



VKM Report 2016: 56

Risk assessment of "other substances" – creatine

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

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2016: 56
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12.12.2016

ISBN: 978-82-8259-246-8
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Cover photo: iStock Photo

Suggested citation: VKM. (2016). Risk assessment of "other substances" – creatine. Opinion of the Panel on Nutrition, dietetic products, Novel Food an Allergy of the Norwegian Scientific Committee for Food Safety, ISBN: 978-82-8259-246-8, Oslo, Norway.

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Acknowledgment

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou. Per Ole Iversen is acknowledged for his valuable work on this opinion. Jan Alexander (the Scientific Steering Committee), Åshild Krogdahl (the Scientific Steering Committee) and Helle Margrete Meltzer (former member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy) constituted a reference group and are acknowledged for their valuable comments and suggestions on this opinion.

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 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 and/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 potential beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of creatine as food supplement, and is based on previous risk assessments and articles retrieved in literature searches.

According to information from the Norwegian Food Safety Authority (NFSA), creatine is an ingredient in food supplements sold in Norway, and NFSA has requested a risk assessment of the following doses of creatine in food supplements: 3.0, 5.0, 10.0 and 24.0 g/day. The average daily intake from the diet is about 1 g creatine, and the endogenous production also amounts to about 1 g/day. Most of the creatine supplements are in the form of creatine monohydrate.

Creatine is an organic acid occurring in the body as either phosphocreatine (2/3) or as free creatine (1/3). Phosphocreatine provides phosphate groups for synthesis of adenosine triphosphate, the major energy-providing compound in the body.

Previous risk assessments (AESAN, 2012; EFSA, 2004; SCF, 2000; VKM, 2010) all concluded that creatine supplementation with 3.0 g/day is unlikely to cause adverse health effects in adults. This is supported by human and animal data obtained in a literature search and assessed in the present report. Most of the studies with daily creatine intake above 3 g often (i) involved few and highly trained individuals of whom some took high daily loading doses of creatine for a short period, and (ii) were designed to test clinical benefit without emphasis on possible adverse effects. VKM therefore considers that there is insufficient evidence to conclude regarding possible adverse effects at doses of creatine above 3 g/day for the general population.

VKM concludes that:

- In adults (≥ 18 years) the specified dose of 3.0 g/day creatine in food supplements is considered unlikely to cause adverse health effects. The documentation for absence of adverse health effects of doses 5.0, 10.0 and 24.0 g/day creatine in food supplements in the general population is limited. Hence, these doses may represent risk of adverse health effects in adults.
- In children (10-14 years) and adolescents (14-17 years), the specified doses of 3.0, 5.0, 10.0 and 24.0 g/day creatine 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 (maks 100 ord) til nettmelding:

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-creatine in food supplements. VKM concludes that:

- In adults (≥ 18 years) a daily dose of 3.0 g/day creatine in food supplements is unlikely to cause adverse health effects. Doses of 5.0, 10.0 and 24.0 g/day creatine in food supplements may represent a risk of adverse health effects.
- In children (10-14 years) and adolescents (14-17 years) the specified doses of 3.0, 5.0, 10.0 and 24.0 g/day creatine in food supplements may represent a risk of adverse health effects.

Key words: Adverse health effect, athlete, creatine, 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 tilsetning av "andre stoffer" i kosttilskudd som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Risikovurderingene gir et vitenskapelig grunnlag for Mattilsynet i arbeidet med å regulere bruken av "andre stoffer".

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

I denne rapporten har VKM vurdert risiko ved kreatin som kosttilskudd. Risikovurderingen er basert på tidligere risikovurderinger av kreatin og artikler som er identifisert gjennom litteratursøk.

Kreatin er en organisk syre som forekommer i kroppen enten som kreatinfosfat (2/3) eller som fritt kreatin (1/3). Kreatinfosfat bidrar med fosfat til dannelse av adenosintrifosfat, kroppens viktigste energimolekyl.

Gjennomsnittlig daglig inntak av kreatin i kosten er ca. 1 g, og endogen syntese utgjør også om lag 1 g. I kosttilskudd forekommer kreatin vanligvis som kreatinmonohydrat.

Ifølge informasjon fra Mattilsynet er kreatin en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet har vært å risikovurdere følgende doser av kreatin i kosttilskudd: 3,0, 5,0, 10,0 og 24,0 g/dag.

Tidligere risikovurderinger av kreatin (AESAN, 2012; EFSA, 2004; SCF, 2000; VKM, 2010) konkluderte alle med at det er usannsynlig at 3 g/dag av kreatin vil forårsake negative helseeffekter hos voksne. Denne konklusjonen støttes av data fra human- og dyrestudier funnet i et nytt litteratursøk. De fleste studiene som omhandler et daglig kreatininntak over 3 g har ofte inkludert (i) et lite antall høyt trente idrettsutøvere hvorav noen tok høye oppstartsdoser av kreatin i en kort periode, og studiene (ii) var stort sett designet for å teste ut nytteeffekt av kreatin uten å vurdere eventuelle bivirkninger. VKM anser derfor at dokumentasjonen for fravær av mulige negative effekter ved inntak av kreatindoser over 3 g/dag i den generelle befolkningen, er utilstrekkelig.

Fordi kreatin skilles ut gjennom nyrene og har et høyt nitrogeninnhold, har det vært bekymringer om hvorvidt kreatin kan være skadelig for nyrefunksjonen. Det er imidlertid ikke rapportert om slike bivirkninger ved de dosene som er rapportert i tidligere risikovurderinger og i litteratursøket i denne rapporten.

