Risk assessment of "other substances" – L-tyrosine

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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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 for regulating the addition of "other substances" to food supplements and other foods.

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

The present report is limited to the use of L-tyrosine in food supplements. Risks related to tyrosine 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 tyrosine and scientific papers retrieved from a comprehensive literature search.

L-tyrosine, an aromatic amino acid, is considered a conditionally indispensable amino acid because it can be synthesised from L-phenylalanine in the liver. The magnitude of endogenous synthesis of L-tyrosine is not known, but is related to the intake of phenylalanine.

L-tyrosine is a precursor of several biologically active substances, including catecholamine neurotransmitters, thyroid hormones and melanin skin pigments. L-tyrosine is available from all protein-containing foods such as meat, eggs, fish, dairy products, grains and pulses.

According to information from the NFSA, L-tyrosine is an ingredient in food supplements sold in Norway. The NFSA has requested a risk assessment of the following doses of L-tyrosine food supplements: 1250 mg/day, 1500 mg/day, 1750 mg/day, and 2000 mg/day. Dietary intake of tyrosine in Norway is not known, but data from NHANES III (USA) suggest a mean dietary intake of about 2.8 g per day.

In phase 1 seven previous reports that assessed the safety of L-tyrosine supplementation in humans were identified. For the present report, a literature search was performed to retrieve relevant human or animal studies on the safety of L-tyrosine. One relevant animal study assessing the toxicity of tyrosine by feeding rats different doses of tyrosine daily by oral gavage for 13 weeks was identified. No human studies have been identified.

No major specific issues related to adverse effects from L-tyrosine used as food supplements were identified in previous reports. However, a lack of studies in healthy adult individuals as
well as in children was pointed out, and in particular the absence of long-term studies in healthy individuals.

A lowest observed adverse effect level (LOAEL) and a no observed adverse effect level (NOAEL) of 2000 and 600 mg/kg bw per day, respectively, for tyrosine have been identified in a 90-day toxicological study in rats. At 2000 mg/kg bw per day, significant increases, were found in weights of livers and kidneys in addition to increased plasma lipids and hypertrophy of centrilobular hepatocytes in both sexes.

The NOAEL at 600 mg/kg per day was used to calculate the margin of exposure (MOE), the ratio of the NOAEL to the specified doses of 1250, 1500, 1750 and 2000 mg/day of L-tyrosine in food supplements. The MOE-values range from 13 for the highest supplement dose in children to 34 for the lowest supplement dose in adults.

Given the low MOE-values (range 13-34), and the severity of the adverse effects at the LOAEL (3.3 times the NOAEL), VKM concludes that all the specified doses may represent a risk of adverse effects.

No evidence was found to assume specific tolerance levels for L-tyrosine for children or adolescents. Therefore, a similar tolerance as for adults relative to body weight was assumed for these age groups.

Based on these data, the Norwegian Scientific Committee for Food Safety (VKM) concludes that:

- In adults (≥18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.
- In adolescents (14 to <18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.
- In children (10 to <14 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.

Children below 10 years were not included in the terms of reference.

**Short summary:**

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of specified doses of L-tyrosine in food supplements. VKM concludes that:

- In adults (≥18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.
- In adolescents (14 to <18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.
In children (10 to <14 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.

**Key words:** Adverse health effect, L-tyrosine, food supplement, negative health effect, 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 vitenskapelige grunnlag for å regulere "andre stoffer" i kosttilskudd.

"Andre stoffer" er 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 sett på potensielle gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

I denne rapporten har VKM vurdert risiko ved inntak av L-tyrosin i kosttilskudd og ikke av tyrosin tilsatt mat eller drikke, proteinhydrolysater eller via et høyt proteininntak. Risikovurderingen er basert på tidligere risikovurderinger av disse stoffene og artikler som er funnet ved et nytt omfattende litteratursøk.

L-tyrosine er en aromatisk aminosyre som dannes fra den essensielle aminosyren L-fenylalanin i leveren. Mengden endogent produsert L-tyrosin er ikke kjent, men er relatert til inntaket av fenylalanin.

L-tyrosin er en forløper til en rekke biologisk aktive forbindelser, og disse inkluderer katekolaminer, nevrotransmittorer, tyroideahormoner og hudpigmentet melanin. L-tyrosin inngår i proteiner og proteinrike matvarer slik som kjøtt, egg, fisk, meieriprodukter, korn og belgfrukter.

Ifølge informasjon fra Mattilsynet er L-tyrosin en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere følgende doser av L-tyrosin i kosttilskudd: 1250, 1500, 1750 og 2000 mg/dag. Inntaket av tyrosin i Norge er ikke kjent, men data fra NHANES III anslår et gjennomsnittlig inntak på 2,8 gram per dag i USA.

