT1/β₀ (SLC7A9) and rBAT (SLC3A1). The glycoprotein 4F2-linked transporters Y(+) LAT1, (SLC7A7) and Y(+) LAT2, (SLC7A6) on the basolateral side mediate export toward the capillaries (Kohlmeier, 2015).

Functions of lysine in proteins

The numerous essential functions of the lysine residue in cell and body proteins are largely related to its ε-amino group. This group may be chemically transformed after incorporation of lysine into the polypeptide structure, as for example by methylation in the first step of the biosynthesis of carnitine. Carnitine is required for transport of long chain fatty acids and is synthesised from lysine and methionine in the liver and kidney. Much more extensive chemical modifications of peptide-bound lysine occur in the biosynthesis of collagen and
elastin, involving the formation from lysine and hydroxylysine of a variety of bi-, tri-, and tetrafunctional crosslinking agents, both enzymatically and nonenzymatically (Flodin, 1997).

### 2.4 Toxicological data/ Adverse effects

#### 2.4.1 Human studies

Two relevant human studies were identified and included in this risk assessment (Table 2.4.1-1).

Table 2.4.1-1: An overview of human studies investigating L-lysine and adverse health effects.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participant characteristics</th>
<th>Country</th>
<th>Number in study groups</th>
<th>Doses</th>
<th>Main end points</th>
<th>Duration of intervention</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wass et al. (2011)</td>
<td>Schizophrenic men and women, (23-56)</td>
<td>Sweden</td>
<td>10</td>
<td>10</td>
<td>6000 mg</td>
<td>8 weeks</td>
<td>No adverse effects</td>
</tr>
<tr>
<td>Cross over study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeinoddini et al. (2014)</td>
<td>Schizophrenic men and women, (18-50)</td>
<td>Iran</td>
<td>36</td>
<td>36</td>
<td>6000 mg</td>
<td>8 weeks</td>
<td>Detailed information on adverse events in both placebo and control group, no difference in adverse events between the two groups</td>
</tr>
</tbody>
</table>

L-lysine as adjunctive treatment in patients with schizophrenia: a single-blinded, randomized, cross-over pilot study. Wass et al., 2011

The objective was to investigate the benefit of L-lysine as an add-on treatment for schizophrenia, based on its interference with the brain’s nitric oxide (NO) production (Wass et al., 2011)(Wass et al., 2011)(Wass et al., 2011)(Wass et al., 2011)(Wass et al., 2011)(Wass et al., 2011)(Wass et al., 2011). L-lysine, 6 g/day, was administered to 10 Swedish men and women (23-45 years old) with schizophrenia as an adjunctive to their conventional antipsychotic medication. The study was designed as a single-blinded, cross-over study where patients were randomly assigned to initial treatment with either L-lysine or placebo and screened at baseline, after four weeks when treatment was crossed over, and after eight weeks. L-lysine treatment caused a significant increase in blood concentration of L-lysine. There is no information of which adverse effects that were registered, only a sentence in the result section stating that L-lysine treatment was not found to induce any adverse effects including extrapyramidal effects.
L-lysine as an adjunct to risperidone in patients with chronic schizophrenia: A double-blind, placebo-controlled, randomized trial. Zeinoddini et al., 2014

Seventy-two chronic schizophrenia inpatients (Iranian men and women, aged 18-50 years) with a Positive and Negative Syndrome Scale (PANSS) total score of >=60 participated in a randomised, double-blind, placebo-controlled trial in the active phase of their disease and underwent 8 weeks of treatment with either L-lysine (6 g/day) or placebo as an adjunctive to the antipsychotic drug risperidone (Zeinoddini et al., 2014). The primary objective was to evaluate the efficacy of L-lysine in improving schizophrenia symptoms. The patients reported adverse events (AE) according to a checklist of 8 items and were also asked an open-ended question at each follow-up visit about the occurrence of any AE which was not mentioned in the checklist. The frequency of AE did not differ significantly between the two treatment groups and no serious AE was observed. However, the safety and efficacy of higher doses of L-lysine and longer treatment periods remain unknown.