Vitenskapskomiteen for mattrygghet (VKM) konkluderer at:

- For voksne (≥ 18 år) er det usannsynlig at en spesifisert dose på 3,0 g/dag med kreatin fra kosttilskudd vil forårsake negative helseeffekter. Dokumentasjon for fravær av negative helseeffekter ved doser på 5,0, 10,0 og 24,0 g/dag kreatin i kosttilskudd i den generelle befolkningen er begrenset. Disse dosene kan representere en risiko for negative helseeffekter hos voksne.
- For barn (10-14 år) og ungdom (14-17 år) vil de spesifiserte dosene på 3,0, 5,0, 10,0 og 24,0 g/dag med kreatin fra kosttilskudd kunne representere en risiko for negative helseeffekter.

Barn under 10 år inngår ikke i oppdraget.

Kort sammendrag til nettmelding [maks 100 ord]: På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av kreatin i kosttilskudd. VKM konkluderer med at:

- For voksne (≥ 18 år) er det usannsynlig at en spesifisert daglig dose på 3,0 g/dag kreatin fra kosttilskudd vil forårsake negative helseeffekter. Dokumentasjon for fravær av negative helseeffekter ved doser på 5,0, 10,0 og 24,0 g/dag kreatin i kosttilskudd i den generelle befolkningen er begrenset. Disse dosene kan representere en risiko for negative helseeffekter hos voksne.
- For barn (10-14 år) og ungdom (14-17 år) vil de spesifiserte dosene på 3,0, 5,0, 10,0 og 24,0 g/dag med kreatin fra kosttilskudd kunne representere en risiko for negative helseeffekter.

Abbreviations and/or glossary

Abbreviations

AESAN	- Spanish Agency for Food Safety and Nutrition
ATP	- adenosine triphosphate
bw	- body weight
CK	- creatine kinase
CKMB	- creatine kinase myocardial isoform
CrM	- creatine monohydrate
DHT:T-ratio:	- ratio between dihydrotestosterone and testosterone
EFSA	- European Food Safety Authority
IGF-1	- insulin-like growth factor-1
LD ₅₀	- lethal dose for 50% of the animals
LOAEL	- lowest observed adverse effect level
NFSA	- Norwegian Food Safety Authority [<i>Norw.</i> : Mattilsynet]
NOAEL	- no observed adverse effect level
RCT	- randomised controlled trial
SCF	- Scientific Committee on Food
UL	- Tolerable upper intake level
VKM	- Norwegian Scientific Committee for Food Safety [<i>Norw.</i> : 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 and World Health Organization (WHO) has established the following definition 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).

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, flavourings, 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 creatine in food supplements at the following doses: 3.0 g, 5.0 g, 10.0 g and 24.0 g/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 of "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 and/or physiological effect*, and may be added to food supplements or e.g. energy drinks.

This risk assessment concerns the substance creatine per se, and no specific products.

VKM has in this series of risk assessments of "other substances" 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), creatine is an ingredient in food supplements sold in Norway, and NFSA has requested a risk assessment of the following doses of creatine in food supplements: 3.0, 5.0, 10.0 and 24.0 g/day.

Creatine is mostly studied in athletes because of its claimed performance enhancing effects, but also in the elderly and other population groups.

Creatine (N-(aminoiminomethyl)-N-methyl glycine) is an organic acid occurring in the body as either phosphocreatine (2/3) or as free creatine (1/3). Phosphocreatine provides phosphate groups for synthesis of adenosine triphosphate (ATP), the major energy-providing compound in the body.

The daily turnover of creatine is estimated to approximately 2 g with about 1 g being produced in the body and 1 g coming from foods (VKM, 2010). Creatine is naturally obtained through foods, mainly meat and fish. Food supplements mostly contain creatine in the form of creatine monohydrate.

2 Hazard identification and characterisation

2.1 Literature

In this risk assessment VKM has evaluated previous risk assessments of creatine by the EU Scientific Committee on Food (SCF, 2000), European Food Safety Authority (EFSA, 2004), the Norwegian Scientific Committee for Food Safety (VKM, 2010) and The Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN, 2012), as well as articles retrieved from literature searches.

2.1.1 Previous risk assessments

Opinion of the Scientific Committee on Food on safety aspects of creatine supplementation. SCF, 2000

In 2000, SCF concluded that "consumption of lower doses of up to 3 g/day is similar to the daily turnover rate of about 2 g/day and unlikely to pose any risk". Furthermore, it concluded that high loading doses should be avoided. The conclusion of SCF (2000) was based on articles retrieved from a MEDLINE search (1998-2000), mostly reviews. SCF (2000) noted that creatine appears to be well tolerated in short term human trials, primarily studied in athletes, but that these results cannot necessarily be extrapolated to the general population. Furthermore, the objective of these studies was to assess beneficial effects on physical performance, and not adverse effects.

Mainly because of high nitrogen content in creatine, renal dysfunction following creatine supplementation was raised as a concern, but results from studies and case reports were conflicting, hence no conclusion could be drawn. Other cited reviews had linked creatine supplementation to weight gain, cramping, dehydration, gastrointestinal distress and dizziness.

SCF (2000) discussed short and long term supplementation and high loading doses, but no specific doses were discussed. Thus, the rationale for concluding that specific doses up to 3 g/day are unlikely to pose any risk was not explained. Potential vulnerable groups, such as pregnant or lactating women, fetuses, or children (including those who are breastfed) and adolescents, were not mentioned in this SCF opinion.

The literature search was not described in the opinion.