I første fase av denne evalueringen av "andre stoffer" ble det funnet syv rapporter som omhandlet risiko ved inntak av L-tyrosin fra kosttilskudd. I denne risikovurderingen er det utført litteratursøk for å innhente human- og dyrestudier som er relevante for risikovurdering av tyrosin. Det ble kun funnet en relevant dyrestudie, som undersøkte negative helseeffekter av ulike daglige doser L-tyrosin i sondenæring til rotter i 13 uker. Det ble ikke identifisert noen relevante studier med mennesker.

Det ble ikke avdekket åpenbare risiko knyttet til bruk av L-tyrosin i kosttilskudd i de tidligere rapportene. Rapportene peker imidlertid på en generell mangel på langtidsstudier med L-tyrosin i den friske befolkningen samt hos barn og ungdom.

I dyrestudien ble det identifisert både en LOAEL (laveste dose med observert negativ helseeffekt) på 2000 mg/kg kroppsvekt per dag og en NOAEL (høyeste dose uten noen observert negativ helseeffekt) på 600 mg/kg kroppsvekt per dag for L-tyrosin i rotter. Ved
2000 mg/kg kroppsvægt per dag ble det funnet økning i vekt av lever og nyrer i tillegg til økte plasmalipidnivåer samt hypertrofi av sentrilobulære hepatocyter hos begge kjønn.

NOAEL fra toksisitetsstudien med rotter på 600 mg/kg kroppsvægt per dag er brukt som utgangspunkt for å beregne "margin of exposure" (MOE), ratioen mellom denne NOAELen og de angitte dosene på 1250, 1500, 1750 og 2000 mg/dag av L-tyrosin i kosttilskudd. MOE-verdiene varierer fra 13 for den høyeste kosttilskuddsdosen hos barn til 34 for den laveste dosen hos voksne.

Tatt i betraktning de lave MOE-verdiene (mellom 13 og 34) samt alvorlighetsgraden av funnene ved LOAEL (som kun er 3,3 ganger over NOAEL), konkluderer VKM at alle de angitte dosene kan representere en risiko for negative helseeffekter.

Det er ikke grunnlag for å anta at barn og unge har en annen toleransegrense for L-tyrosin enn voksne korrigert for kroppsvægt.

Vitenskapskomiteen for mattrygghet (VKM) konkluderer med at:

**L-tyrosin**

- For voksne (≥18 år), er det sannsynlig at de spesifiserte dosene på 1250, 1500, 1750, og 2000 mg/dag L-tyrosin vil kunne representere en risiko for negative helseeffekter.
- For ungdom (14 to <18 år) er det sannsynlig at de spesifiserte dosene på 1250, 1500, 1750, og 2000 mg/dag L-tyrosin vil kunne representere en risiko for negative helseeffekter.
- For barn (10 to <14 år), er det sannsynlig at de spesifiserte dosene på 1250, 1500, 1750, og 2000 mg/dag L-tyrosin vil kunne representere en risiko for 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 av spesifikke doser av L-tyrosin i kosttilskudd. VKM konkluderer med at:

- For voksne (≥18 år), er det sannsynlig at de spesifiserte dosene på 1250, 1500, 1750, og 2000 mg/dag L-tyrosin vil kunne representere en risiko for negative helseeffekter.
- For ungdom (14 to <18 år) er det sannsynlig at de spesifiserte dosene på 1250, 1500, 1750, og 2000 mg/dag L-tyrosin vil kunne representere en risiko for negative helseeffekter.
- For barn (10 to <14 år), er det sannsynlig at de spesifiserte dosene på 1250, 1500, 1750, og 2000 mg/dag L-tyrosin vil kunne representere en risiko for negative helseeffekter.
Abbreviations and glossary

Abbreviations

AESAN - Spanish Agency for Food Safety and Nutrition
AFSSA - French Food Safety Agency (up to 1st July 2010)
ANSES - French Agency for Food, Environmental and Occupational Health and Safety (since 1st July 2010)
bw - body weight
EFSA - European Food Safety Authority
FDA - Food and Drug Administration, USA
GLP - good laboratory practice
GABA - gamma-aminobutyric acid
GI - gastrointestinal
IOM - Institute of Medicine, USA
JECFA - Joint FAO/WHO Expert Committee on Food Additives
LD₅₀ - lethal dose for 50% of the animals
LOAEL - lowest observed adverse effect level
MOE - margin of exposure
NFSA - Norwegian Food Safety Authority [Norw.: Mattilsynet]
NOAEL - no observed adverse effect level
OECD - Organisation for Economic Co-operation and Development
SAE - serious adverse event
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. VKM uses the definition established by World Health Organization (WHO) for "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).
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).