2.4.2 Other studies

According to a review by Flodin (1997), single doses of lysine from 5 to 40 g/day in short-term studies have not caused any adverse health effects. Flodin (1997) concludes: "For individuals eating American diets of usual components, supplemental intakes of lysine up to 3 g/day (3.75 g lysine monohydrochloride), taken with food and divided among meals, appear to be safe for chronic use as demonstrated in adults and prepubertal children. Judging from animal feeding studies and high-dose trials in humans, double this amount is probably also safe for long-term use, but so far, there is no confirmed evidence of value in such dosage".

The literature search did not identify any relevant studies in children.

2.4.2.1 Interactions

L-Lysine shares an intestinal transport system with L-arginine and competes with L-arginine for reabsorption from renal tubules (IOM, 2005). Acute intake of high levels of lysine competes with the transport of arginine, suggesting that potential adverse effects from high levels of lysine are more likely to occur if protein intake or dietary arginine intake is low (IOM, 2005). Casein-based diets which are marginal in arginine content relative to lysine, can be used to study the effect of excess lysine on arginine metabolism, growth, and other biological variables, as well as the opposing effect of arginine supplements. With 18% casein as the basal protein source, even a small excess of 1.5% added lysine reduced the growth rate of young rats by 9%; this addition raised the lysine/arginine ratio from 2.2 to 3.9. Use of a commercial 24.4% protein stock diet, which would lower the lysine/arginine ratio of a lysine supplemented diet, overcame most of the growth depression. The growth depression could also be overcome by a 1% arginine supplement (Flodin, 1997). The growing dog and pig appear less sensitive to an elevated lysine/arginine ratio than the young rat. In a study where puppies received a basal diet containing a lysine/arginine ratio of 2.3, increasing of
the dietary lysine/arginine ratio to 4.8 and 7.3 by adding 1% and 2% L-lysine, respectively, did not reduce weight gain or the gain/feed ratio. Addition of 4% of lysine as the acetate depressed growth and food intake, with classic signs of arginine deficiency. Supplemental arginine alleviated most of these side effects (Czarnecki et al., 1985). Edmonds and Baker fed young pigs a diet based on casein, whey, and soybean meal as the protein source, formulated to supply 14.41% crude protein, 1.15% lysine, and 0.53% arginine. Neither weight gain nor gain/feed ratio was reduced in pigs fed twice the recommended level of lysine (i.e., 2.30%) added as lysine monohydrate. Lysine levels at 3 or 4 times the basal level lowered both weight gain and feed intake without lowering feed efficiency. Tissue levels of arginase and ornithine transcarbamoylase were uninfluenced by the level of lysine ingested (Edmonds and Baker, 1987).

2.4.2.2 Allergic sensitisation (including adjuvant effects)

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

2.4.3 Mode of action for adverse effects

No mode of action for adverse effects has been identified.

2.4.4 Vulnerable groups

Vulnerable groups may be people with inadequate income to purchase sufficient animal protein foods, poor appetite and dentition problems in the elderly, vegetarian diets without adequate consumption of high lysine legumes, and generally poor dietary habits (Flodin, 1957).

2.4.5 Animal studies

The literature search for animal studies identified 922 titles and abstracts. Eight studies were reviewed in fulltext. One relevant study was identified from the animal studies literature search and included in the present report (Table 2.4.5-1).
Table 2.4.5-1: An overview of included animal studies investigating possible adverse health effects of L-lysine.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animals</th>
<th>Substance</th>
<th>Doses</th>
<th>Main endpoints</th>
<th>Duration of exposure</th>
<th>Adverse effects</th>
<th>NOAEL2 (mg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsubuku et al. (2004)</td>
<td>75 Sprague-Dawley rats female and male sex</td>
<td>L-lysine</td>
<td>Powder diet containing 1.25, 2.5, and 5.0% L-lysine</td>
<td>Urinalysis, hematology, serum biochemistry, organ weights, gross- and histopathological examination</td>
<td>13 weeks</td>
<td>None</td>
<td>M: 3357 F: 3986</td>
</tr>
</tbody>
</table>