Opinion related to creatine monohydrate for use in foods for particular nutritional uses. EFSA, 2004

EFSA (2004) concluded that the consumption of supplemental creatine monohydrate of high purity (99.5%) in doses not exceeding 3 g/day, similar to the daily turnover rate of 2 g creatine per day (SCF, 2000), is unlikely to pose any risk in healthy adults. The safety of creatine monohydrate was considered to be similar to that of creatine which was evaluated by SCF in 2000. EFSA (2004) additionally quoted a study by Kreider et al. (2003) which concluded that a long-term dose (i.e. maintenance dose) of mean (range) creatine supplementation of 5 (5-10) g/day for up to 21 months, preceded by an initial high dose (i.e. loading dose) for five days with 15.75 g/day, did not adversely affect biochemical markers of health status in athletes undergoing intense training compared to athletes not receiving creatine supplementation.

EFSA (2004) also presented animal data showing that the acute toxicity of creatine is low (LD_{50} in the rat is higher than 2 g/kg bw), and that it is not mutagenic in the Ames test (i.e. exposure of bacteria to a chemical compound in order to determine the mutagenic potential of that compound). Creatine had also been tested in a 28-day rat study in which no treatment related adverse effects were reported after dose levels up to 2 g/kg bw per day. The original data from these animal studies are not listed in the references in the EFSA (2004) opinion, and are thus not available to VKM.

Assessment of creatine in sports products. VKM, 2010, Norway

The VKM opinion from 2010 addressed both the possible benefits and risks of using creatine supplements, and it was based on five previous safety reports and assessments published during 2001-2009.

In addition the VKM (2010) used information retrieved from 23 original papers and 14 reviews/meta-analyses published after 2004 for safety evaluation of creatine supplementation. The use of creatine evaluated in most of these studies included a loading dose of 20 g/day for 4-7 days followed by a maintenance dose of 2-5 g/day. The total supplementation period varied from 1 week to 6 months in most of the studies in non-athletes. Notably, these studies included both healthy subjects and patients with various diseases, usually with few (< 30) included participants. VKM (2010) supported the EFSA (2004) that supplementation with creatine up to 3 g/day was unlikely to pose any risks if the purity of the creatine compound is adequate. It also stated that scientific long-term studies with doses up to 5-10 g/day in adult athletes have shown no harmful effects.

The potential adverse health effects reported (e.g. impaired kidney function, weight gain and gastrointestinal disturbances) were not supported by controlled systematic studies on healthy subjects. Moreover, VKM (2010) stated: "It has been indicated that individuals with impaired kidney functions should refrain from creatine supplements".

Details about the literature search were presented (time period from 2004 to 2010).

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

AESAN (2012) conducted a risk assessment of creatine monohydrate in 2012. This report relied partly on an ASEAN report from 2008 and an Italian legislative proposal from 2012. In addition this AESAN (2012) report based its risk assessment on more than 70 studies of human safety regarding intake of creatine. These studies differed widely in design, participant number (usually low, i.e. < 50) and duration of creatine supplementation. Among these studies, some had used loading doses up to 26 g/day for less than a week followed by maintenance doses of 3-5 g/day, and with supplementation periods usually lasting between 1 and 3 months. Moreover, the participants were usually healthy athletes. In some studies, an increase in serum concentration of creatine was noted whereas in others, no changes were detected. The AESAN (2012) considered that an observed safe level of 5 g creatine per day had been identified from the data on healthy individuals (Shao & Hathcock, 2006). Therefore, they suggested a tolerable upper intake level (UL) of 5 g creatine per day. The ASEAN report summarised the results of the risk analysis of creatine monohydrate considering data from clinical tests on humans described in scientific literature as follows:

- NOAEL (no observed adverse effect level) or LOAEL (lowest observed adverse effect level) in humans: > 10 g/day
- Observed safe level: 5 g/day.
- UL (tolerable upper intake level): as 5 g/day was the dose administered to healthy adults with a normal diet, the observed safe level does not require correction, and therefore the observed safe level= UL= 5 g/day.

In the AESAN (2012) report, references were given to murine studies showing that at doses ranging from 0.05 to 2 g creatine/kg bw per day for 2 and 8 weeks, no alterations that compromised the renal function were found.

AESAN (2012) concluded that a maximum amount of 3.0 g/day creatine monohydrate was acceptable from a safety point of view for use as a food supplement; however a maximal duration of such use was not determined.

The literature search was not described in the report.

2.1.2 Literature search

For this risk assessment several literature searches have been performed:

1. Relevant publications listed in the VKM (2010) opinion (Annex 2 in that opinion) were identified.
2. A literature search was performed in MEDLINE and EMBASE in order to retrieve publications on adverse effects caused by creatine in human studies. These databases were chosen to ensure comprehensive study retrieval. This main literature

search for human studies published since 2009 was to complement the evidence considered in previous reports, and was performed on 24 May 2016.

3. When writing this risk assessment it was considered that a specific literature search for children and adolescents was needed. This search was performed on 4 June 2015 and had no restriction on publication year.
4. An additional search for animal studies was conducted on 10 September 2015, limited back in time to the year 2000.

The strategies for these additional searches are also included in Appendix 1.

2.1.2.1 Publication selection and data extraction

The study types for inclusion in this opinion have been human and animal studies. The criteria for inclusion were:

- Creatine in relation to adverse effect must be addressed in the abstracts of the paper
- Result not affected by other substances than creatine
- Oral route of exposure to creatine in human and animal studies
- Human studies were performed in apparently healthy individuals or patient groups who are assumed to have normal creatine absorption and metabolism.

In vitro studies were not included. Also papers in languages other than English, Norwegian, Danish or Swedish were excluded.

Nine of 23 publications from the literature search in the VKM (2010) opinion (Annex 2 in that opinion) were included according to the criteria given above.