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. 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-tyrosine in food supplements at the following doses:
L-tyrosine: 1250, 1500, 1750 and 2000 mg/day

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

Safety assessments for "other substances" present in food supplements shall be carried out for a general population, ages 10 years and above.
Assessment

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 or physiological effect, and may be added to food supplements or e.g. energy drinks.

VKM has in this series of risk assessments of "other substances" not evaluated any potential beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway.

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

According to information from the Norwegian Food Safety Authority (NFSA), L-tyrosine is an ingredient in food supplements purchased in Norway. NFSA has requested a risk assessment of the following doses of L-tyrosine from food supplements: 1250, 1500, 1750 and 2000 mg/day.

L-tyrosine is an aromatic amino acid which is considered conditionally indispensable because it can be synthesised from L-phenylalanine in the liver. L-tyrosine is a precursor of several biologically active substances, including catecholamine neurotransmitters, hormones, and melanin skin pigments. An estimated average requirement of L-tyrosine has been set to 6 mg/kg bw (IOM, 2005). Studies of nitrogen balance and oxidation with aromatic amino acid markers indicate that the daily requirement of aromatic amino acids (L-phenylalanine or L-tyrosine) is 25 mg/kg bw (WHO, 2007).

Common food sources of L-tyrosine are protein foods (meat, eggs, fish, dairy products and pulses. Based on distribution data from the 1988–1994 NHANES III, the mean intake for all life stage and gender groups of tyrosine from food and supplements is 2.8 g/day (IOM, 2005). Information on habitual dietary intake of L-tyrosine in Norway is not available. L-tyrosine may be used as a flavouring agent, but in negligible magnitude compared with use in food supplements (JECFA, 2006).
2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on previous risk assessments of L-tyrosine, and on evidence extracted from articles retrieved in a comprehensive literature search aiming to identify human and animal studies on adverse effects caused by L-tyrosine.

2.1.1 Previous risk assessments

Risks related to L-tyrosine has previously been evaluated by the Institute of Medicine (IOM), USA, 2005; JECFA (Joint FAO/WHO Expert Committee on Food Additives), WHO Food Additives Series 54, WHO, 2006; AFSSA (The French Food Safety Agency), 2007; EFSA (European Food Safety Authority) 2008; ANSES (The French Agency for Food, Environmental and Occupational Health & Safety), 2011 the Norwegian Scientific Committee for Food Safety (VKM), Norway, 2011; AESAN (The Scientific Committee of the Spanish Agency for Food Safety and Nutrition), 2012.

Of the reports mentioned above, only the Norwegian Scientific Committee for Food Safety (VKM), Norway, 2011 report describes a literature search underlying the report.

These reports are summarised in Table 2.1.1-1.

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

<table>
<thead>
<tr>
<th>Risk assessment body, country and 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 for L-tyrosine and other nutrients. Includes a discussion of potential toxicity.</td>
<td>L-tyrosine: The data on supplements are conflicting and are not sufficient for a dose-response assessment and for derivation of a tolerable upper intake level (UL) for L-tyrosine.</td>
<td>L-tyrosine: Not established</td>
</tr>
<tr>
<td>Risk assessment body, country and publication year</td>
<td>Objective</td>
<td>Conclusion</td>
<td>Suggested doses</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<td>------------</td>
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</tr>
<tr>
<td>JECFA (Joint FAO/WHO Expert Committee on Food Additives), WHO Food Additives Series 54, WHO, 2006</td>
<td>To evaluate the safety of a group of 20 flavouring agents, including L-tyrosine</td>
<td>The 11 α-amino acids are macronutrients and normal components of protein, hence the use of these substances would not raise any safety concerns at estimated current intakes. L-tyrosine: No safety concern</td>
<td>L-tyrosine: Not established</td>
</tr>
<tr>
<td>AFSSA, France, 2007</td>
<td>As one of several tasks to assess minimum and maximum protein and amino acid intake levels in diets in different situations and for different populations</td>
<td>A tolerable upper intake level is not proposed for either nitrogen or amino acids, due to a lack of experimental and epidemiological data.</td>
<td>L-tyrosine: Not established</td>
</tr>
<tr>
<td>EFSA, 2008</td>
<td>To evaluate the safety of a group of 19 amino acids and related substances, including L-tyrosine</td>
<td>The human exposure of L-tyrosine through food is in orders of magnitude higher than the anticipated levels of exposure from the use as flavouring substance. L-tyrosine: No safety concern</td>
<td>L-tyrosine: Not established</td>
</tr>
<tr>
<td>ANSES, France, 2011</td>
<td>To consider whether use of substances with nutritional or physiological effects in foods should be restricted or prohibited</td>
<td>Metabolic effects are expected to be silent at first, but can then reveal themselves in the medium to long term. The complexity of amino acid metabolism and the scarcity of toxicological data do not allow a proper risk assessment. No conclusion drawn.</td>
<td>L-tyrosine: Not established</td>
</tr>
<tr>
<td>VKM, Norway, 2011</td>
<td>To qualitatively rank 30 amino acids according to high, medium or low risk</td>
<td>Tyrosine was categorised as having &quot;moderate&quot; risk</td>
<td>L-tyrosine: Not established</td>
</tr>
<tr>
<td>AESAN, Spain, 2012</td>
<td>The use of L-tyrosine + L-phenylalanine as a food supplement was assessed</td>
<td>A maximum daily amount of 1900 mg for the sum of L-tyrosine and L-phenylalanine is acceptable from the safety point of view for use as a food supplement.</td>
<td>L-tyrosine + L-phenylalanine Sum of 1900 mg/day acceptable</td>
</tr>
</tbody>
</table>

*Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients) Chapter 10 “Protein and Amino Acids. Institute of Medicine (IOM). USA, 2005*

No adverse effects have been reported for L-tyrosine from food. Large single doses of L-tyrosine (500 mg/kg bw/day) or smaller daily doses (100 mg/kg bw/day) have not been
associated with any adverse effects (Al-Damluji et al., 1988; Glaeser et al., 1979; Sole et al., 1985 cited in IOM (2005)). The IOM stated the following:

"Loads of L-tyrosine of 100 to 150 mg/kg bw/day have not been found to have any adverse effects on physiological systems (Benedict et al., 1983; Glaeser et al., 1979; Neri et al., 1995 cited in IOM (2005)). Even for well-studied amino acids, adequate dose-response data from human or animal studies on which to base a tolerable upper intake level (UL) were not available, but this does not mean that there is no potential for adverse effects resulting from high intakes of amino acids from dietary supplements. Since data on the adverse effects of high levels of amino acids intakes from dietary supplements are limited, caution may be warranted."

"In conclusion, the absence of dose response data to describe more fully the relationship of L-tyrosine loads to alteration in catecholamine synthesis, physiological function, and corneal lesions in humans, a UL for L-tyrosine cannot be set for apparently healthy humans."


The Committee was of the opinion that the use of the Procedure for the Safety Evaluation of Flavouring Agents (Annex 1, reference 131) was inappropriate for the 11 L-form alpha-amino acids (L-cysteine, No. 1419; L-glutamic acid, No. 1420; glycine, No. 1421; L-leucine, No. 1423; L-phenylalanine, No. 1428; L-aspartic acid, No. 1429; L-glutamine No. 1430; L-histamine, No. 1431; L-tyrosine, No. 1434; L-arginine, No. 1438; L-lysine, No. 1439) and the one alpha-imino acid (L-proline, No. 1425). The Committee stated that: "These substances are macronutrients and normal components of protein and, as such, human exposure through food is orders of magnitude higher than the anticipated level of exposure from use as flavoring agents. Thus, the use of these substances would not raise any safety concerns at estimated current intakes" (JECFA, 2006).


A tolerable upper intake level is not proposed for either nitrogen or amino acids, due to a lack of experimental and epidemiological data (AFSSA, 2007).
Opinion of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs. France, 2011

The ANSES considered that the complexity of amino acid metabolism and the scarcity of toxicological data did not allow a proper risk assessment. No conclusion was drawn (ANSES, 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. It was emphasised that the VKM report from 2011 had several limitations and could only be regarded as an initial screening and not as a risk assessment of the many amino acids.

The task was to evaluate individual amino acids to place them into one of three groups: high, moderate or low potential risk for adverse health effects, based on studies retrieved in a broad literature search. No relevant studies were found and based merely on the fact that amino acids are bioactive compounds L-tyrosine was categorised as moderate risk (VKM, 2011).

Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements – 1. Spain, 2012

The Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) pointed out that a significant number of studies carried out prior to the 1980s concluded that increases in the intake of L-phenylalanine (diets enriched with 3-7% L-phenylalanine) resulted in an increase in the circulating levels of L-tyrosine (AESAN, 2012). Therefore, the toxic effects of L-phenylalanine were linked to those of L-tyrosine (Benevenga and Steele, 1984; Harper et al., 1970). Based on animal and human studies and the protein reference intake for L-phenylalanine recommended by the WHO for the adult population (WHO, 2007), AESAN (2012) concluded that a maximum daily amount of 1900 mg for the sum of L-tyrosine and L-phenylalanine is acceptable from a safety point of view for use as a food supplement.

2.1.2 Literature search

2.1.2.1 Search strategies

A systematic literature search for published literature covering the period from 2005 was performed in MEDLINE and EMBASE, in order to retrieve publications on adverse effects caused by tyrosine published after the IOM-report. These databases were chosen to ensure comprehensive study retrieval. This literature search was performed by the project...
leader/panel coordinator on 22 February 2016. Both human and animal studies were included in the search. A separate search was performed to possibly find publications on children and adolescents, with no restriction on publication year. This literature search was conducted 26 October 2016.