Thirteen-Week Oral Toxicity Study of L-Lysine Hydrochloride in 75 Rats by Tsubuku et al., 2004

This study with male and female Sprague-Dawley rats evaluated toxicological and behavioral effects of lysine (Tsubuku et al., 2004). The amino acid was incorporated into a standard diet at doses equal to 1.25%, 2.5%, and 5.0% (w/w). A control group of rats received a standard diet. All diets were administered ad libitum for 13 consecutive weeks. To examine stability of any potential effects, the administration period was followed by a 5-week recovery period, during which only the standard diet was provided to all animals. In male and female rats in each concentration group, treatment-related changes were not observed in clinical signs, body weight, food consumption, water intake, ophthalmology, gross pathology, organ weights, or histology. A lysine related drop in serum concentration and an increase in urine excretion of chlorides was a compensatory reaction to the ingested hydrochloride. No functional, biochemical, or histological changes in renal function were found. The NOAEL for lysine was estimated at 5.0% for both genders (male, 3.36 ± 0.12 g/kg bw per day; female, 3.99 ± 0.28 g/kg bw per day). The study was conducted in compliance with the Good Laboratory Practice Standards for Safety Studies on Drugs and Guidelines for Toxicity Studies Required for Applications for Approval to Manufacture (Import) Drugs.

2.5 Summary of hazard identification and characterisation

Literature searches including both human and animal studies have been conducted, including previous reports (IOM, 2005; VKM, 2011). Lysine has only been investigated in studies of short duration, and no long-term studies in healthy individuals were identified that could be used for this risk assessment. Two RCTs of short duration (Wass et al., 2011; Zeinoddini et al., 2014) in which 6 g/day L-lysine were given orally to schizophrenic patients during 8 weeks were identified. No adverse health effects were reported in these studies.

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

1. No long-term studies on L-lysine in healthy children, adolescents or adult humans were found.
2. Several clinical trials of lysine intakes from 0.6 to 3.0 g/day for 3 to 6 months did not report any adverse effects.

3. In humans, two RCTs of short duration on schizophrenic patients in which 6 g/day L-lysine were given orally during 8 weeks reported no adverse effects.

4. Single doses ranging from 5 to 40 g/day in studies of short duration have been given without any adverse health effects.

5. L-lysine shares an intestinal transport system with L-arginine and competes with L-arginine for reabsorption from the renal tubules.

6. No short or long-term studies in humans have reported inhibition of intestinal or glomerular arginine uptake caused by lysine.

7. In rats, one 90-days subchronic toxicity study was identified, with a NOAEL of 3357 mg/kg bw per day in males and 3986 mg/kg bw per day in females. No adverse health effects were reported at the highest dose tested.

For the risk characterisation of L-lysine, in the absence of long-term human studies in healthy individuals, VKM will base the value of comparison on the highest dose tested in two human RCTs. The value of comparison is set to 86 mg/kg bw per day, corresponding to 6000 mg per day in a 70 kg adult.
3 Exposure / Intake

Exposure of L-lysine 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 1000, 2000, 2500, 2750 and 3000 mg/day of L-lysine 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. The exposures per kg bw are given in Table 3.1-1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Daily doses (mg)</th>
<th>Body weight (kg)</th>
<th>Exposures (mg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (10 to &lt;14 years)</td>
<td>1000, 2000, 2500, 2750 and 3000</td>
<td>43.4</td>
<td>23, 46, 58, 63 and 69</td>
</tr>
<tr>
<td>Adolescents (14 to &lt;18 years)</td>
<td>1000, 2000, 2500, 2750 and 3000</td>
<td>61.3</td>
<td>16, 33, 41, 45 and 49</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>1000, 2000, 2500, 2750 and 3000</td>
<td>70.0</td>
<td>14, 29, 36, 39 and 43</td>
</tr>
</tbody>
</table>