The literature search for human studies identified 106 articles. Study titles, abstracts and some full text articles were reviewed by two Panel members, resulting in selection of 17 full text articles. After a secondary screening of these 17 articles, eight of them were considered relevant.

The literature search specified for children and adolescents identified 143 titles and abstracts, but did not result in any selection of relevant for the current risk assessment.

The search specified for animal studies identified 603 publications. Nine of these were examined in full text, resulting in inclusion of three publications.

During the scrutiny of the animal studies we became aware of four human studies which were published prior to 2009 and thus not identified in the other literature searches. These four references have been included in the present risk assessment.

A final total of 21 studies in humans and 3 animal model studies were included in the results in this report (see Figure 2.1.2.1-1).

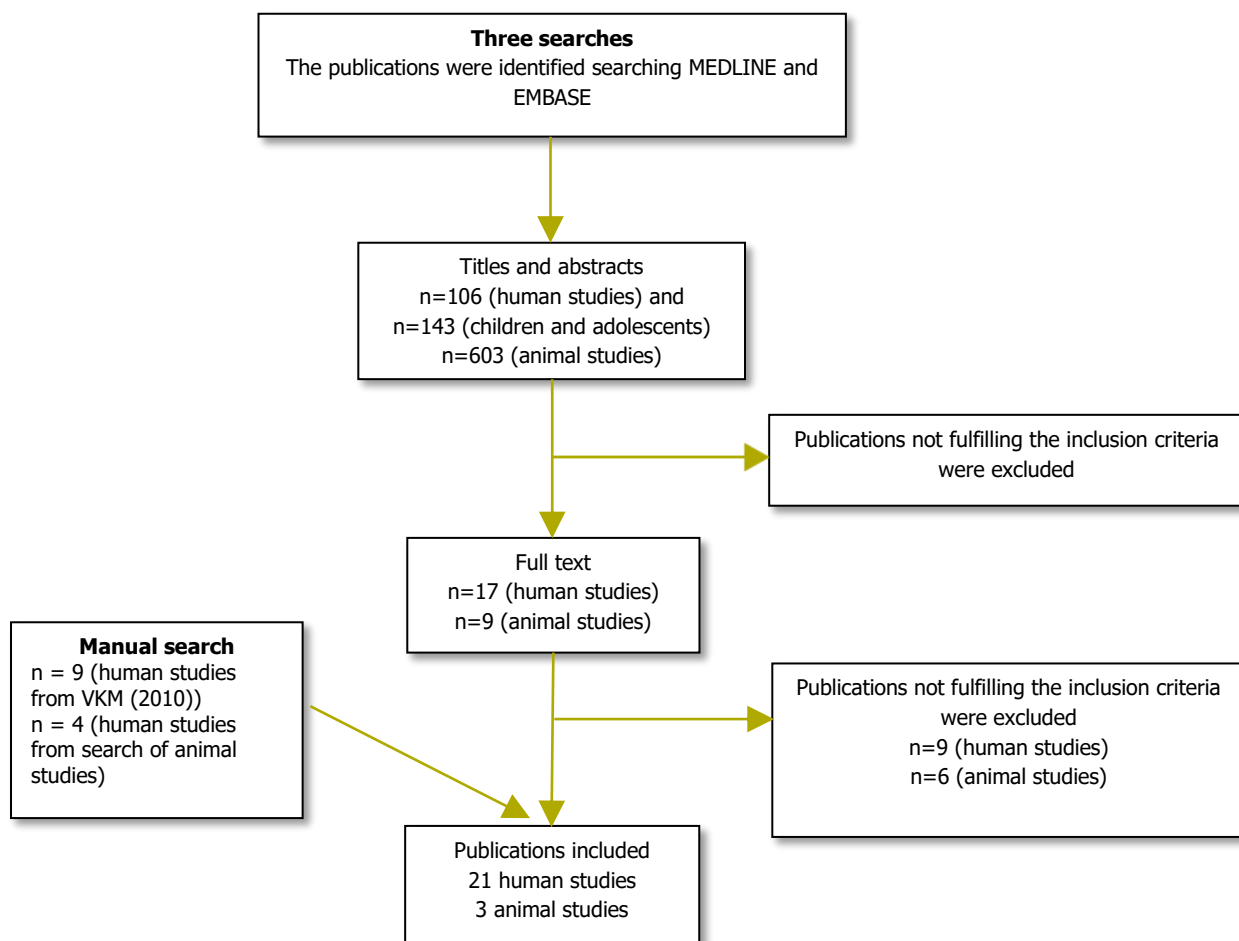


Figure 2.1.2.1-1: Flow chart for publication selection for creatine literature searches.

2.2 General information

2.2.1 Chemistry

Creatine, a water soluble compound, has CAS-number 57-00-1 and the chemical formula is $C_4H_9N_3O_2$.

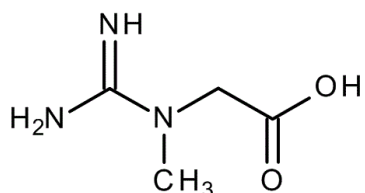


Figure 2.1.1.-1: Structural formula for creatine.

2.2.2 Occurrence

Endogenous creatine is synthesised from the essential amino acids arginine and glycine through enzymatic reactions in the kidneys to yield guanidinoacetate that is blood-borne to the liver to be methylated to creatine with methionine as methyl donor. In addition to the endogenous production, creatine is obtained through foods, mainly meat and fish, and from food supplements. The daily turnover of creatine is estimated to approximately 2 g with about 1 g being produced in the body and 1 g coming from foods (VKM, 2010).