The search strategies are shown in Appendix 1.

2.1.2.2 Publication selection

The main literature search identified 843 articles after removal of duplicates, and the search specified for children adolescents identified 87 articles. In the primary screening titles and abstracts of all unique publications retrieved were independently screened against the inclusion criteria checklist. In addition, a manual search identified six articles.

Inclusion criteria checklist:

- An adverse effect/adverse effects in relation to the substance alone is addressed
- Route of exposure for humans = oral
- Route of exposure for animals = oral, in addition, subcutaneous exposure is included if the toxico-kinetic is equal as by oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal tyrosine absorption and metabolism.
- Animal model studies address adverse effects relevant to human health

For the animal studies search, retrieved papers were included if they reported results from chronic or sub-chronic toxicity or feeding studies.

In vitro studies were not included, but were read as background information with regard to potential toxic properties of L-tyrosine.

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

In the main search study titles and abstracts were screened by the author of this report in addition to a second member of the panel according to the inclusion criteria listed above. After screening 15 articles were obtained and read in full-text and finally one article was included in the assessment. Totally 14 articles were excluded due to no oral exposure of tyrosine (13 papers) or no focus on adverse effects (1 paper).

The included article is a 13-week repeated dose toxicity study of L-tyrosine in rats by daily oral administration.

Titles and abstracts from the additional literature search specified for children and adolescents were screened by the author of this report. Two articles were read in full-text, but these were not relevant for inclusion.
2.2 General information

2.2.1 Chemistry

L-tyrosine (CAS registry number 60-18-4), chemical formula C_{9}H_{11}NO_{3} is an aromatic amino acid (see structural formula, Fig. 2.2.1-1) with molecular weight 181.2 g/mol. L-tyrosine is considered a conditionally indispensable amino acid because it can be synthesised from L-phenylalanine in the liver. This assessment includes L-tyrosine, naturally occurring in the body and used in supplements. Little is known about the function and metabolism of the D-form of tyrosine.
2.2.2 Occurrence

L-tyrosine is available from all protein-containing foods such as meat, eggs, fish, dairy products, grains and pulses. In a 70 kg male with moderate lipid stores, body protein level is about 15% (i.e. 10.5 kg protein) of which 2-3% is estimated to be L-tyrosine (based on data from growing pigs) (Bikker et al., 1994), i.e. 200-300 g L-tyrosine.

2.3 Absorption, distribution, metabolism and excretion

L-tyrosine can be synthesised in the body from L-phenylalanine, an essential amino acid, by hydroxylation catalysed by phenylalanine hydroxylase (PAH). Free alpha-amino acids, whether ingested as food supplements or released after the digestion of proteins by proteolytic enzymes, are absorbed through the intestinal mucosa and enter the portal blood to the liver. In the liver L-tyrosine may be incorporated into protein or passed onward to the peripheral circulation. Once in the peripheral circulation, a variety of carrier systems transport free alpha-amino acids into cells (Kilberg, 1982). These amino-acid carriers are mostly sodium ion-dependent systems that are specific to a particular class of alpha-amino acids (e.g. neutral amino acids with short side-chains, neutral amino acids with branched or aromatic side-chains, basic amino acids, and dicarboxylic amino acids). The carrier systems are adaptive and under hormonal regulatory control. Although small amounts of di-, tri-, and polypeptides may be absorbed by a transport system involving membrane-bound gamma-glutamyl transferase, most amino acids enter the cells unchanged (Nelson and Cox, 2000). Alpha-amino acids are used in protein synthesis or rapidly metabolised to intermediates in the citric acid cycle, as evidenced by the presence of only low amounts of alpha-amino acids in plasma. The excretion of alpha-amino acids is regulated by renal tubular reabsorption, in which the proximal tubules conserve alpha-amino acids. The daily excretion of alpha-amino acids in the urine amounts to only 20–150 mg/day in humans (Tietz, 1986). Minimal loss of alpha-amino acids occurs in the urine and faeces.

Stable-isotope-tracer methods to study whole-body tyrosine kinetics in 12 young healthy adults (six female and six male) revealed that adaptation to a marginal intake of dietary protein led to an overall reduction in protein turnover, net protein catabolism, and the rate of nitrogen excretion. Despite the reduction of tyrosine derived from whole-body proteolysis, the flux of tyrosine was maintained, indicating that the conserved nitrogen was sufficient to maintain endogenous synthesis and supply of tyrosine (Gibson et al., 2002).
L-tyrosine is component of all proteins in the human body, and a precursor of several biologically active substances, including catecholamine neurotransmitters, and thyroid hormones and melanin skin pigments. In addition, tyrosine has been shown to be an important part of acute phase proteins in host-defense mechanisms synthesised by the liver, and their rates of synthesis increase several fold under stress (Reeds et al., 1994).