3.2 Other sources

According to NHANES III (1988-1994), the overall mean intake of L-lysine from food and food supplements in the United States was 5.3 g/day. The median dietary intake of lysine by adult women during 1988–1994 ranged from 3.6 to 4.6 g/day, and by adult men from 4.7 to 7.5 g/day (IOM, 2005).
4 Risk characterisation

The doses received from NFSA for assessment were 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements, and the estimated exposures for adults, adolescents and children 10 years and older derived from these dose levels are given in chapter 3.

In the present report, VKM has based the value for comparison with the estimated exposures on the highest dose of L-lysine tested (86 mg/kg bw per day derived from a daily dose of 6000 mg to a 70 kg adult) for 8 weeks in two RCTs on schizophrenic patients. This value was used to calculate the margins of exposure (MOE), calculated by dividing the highest dose tested in humans with the exposure to L-lysine from food supplements (Table 4-1).

Our literature review did not reveal any studies of L-lysine in children or adolescents. There are no data indicating that children and adolescent are more vulnerable than adults for L-lysine are. No tolerance level is set for L-lysine specifically for children or adolescents. Assuming similar tolerance for these age groups as for adults, the same value for comparison as for adults are used for children and adolescents (86 mg/kg bw per day).

**Table 4-1:** The calculated margins between the highest dose tested in humans not associated with adverse effect (86 mg/kg bw per day) from two RCTs and the exposure to L-lysine from food supplements (MOE-values) for the various age groups.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>1000 mg/day</th>
<th>2000 mg/day</th>
<th>2500 mg/day</th>
<th>2750 mg/day</th>
<th>3000 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (10 to &lt;14 years)</td>
<td>3.7</td>
<td>1.9</td>
<td>1.5</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>(43.4 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents (14 to &lt;18 years)</td>
<td>5.3</td>
<td>2.6</td>
<td>2.1</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>(61.3 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (≥18 years) (70 kg)</td>
<td>6.0</td>
<td>3.0</td>
<td>2.4</td>
<td>2.2</td>
<td>2</td>
</tr>
</tbody>
</table>

The calculated MOE-values for data from the human studies ranged from 1.2 to 6.0 (Table 4-1) for a daily intake of 1000-3000 mg/day of L-lysine.

The suggested NOAEL derived from the highest dose tested in the included study with rats is 3357 mg/kg bw per day. The MOE-values between the NOAEL of 3357 mg/kg bw per day and the exposure of L-lysine from food supplements are presented in Table 4-2.
Table 4-2:  The calculated margins between the NOAEL (3357 mg/kg bw per day) from a rat study and the exposure to L-lysine from food supplements (MOE values) for the various age groups.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>1000 mg/day</th>
<th>2000 mg/day</th>
<th>2500 mg/day</th>
<th>2750 mg/day</th>
<th>3000 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (10 to &lt;14 years) (43.4 kg)</td>
<td>146</td>
<td>73</td>
<td>58</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Adolescents (14 to &lt;18 years) (61.3 kg)</td>
<td>206</td>
<td>103</td>
<td>82</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>Adults (≥18 years) (70 kg)</td>
<td>235</td>
<td>118</td>
<td>94</td>
<td>85</td>
<td>78</td>
</tr>
</tbody>
</table>

The calculated MOE-values for the NOAEL from the animal study ranged from 49 to 235 (Table 4-2) for a daily intake of 1000-3000 mg/day of L-lysine.

The NOAEL suggested in the 90 days subchronic rat study supports the assumption that the specified doses are well tolerated in humans.