2.3 Absorption, distribution, metabolism and excretion

Following the intestinal absorption of creatine it is transported in blood, mainly to the skeletal muscles where 95% of the total creatine pool is located. The main breakdown of creatine and phosphocreatine to creatinine takes place in the muscles. When energy demand increases, phosphocreatine donates its phosphate group to adenosine diphosphate to produce ATP. Phosphocreatine may, under certain conditions (e.g. lack of other energy-yielding substrates), become a limiting factor for ensuring adequate amounts of ATP during short term exercise. Supplementation of creatine increases phosphocreatine in skeletal muscle.

The kidneys have a dual role in creatine metabolism, partly by providing guanidinoacetate and partly by excreting creatine into the urine as creatinine. Moreover, the blood concentration of creatinine is dependent of the size of the muscle mass. Supplemented creatine in excess of what is stored in skeletal muscles is, with loss of water, non-enzymatically converted to creatinine and excreted through the kidney into urine mainly by filtration, but also by tubular secretion. There is little tubular reabsorption. Retention of creatinine is usually a sign of renal impairment. However, in otherwise healthy subjects, creatine supplementation in excess of what is stored in skeletal muscle may temporarily lead to elevated serum concentrations of creatinine which should not necessarily be regarded as a sign of renal dysfunction.

2.4 Adverse effects

2.4.1 Human studies

Table 2.4.1-1 summarises the publications retrieved in the literature searches. A more in-depth description of the various studies is given in chapter 2.4.1.1 and 2.4.1.2. The methods for evaluating adverse health effects sometimes either lack or are only superficially described.

Table 2.4.1-1: Overview of human studies investigating creatine and adverse health effects.

Reference	Participant characteristics	Country	Number in study groups		Doses	Main end points	Duration of intervention	Adverse effects
			Creatine	Control				
RCTs								
Lobo et al. (2015)	Postmenopausal women, aged 58 years	Brazil	56	53	1 g/d	Body composition	1 year	No significant difference in body composition or blood concentrations of Ca, creatinine of urinary creatinine and –albumin between the two study groups
Cooke et al. (2014)	20 healthy males aged 55-70 years	USA	10	10	20 g/d for 7 days then 0.1 g/kg bw for 7 days	Body composition and muscle strength	2 weeks	No significant difference in body composition or muscle strength or blood concentrations of IGF-1 or testosterone between the two study groups
Atashak and Jafari (2012)	18 young male soccer players	Iran	9	9	0.3 g/d	Markers of cellular damage	1 week	Significantly increased activity of creatine phosphokinase and its myocardial isoform in the intervention group
van der Merwe et al. (2009)	20 male (aged 18-19 yrs) rugby players, cross-over study	South Africa	20	20	25 g/d for 7 days followed by 5 g/d for 14 days	Ratio of dihydrotestosterone (DHT) to testosterone (T)	21 days	The ratio of DHT:T increased significantly after creatine supplementation
Ostojic and Ahmetovic (2008)	Male soccer players	Serbia	20 (5 gx2) 19 (10 gx1)	20	5 gx2 daily 10 gx1 daily	Gastrointestinal stress	28 days	Diarrhea was significantly more pronounced in the 10x1 g group than in placebo
Gualano et al. (2008)	18 healthy men aged 18-35 years	Brazil	9	9	10 g/d	Renal function	3 months	No significant difference in any of the measured markers (cystatin C, urinary Na and K) was observed between the two study groups
Gotshalk et al. (2008)	Healthy women (n=30), aged 58-71 years	USA	15	15	0.3 g/kg bw	Body composition and muscular strength	7 days	In the intervention group muscular strength, body weight and fat free mass increased significantly. No adverse effects were observed in any group
Cancela et al. (2008)	Male (n=14) soccer players	Uruguay	7	7	15 g/day for 7 days then 3 g/d for 49 days	Biomarkers	56 days	No significant difference in blood or urine markers of liver and renal function between the two study groups
Armentano et al. (2007)	15 female and 20 male army volunteers, 22-33 years; cross-over study	USA	35	35	20 g/d	Exercise performance (push-ups), renal function and blood pressure	7 days	No significant difference in exercise performance or blood pressure between the two groups; intervention group had significantly higher serum creatine

Reference	Participant characteristics	Country	Number in study groups		Doses	Main end points	Duration of intervention	Adverse effects
			Creatine	Control				
Poortmans et al. (2005)	20 healthy men, mean (SEM) age 24.1 (1.3) years	Belgium	10	10	21 g/d	Biomarkers of renal function	14 days	A significant increase in blood and urine creatine was observed in the intervention group, but no significant difference in creatinine or urinary albumin. The 24 h urine excretion of methylamine and formaldehyde increased significantly in the intervention group
Mihic et al. (2000)	15 women (58-64 kg) and 15 men (81-82 kg), age 21-23 years	Canada	15	15	5 gx4/day for 5 days	Total and lean body mass	5 days	No significant difference in creatinine, creatine kinase or blood pressure between intervention-and control groups
Robinson et al. (2000)	Healthy subjects, men and women mean age 22-24 years	UK	7 (5 days) 7 (8 weeks)	13	5 gx4/day for 5 days 5 gx4/day for 5 days, then 3 g/day for 8 weeks	Biomarkers for organ functions	5 days + 8 weeks	No significant difference in biomarkers of hematology, kidneys, liver or skeletal muscle between intervention-and control groups
Other studies								
Pereira et al. (2015)	Cross-over study of healthy 10 females and 11 males; aged (mean± SD) 29±4 yrs	Brazil	21	21	7 g/d for 7 days, then 2 g/d for 23 days	Production of heterocyclic amines	30 days	No significant difference in urinary heterocyclic amines between the creatine and placebo groups
Murphy et al. (2005)	Prospective study of 18 healthy males performing a cycling exercise	Australia	9	9	20 g/day for 7 days followed by 10 g/day for 21 days	Cardiac function	28 days	No significant difference in echocardiographic evaluation of the heart or blood pressure between intervention-and control groups
Schroder et al. (2005)	Prospective study of 18 professional male basketball-players, mean age 24 years, mean BMI 24.2 kg/m ²	USA			Loading dose 20 g/day for 5 days, then maintenance dose of 5 g/day	Clinical health parameters measured as biomarkers	3 seasons, each lasting 8 months	No abnormal values detected for creatinine, lipids or liver enzymes
Santos et al. (2004)	Prospective study of 34 male athletes aged 21.4-30.1 years running a 30 km race	Brazil	17	17	20 g/d (4 times 5 g)	Inflammation markers	5 days	In the control group creatine kinase, lactate dehydrogenase, prostaglandin E2 and tumor necrosis factor alpha increased significantly compared to the creatine group. No adverse effects were observed in any of the two study groups
Schilling et al. (2001)	Retrospective study of 8 female and 18 male athletes, mean age 24 years	USA			Loading dose 13.7 ± 10.1 g/day; maintenance dose 9.7 ± 5.7 g/day	Biomarkers for organ functions	0.8-4 years	No reported clinical adverse effects. No abnormal biomarker value found