2.4 Toxicological data/ Adverse effects

2.4.1 Human studies

No relevant human studies were identified.

2.4.2 Animal studies

One relevant animal study was identified and an overview of the study is presented in Table 2.4.2-1.

Table 2.4.2-1: Overview of the included animal study for L-tyrosine.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animals</th>
<th>Doses</th>
<th>Main endpoints</th>
<th>Duration of exposure</th>
<th>Adverse effects</th>
<th>NOAEL (mg/ kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibui et al. (2016)</td>
<td>Crl:CD(SD) rats, male and female</td>
<td>200, 600 or 2000 mg/kg bw/day by oral gavage</td>
<td>Clinical observation, clinical pathology and postmortem evaluation</td>
<td>13 weeks</td>
<td>Oedema of the corneified layer at the limiting ridge of the forestomach, increased weight and hypertrophy of centrilobular hepatocytes, altered blood lipids</td>
<td>200 - females, 600 - males</td>
</tr>
</tbody>
</table>

Thirteen-week oral toxicity study of L-tyrosine in Crl:CD(SD) rats. Shibui et al., 2016.

This study was conducted in accordance with the OECD Test Guidelines 408 for ‘Repeated dose 90-day oral toxicity study in rodents’. After a week of acclimatisation, four groups of 10 rats (age 6 weeks) were randomised by a complete block design with body weight stratification to ensure homogenous weight. For a 13-week period the rats were fed either 200, 600 or 2000 mg/kg bw per day L-tyrosine, or only the vehicle (negative control group) by oral gavage (Shibui et al., 2016). The animals were observed twice daily (pre-dose and post-dose) for clinical signs including appearance/posture, behaviour, faeces/urine, body surface, fluid one and two, and weekly thereafter. Individual food and water consumption was measured on day two and weekly thereafter. In addition to a comprehensive list of analyses a thorough post-mortem microscopic evaluation on a number of organ and tissue samples was also done. There were no deaths during the administration period in any of the groups, nor any differences between groups in body weights, food and water consumption.
and no tyrosine-related ophthalmic signs were noted. A significant increase in red blood cells was noted in males at 2000 mg/kg bw per day. Significant increases, or a tendency thereof, in alanine aminotransferase, aspartate aminotransferase, triglycerides, total cholesterol, phospholipids, potassium ion, calcium, total protein, and alpha-1 globulin, were noted in males and females at 2000 mg/kg bw per day. Significant increases, or a tendency thereof, were found in absolute and relative weights of liver and kidneys in males and females at 2000 mg/kg bw per day. Thus 2000 mg/kg bw per day represents the lowest-observed-adverse-effect level (LOAEL). The authors considered that the no-observed-adverse-effect level (NOAEL) of L-tyrosine was 600 mg/kg bw per day for males and 200 mg/kg bw per day for females.

The authors' conclusion to distinguish NOAELs according to sex was based on the presence of oedema in the limiting ridge of the stomach in 2/10 female rats given 600 mg/kg bw per day of L-tyrosine. The anatomical structure "limiting ridge" is to the best of VKM's knowledge not identifiable in humans. According to Figure 1 in the report by Shibui et al. (2016) the extent of oedema appears quite small. It is unclear what effect this small oedema may have on the rat well-being, and whether it poses any adverse effects at all. It was only in 20% of the female rats that this adverse effect was noted. In all male rats and 80% of female rats, no adverse effects were noted at the dose of 600 mg/kg bw per day. For the purpose of this risk assessment VKM therefore finds that the appropriate NOAEL for both genders is 600 mg/kg bw per day.

2.4.3 Mode of action for adverse effects

No mode of action for adverse effects has been identified.

2.4.4 Vulnerable groups

Children and adolescents: No data on children and adolescents were identified.

Foetuses, pregnant and lactating women: It is not known whether moderate supplementation with L-tyrosine has any effect on the human foetus, or whether tolerance is different in pregnant and lactating women. It should be noted that pregnant and lactating women may constitute a health-conscious group prone to ingest dietary supplements.

The elderly: No data on elderly were identified.

Mental disorders: No direct scientific evidence that the intake levels of tyrosine affect mental function negatively has been retrieved.
2.4.4.1 Interactions, allergic sensitisation and adjuvant effects

Concerning allergic sensitisation or allergy adjuvant effects, there was no information in the literature reviewed in the present risk assessment. The scarce 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

In previous risk assessments of L-tyrosine no tolerable upper intake level has been established for humans (see section 2.1.1). AESAN (2012) concluded that a maximum daily amount of 1900 mg for the sum of L-tyrosine and L-phenylalanine was acceptable from the safety point of view for use as food supplements. However, it was pointed out that increases in the intake of L-phenylalanine (diets enriched with 3-7% L-phenylalanine) implied an increase in the circulating levels of L-tyrosine and that the toxic effects of L-phenylalanine were linked to those of L-tyrosine (Benevenga and Steele, 1984; Harper et al., 1970).