MOE-values below 10 in Table 4-1 (for interindividual differences in humans) and MOE-values below 100 in Table 4-2 (for interspecies and interindividual differences) were regarded as acceptable since L-lysine is a nutrient that does not cause any known adverse health effects. In addition, the overall mean lysine intake according to NHANES III (5.3 g/day) is close to the doses considered in the present risk assessment. The requirement for lysine, 30 mg/kg bw per day, corresponding to 2.1 g/day is close to the doses considered in the present risk assessment.

VKM considers that:

In adults (≥18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.

In adolescents (14 to <18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.

In children (10 to <14 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.
5 Uncertainties

- A major uncertainty for the conclusion is the lack of long-term studies in healthy adults, adolescents and children reporting potential adverse health effects of L-lysine supplementation.

- No dose-response related to adverse effects have been observed; hence, the documentation supporting a daily dose of 6.0 g is limited.
6 Conclusions with answers to the terms of reference

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of L-lysine in food supplements at the doses 1000, 2000, 2500, 2750 and 3000 mg/day for the general population, ages 10 years and above. The literature search was conducted 11 May 2016 and 28 September 2016, and included both human studies and animal studies.

The literature search did not reveal any relevant studies in children (10 to <14 years) and adolescents (14 to <18 years). No data have been found indicating that children or adolescents are more vulnerable than adults for L-lysine and no tolerance level is set for L-lysine specifically for children or adolescents. The conclusions are therefore based on the assumption of similar tolerance for children and adolescents as for adults.

Two human RCTs and one subchronic rat study are included in this report. For the risk characterisation of L-lysine, in the absence of long-term human studies in healthy individuals, VKM will base the value of comparison on the highest dose tested in two 8 weeks RCTs on humans. The value of comparison is set to 86 mg/kg bw per day, corresponding to 6000 mg per day in a 70 kg adult. The NOAEL suggested in the 90 days subchronic rat study support the suggestion that these doses will be well tolerated in humans. MOE-values from 1.2 to 6 in humans were regarded as acceptable since L-lysine is a nutrient that does not cause any known adverse health effects. In addition, the overall mean lysine intake according to NHANES III (5.3 g/day) is close to the doses considered in the present risk assessment. The requirement for lysine, 30 mg/kg per day, corresponding to 2.1 g/day is close to the doses considered in the present risk assessment.

No particular vulnerable groups for L-lysine supplements have been identified.

VKM concludes that:

In adults (≥18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.

In adolescents (14 to <18 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.

In children (10 to <14 years), the specified doses 1000, 2000, 2500, 2750 and 3000 mg/day L-lysine in food supplements are unlikely to cause adverse health effects.

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

<table>
<thead>
<tr>
<th>Age groups</th>
<th>1000 mg/day</th>
<th>2000 mg/day</th>
<th>2500 mg/day</th>
<th>2750 mg/day</th>
<th>3000 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (10 to &lt;14 years)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
<tr>
<td>Adolescents (14 to &lt;18 years)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
</tbody>
</table>
7 Data gaps

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

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


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.


Appendix 1

Search strategies for this risk assessment

Search strategy human studies

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

1. lysine*.ti. (26002)
2. methyl*.ti. (317050)
3. 1 not 2 (23981)
4. (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)
5. 3 and 4 (4752)
6. (conference abstract* or letter* or editorial*).pt. (4985529)
7. 5 not 6 (4570)
8. limit 7 to (danish or english or norwegian or swedish) (4374)
9. limit 8 to human (1481)
10. remove duplicates from 9 (919)

Search strategy animal studies

Database: Embase <1974 to 2016 August 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1. lysine*.ti. (26346)
2. methyl*.ti. (321226)
3. 1 not 2 (24261)
4. (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. (10139037)
5. 3 and 4 (4850)
6. (conference abstract* or letter* or editorial*).pt. (5121834)
7. 5 not 6 (4660)
8. limit 7 to (danish or english or norwegian or swedish) (4464)
9. limit 8 to animals (1339)
10. remove duplicates from 9 (922)