Reference	Participant characteristics	Country	Number in study groups		Doses	Main end points	Duration of intervention	Adverse effects
			Creatine	Control				
Reviews								
Hall and Trojjan (2013)	Non-systematic review, wide range of study subjects				Typically loading dose of 0.3 g/kg bw and maintenance dose of 0.03 g/kg bw.		Short term concerning loading dose (5-7 days) and maintenance dose for 4-6 weeks	No adverse effects on renal function, report some cases of water retention
Gualano et al. (2012)	Athletes, healthy subjects, heterogeneous patient-groups				3-20 g/day		< 5 years	No negative effects of creatine on biomarkers of liver and kidney function
Kim et al. (2011)	Athletes, healthy subjects				3-20 g/day		< 3 years	No negative effects of creatine on biomarkers of liver and kidney function. Inconclusive if creatine increases the formation of heterocyclic amines (mutagenic/carcinogenic compounds)
Jager et al. (2011)	Systematic review				Not detailed		Not detailed	Concluded that creatine supplementation is not associated with adverse effects

2.4.1.1 Randomised controlled trials

Lobo et al. (2015) performed a double-blind randomised controlled trial (RCT) on postmenopausal women consuming 1 g/day of creatine or placebo for 1 year. They could not detect any significant difference in body composition or blood concentrations of calcium, creatinine of urinary creatinine and –albumin between the two study groups.

Cooke et al. (2014) performed a double-blind RCT on healthy men consuming 20 g creatine per day for 1 week followed by consumption of 0.1 g creatine per kg bw for 1 week or placebo. No significant differences in body composition, muscle strength or blood concentrations of IGF-1 or testosterone were detected between the two study groups after a period of 12 weeks training following the creatine supplementation.

Atashak and Jafari (2012) performed a double-blind RCT among 18 young male soccer players consuming 0.3 g/kg bw per day of creatine monohydrate (CrM) for 1 week or placebo. The endpoint was markers of cellular damage including creatine phosphokinase (CK) and its myocardial isoform (CKMB). They concluded that "The present results suggest that serum CK and CKMB activity as indirect markers of cellular damage increases by the oral short-term CrM supplementation in young male soccer players." VKM notes that the increase in CKMB in the creatine supplemented group was only from about 20 to 22 IU/l, the corresponding ratio of CKMB to CK being about 0.06, meaning that one cannot conclude that the increase in CKMB reflects tissue injury, as also cautioned by the authors themselves.

Hence, VKM has not emphasised this study in the overall-risk assessment in the present report.

van der Merwe et al. (2009) performed a double-blind crossover RCT with a 6 week washout period. A daily dose of 25 g creatine was consumed for 1 week followed by a daily maintenance dose of 5 g creatine for 2 weeks. The ratio of dihydrotestosterone to testosterone increased significantly by 36% after 7 days of creatine supplementation and remained elevated by 22% after the maintenance period. The authors called for more studies on possible effects of creatine supplementation on androgen conversion.

Ostojic and Ahmetovic (2008) studied gastrointestinal discomfort among 59 top level male soccer players in a double-blind placebo RCT lasting 28 days, with 3 groups: 1 group receiving 5 g of creatine 2 times a day (n=20); 1 group receiving 10 g/daily (n=19) and a placebo-group (n=20). They reported significantly more diarrhea among the group receiving 10 g daily of creatine compared with placebo. No other significant signs of gastrointestinal discomfort were observed. No other adverse effects were mentioned.

In a double-blind RCT, 9+9 healthy sedentary men received 10 g of creatine for a 3 month period (Gualano et al., 2008). While serum creatinine decreased significantly in the placebo group, no significant changes were observed in blood cystatin C or urinary potassium or - sodium between the two study groups.

Gotshalk et al. (2008) performed an RCT among 30 women (58-71 years) consuming either creatine (0.3 g/kg bw) or placebo for one week. Whereas muscular strength, body weight and fat free mass increased significantly in the intervention group, no adverse effects were observed in any group.

In a double-blind RCT, Cancela et al. (2008) studied blood and urinary biomarkers of renal and hepatic function among 7+7 male soccer players consuming 15 g creatine per day for one week followed by a daily intake of 3 g creatine for 7 weeks. No significant difference between the two study groups was observed for any of the measured hepatic (transaminases) or renal markers (creatinine levels).