For L-tyrosine no new human studies reporting on adverse effects (or the absence of such effects) in healthy individuals were retrieved, and long-term studies in humans are still missing.

Specific information about potential negative health effects and the associated doses can only be derived from the information retrieved in one animal study (Shibui et al., 2016). A LOAEL and a NOAEL of 2000 and 600 mg/kg bw per day, respectively, for L-tyrosine has been identified in a 90-day toxicological study in rats (see section 2.4.2). At 2000 mg/kg bw per day, significant increases, were found in weights of livers and kidneys in addition to increased plasma lipids and hypertrophy of centrilobular hepatocytes in both sexes.

VKM will use the NOAEL at 600 mg/kg bw per day as a value for comparison in the risk characterisation of the specified doses of L-tyrosine in chapter 4.
3 Exposure

Exposures of L-tyrosine was estimated from the intake of food supplements for the age groups 10-14 years, 14-18 years and adults (≥18 years).

3.1 Food supplements

The NFSA has requested a risk assessment of the doses 1250, 1500, 1750 and 2000 mg/day of L-tyrosine in food supplements. The default body weights (bw) for the relevant consumer groups determined by the EFSA were used: 10 to <14 years=43.4 kg, 14 to <18 years=61.3 kg, and adults=70 kg. The intakes per kg bw is given in (Table 3.1-1)

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

<table>
<thead>
<tr>
<th>Groups</th>
<th>Daily doses, L-tyrosine, mg</th>
<th>Body weight</th>
<th>Exposures (mg/ kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (10 to &lt;14 years)</td>
<td>1250, 1500, 1750, 2000</td>
<td>43.4</td>
<td>29, 35, 40, 46</td>
</tr>
<tr>
<td>Adolescent (14 to &lt;18 years)</td>
<td>1250, 1500, 1750, 2000</td>
<td>61.3</td>
<td>20, 25, 29, 33</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>1250, 1500, 1750, 2000</td>
<td>70.0</td>
<td>18, 21, 25, 29</td>
</tr>
</tbody>
</table>

Exposure of L-tyrosine was estimated from the intake of food supplements alone.

3.2 Other sources

There are no data available concerning dietary intake of L-tyrosine in Norway. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of tyrosine from food and supplements is 2.8 g/day. Men 31 through 50 years of age had the highest intakes at the 99th percentile of 6.4 g/day (IOM, 2005).
4 Risk characterisation

The doses of L-tyrosine requested from NFSA in food supplements doses were 1250, 1500, 1750 and 2000 mg/day. The estimated exposures for adults, adolescents and children above 10 years based on these doses are given in chapter 3.

No relevant studies with tyrosine in children were found. However, there are no data known indicating that children and adolescents are more vulnerable than adults for tyrosine. No tolerance level is set for tyrosine specifically for children or adolescents.

A LOAEL and a NOAEL of 2000 and 600 mg/kg bw per day, respectively, have been identified in a 90-day sub-chronic toxicity study in rats (Shibui et al., 2016). The dose 2000 mg/kg bw per day caused adverse effects including increased organ weights (liver and kidney), increased plasma lipids and hypertrophy of centrilobular hepatocytes in both sexes.

The NOAEL at 600 mg/kg per day from the animal toxicity study in rats has been used to calculate the margin of exposure (MOE), defined as the ratio of the NOAEL to the specified doses of L-tyrosine. The 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-tyrosine from food supplements (MOE values) for the various age groups.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>1250 mg/ day</th>
<th>1500 mg/ day</th>
<th>1750 mg/ day</th>
<th>2000 mg/ day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (10 to &lt;14 years)</td>
<td>20.8</td>
<td>17.4</td>
<td>14.9</td>
<td>13.0</td>
</tr>
<tr>
<td>(43.4 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents (14 to &lt;18 years)</td>
<td>29.4</td>
<td>24.5</td>
<td>21.0</td>
<td>18.4</td>
</tr>
<tr>
<td>(61.3 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>33.6</td>
<td>28.0</td>
<td>24.0</td>
<td>21.0</td>
</tr>
<tr>
<td>(70 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The margins range from 13 for the highest supplement dose in children to 34 for the lowest supplement dose in adults. In toxicology, an acceptable MOE value for a NOAEL-based assessment of chemicals based on an animal study is ≥100, which includes a factor 10 for extrapolation from animals to humans and a factor 10 for inter individual human variation. A MOE below 100 may also be acceptable; however, such assessments must be based on supporting scientific literature and expert judgement.
Considering the low MOE-values (range 13-34) and the severity of the findings at the LOAEL (3.3 times the NOAEL), VKM concludes that all the specified doses may represent a risk of adverse effects.