In a double-blind randomised cross-over study, Armentano et al. (2007) studied the effect on exercise performance (push-ups), serum creatine and blood pressure among 15 female and 20 male US army volunteers after daily consumption of either creatine (20 g/day) or taurine (as placebo) for 7 days. Although no significant differences were observed in exercise performance or blood pressure between the two study groups, an increase in serum creatine ($p < 0.001$) was detected in the intervention group compared to the control group.

In a double-blind RCT of 20 healthy men consuming 21 g/day of creatine for two weeks, a significant increase in blood- and urine creatine, but no change in creatinine or urinary albumin, was detected in the intervention group compared to the control group (Poortmans et al., 2005). The 24 h urine excretion of methylamine and formaldehyde increased significantly in the intervention group compared to the control group.

In a RCT by Mihic et al. (2000), healthy men (n=15) and women (n=15) randomly received 5 g creatine 4 times daily for 5 days (n=15) or placebo (n=15). They found that supplementation of creatine resulted in no significant difference in the blood concentrations of biomarkers renal (creatinine, creatinine clearance) or skeletal muscle function (creatine kinase) or in blood pressure compared with placebo.

In a RCT by Robinson et al. (2000), healthy men and women were received either 1) 5g creatine 4 times daily for 5 days (loading dose; n=7), 2) 5 g creatine 4 times (loading dose) daily plus 3 g creatine per day for 8 weeks (maintenance dose; n=7) or 3) placebo (n=13). They found no significant difference in the blood concentrations of biomarkers for hematological (blood cell counts), renal (urea, creatinine), hepatic (albumin, bilirubin) or skeletal muscle function (creatine kinase) after supplementation of creatine compared to placebo.

2.4.1.2 Other studies

Pereira et al. (2015) examined healthy women and men consuming 7 g/day of creatine for one week followed by 2 g/day for 23 days. They could not find any significant difference in urinary heterocyclic amines between the creatine and placebo groups.

Pereira et al. (2015) wrote a non-systematic review capturing a wide range of study participants, typically using a loading dose of 0.3 g/kg bw per day lasting 5-7 days followed by a maintenance dose of 0.03 g/kg bw for 4-6 weeks. With the exception of a few cases of water retention, neither adverse renal effects nor other adverse effects were reported. Reportedly, there is no pertinent data on use of creatine supplementation among subjects < 18 years.

Gualano et al. (2012) published a narrative review reporting possible beneficial and harmful effects of creatine supplementation (3-20 g/day for up to 5 years) in athletes, healthy subjects and patients diagnosed with various disorders. They concluded that creatine had an "excellent safety profile".

Jager et al. (2011) presented a systematic review of various aspects related to creatine supplementation, including inter alia chemical aspects, various forms of creatine and country-specific regulation. They concluded that "No medically significant side effects have been reported from creatine supplementation despite the widespread worldwide use and the regulatory status of creatine not being well established. Conversely, the efficacy, safety, and regulatory status of most of the newer forms of creatine found in dietary supplements have not been well established."

In a non-systematic review, Kim et al. (2011) quoted a number of studies testing creatine 3-20 g/day for up to 3 years in heterogeneous populations. They concluded that no abnormal change was established for blood biomarkers of liver- and renal function. They discussed whether high doses of creatine supplementation may increase the concentration of

heterocyclic amines, compounds with potential mutagenic/carcinogen effects. However, no firm conclusion was drawn due to conflicting data.

Murphy et al. (2005) studied 18 males undertaking an ergometer cycling exercise. Nine participants received creatine (20 g/day for 7 days, then 10 g/day for 21 days), while 9 participants served as a control group. No significant difference was detected between the two groups in terms of ultrasound examination of the heart or in blood pressure values.

Schroder et al. (2005) prospectively studied long term (3 times periods of 8 months) use of creatine given as loading dose of 20 g/day for 5 days and then a maintenance dose of 5 g/day to 18 professional basketball-players. No abnormal blood concentration was noted for creatinine, lipids or liver enzymes.

Jager et al. (2011) studied 34 male marathon runners performing a 30 km running race after receiving 20 g creatine per day (divided in 4 doses) for the previous 5 days or placebo. In the control group, creatine kinase, lactate dehydrogenase, prostaglandin E2 and tumor necrosis factor alpha increased significantly compared to the intervention group. No adverse effects were observed in any of the two study groups

Schilling et al. (2001) retrospectively studied long term (0.8-4 years) use of creatine given as loading dose (duration not specified; mean \pm SD) of 13.7 ± 10.1 g/day or a maintenance dose of 9.7 ± 5.7 g/day to 26 athletes. No clinical adverse effects were found (based on a questionnaire) and no abnormal biomarker values of liver (enzymes) or renal (creatinine) function were noted.

2.4.1.3 Interactions

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

2.4.1.4 Allergic sensitisation and adjuvant effects

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

2.4.2 Animal studies

The EFSA (2004) opinion presented animal data showing that the acute toxicity of creatine is low (LD_{50} in the rat is higher than 2 g/kg), and that it is not mutagenic according to the Ames test. Creatine had also been tested in a 28-day rat study in which no treatment related adverse effects were reported after dose levels up to 2 g/kg bw per day.

In the report by AESAN (2012) references were given to murine studies showing that at doses ranging from 0.05 to 2 g creatine/kg bw per day for 2 and 8 weeks, no effects or alterations that compromised the renal function (determined as tissues concentration of creatine and inulin clearance) were found.

Taes et al. (2003) studied 10 male Wistar rats (200-230 g) given a creatine supplement (mean 0.9 g/kg bw per day) for 4 weeks. Compared to a placebo-group (n = 10) no impairment in renal function (measured as clearance for urea and creatinine and inulin and urinary protein excretion) was noted.