VKM considers that:

In adults (≥18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.

In adolescents (14 to <18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.

In children (10 to <14 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.
5 Uncertainties

- A major uncertainty is the lack of studies in healthy adults, children and adolescents reporting on potential adverse health effects of L-tyrosine supplementation.
- Data on long-term metabolic effects (e.g. diabetes) and long-term effects on e.g. central nervous function and immune system function are not available.
- Uncertainty about relevant safety factors for extrapolation to humans from toxicological studies on major nutrients in rodents.
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-tyrosine in food supplements at the following doses: 1250 mg/day, 1500 mg/day, 1750 mg/day, and 2000 mg/day for the general population, ages 10 years and above.

For L-tyrosine specific information about potential negative health effects and the associated doses has mainly been derived from the information retrieved in the updated literature search, and has been evaluated against the background information summarised in previous safety assessment reports.

No evidence was found to assume specific tolerance levels for L-tyrosine for children or adolescents. Therefore, a similar tolerance as for adults relative to body weight was assumed for these age groups.

The NOAEL of 600 mg/kg bw per day from a 90-days subchronic toxicity study in rats was used to calculate the MOE. The specified doses are relatively high compared to the intake of L-tyrosine from food. Given the low MOE-values (range 13-34), and the severity of the adverse effects at the LOAEL (3.3 times the NOAEL), VKM concludes that all the specified doses may represent a risk of adverse effects.

VKM concludes that:

In adults (≥18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.

In adolescents (14 to <18 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects.

In children (10 to <14 years), the specified doses of 1250, 1500, 1750, and 2000 mg/day L-tyrosine in food supplements may represent a risk of adverse health effects. An overview of the conclusion is presented in Table 6.1.
Table 6.1: An overview of the conclusions for L-tyrosine in food supplements. Red: Estimated exposures to L-tyrosine are likely to cause adverse health effects.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1250 mg/day</td>
</tr>
<tr>
<td>Children (10 to &lt;14 years)</td>
<td></td>
</tr>
<tr>
<td>Adolescents (14 to &lt;18 years)</td>
<td></td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td></td>
</tr>
</tbody>
</table>
7 Data gaps

- **Lack of human toxicity studies on adverse effects as primary outcome of L-tyrosine supplementation, with the possibility to establish a dose-response relationship:** The large majority of intervention studies are designed to detect health-protective and health-promoting effects of L-tyrosine. There is a need for human studies that are well-designed (randomised, blinded, placebo-controlled, multicenter)
  - with L-tyrosine given as a single supplement as the intervention
  - with graded doses
  - of sufficient sample size
  - designed to study long-term effects – i.e. sufficient duration of intervention and sufficient duration of follow-up
  - performed in healthy subjects representative of the general population

- **Lack of data in children and adolescents:** A systematic literature search in children and adolescents with no restriction concerning publication year retrieved no relevant studies, revealing a severe lack of data about potential adverse health effects of L-tyrosine in children and adolescents.
  -

- **With only one study there is a general lack of toxicological studies in rodents that are:**
  - performed according to OECD Guidelines or similar
  - with L-tyrosine given as a single supplement as the intervention
  - with graded, sufficiently high doses
  - designed to study long-term effects – i.e. sufficient duration of intervention
References


ANSES. (2011) Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs, French Agency for Food, Environmental and Occupational Health and Safety, France.


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 strategies for human and animal 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. tyrosine*.ti. (80581)
2. amino acid*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui] (1523422)
3. 1 and 2 (13835)
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. (9673918)
5. 3 and 4 (3500)
6. (conference abstract* or letter* or editorial*).pt. (4875670)
7. 5 not 6 (3440)
8. limit 7 to (danish or english or norwegian or swedish) (3418)
9. limit 8 to yr="2005 -Current" (1180)
10. remove duplicates from 9 (843)

Search strategy for studies in children and adolescents

Database: Embase <1974 to 2016 October 25>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1. tyrosine*.ti. (83747)
2. tyrosinemi*.ti. (1109)
3. kinase*.ti. (304380)
4. hydroxylase*.ti. (34148)
5. phosphatase*.ti. (78894)
6. 2 or 3 or 4 or 5 (412414)
7. 1 not 6 (28372)
8. (child* or adolescent* or teenage* or college* or high school).tw. (3101342)
9. 7 and 8 (183)
10. limit 9 to (danish or english or norwegian or swedish) (138)
11. remove duplicates from 10 (87)