Ferreira et al. (2005) studied male Wistar rats receiving 2 g of creatine per kg consumed food daily for 10 weeks. Four groups were included: One with creatine supplementation only (n=10); one with creatine supplementation plus treadmill exercise (n=12), one with exercise only (n=7) and one control group (n=7). The use of creatine alone induced a significant reduction of both renal perfusion and glomerular filtration rate. The amount of consumed creatine was expressed per mass consumed food, and whether the animals actually ate all the food was not controlled. In addition these values were measured in the anesthetised animal after open surgery, thus probably not mimicking renal physiology in awake, free living mammals. Hence, VKM has not included this study in the overall-risk assessment in the present report.

Souza et al. (2013) studied male Wistar rats (7 per group) weighing (mean \pm SD) 105 ± 4 g. They were divided in five groups: control, oral creatine supplementation, moderate exercise training, moderate exercise training plus oral creatine supplementation and pathological group (positive control for liver and kidney injury) by the administration of rifampicin. The oral creatine group was given a loading dose of 5 g/kg bw per day for one week followed by 1 g/kg bw per day for 40 days. A significant increase in the activity of liver enzymes as well as in the blood concentrations of urea and creatinine were found among the creatine-treated rats compared to the controls at the end of the study period. However, the liver enzymes increased both in the control and in the creatine treated groups. Notably, these increases were far below that noted in rats treated with rifampicin, a drug known to cause liver and kidney injury. Importantly, the urine excretion of albumin was not affected upon creatine consumption. Hence, VKM has not emphasised this study in the overall-risk assessment in the present report.

Baracho et al. (2015) studied 4 groups of male Wistar rats (200-250 g): group 1 received 0.5 g/kg bw per day of creatine; group 2 received 1 g/kg bw per day, group 3 received 2 g/kg bw per day, and group 4 served as a placebo-control. The treatment lasted for 2 weeks. No significant changes were noted between the 3 treated groups and the placebo group concerning liver enzymes, lipid profile or creatinine clearance. Due to the low number of rats per group (n=6) and short duration (2 weeks), VKM finds the data insufficient to conclude that the applied doses in this study would be without adverse effects in humans.

2.4.3 Mode of action for adverse effects

No specific modes of action for adverse effects have been identified.

2.4.4 Vulnerable and high intake groups

There is no relevant, specific information in the four previous risk assessments (AESAN, 2012; EFSA, 2004; SCF, 2000; VKM, 2010) or the literature search relating to vulnerable groups (e.g. fetuses, children, pregnant/lactating women and the elderly). Previous risk assessments caution about the use of creatine supplements by patients suffering from impaired renal function. In addition, "athletes" have been reported to tolerate higher doses of creatine than the 3 g/day that is given as the maximal daily dose for adults in general by the previous risk assessments. However, the definition, and consequently the metabolism, of "athletes" in previous studies and reports are highly variable, constituting both professional sportsmen and people performing recreational activities in various types of exercise. Thus, for the present assessment we do not consider "athletes" to represent any particular population subgroup, but rather to constitute a part of the general population to which dietary supplements are marketed.

2.5 Summary of hazard identification and characterisation

SCF (2000) concluded that intake of creatine in doses not exceeding 3 g/day is unlikely to pose any risk. It was not explicitly stated how the conclusion on 3 g was reached. Furthermore it was stated that high loading doses should be avoided. EFSA (2004) based its data mainly on SCF (2000) and concluded likewise.

VKM (2010) supported EFSA (2004) that supplementation with creatine up to 3 g/day was unlikely to pose any risks. It was stated that long-term studies with doses up to 5-10 g/day in adult athletes had shown no harmful effects.

The tested doses in studies reported by AESAN (2012) varied from about 1.0 to 30.0 g/day and usually for periods shorter than one month, and AESAN (2012) concluded that a maximum amount of 3.0 g/day of creatine monohydrate was acceptable from a safety point of view for use as a food supplement. Similar to VKM (2010), AESAN (2012) reported that long-term studies with doses up to 5-10 g/day in adult athletes had shown no adverse effects.

According to the VKM opinion from 2010 gastrointestinal and cardiac symptoms (unspecified) have been reported, but these adverse effects had not been verified in well-controlled studies.

Data from the literature searches are heterogeneous in terms of study subjects (e.g. athletes or healthy persons, i.e. study populations that may differ widely in skeletal muscle mass and endurance capacity, aspects that are likely to influence creatine metabolism), supplemental

dose of creatine, and duration of the studies. Most of the studies (including the RCTs) conclude that doses up to 3 g/day for shorter periods (1-4 weeks) are safe. The studies based on long term exposure (i.e. 1-5 years) and/or with daily creatine intake > 3 g (range 5-21 g) often (i) involved few and highly trained individuals of whom some took high daily loading doses of creatine (range 2-25 g) for a short period (usually < 1 week), and (ii) were designed to test clinical benefit without emphasis on adverse effects, in particular firm clinical endpoints, i.e. information about possible organ dysfunctions, are lacking. Overall therefore, the documentation for absence of adverse health effects of doses above 3 g per day of creatine in food supplements in the general population is limited and these doses may therefore represent a risk of adverse health effects in adults.

Due to the important role of the kidneys in creatine metabolism and clearance from the blood, the kidneys have been of particular focus in many studies. However, renal function has mostly been inadequately assessed since usually blood biomarkers such as creatinine have been measured (see section 2.3). Studies with more relevant endpoints like renal perfusion, glomerular filtration rate, hormonal outputs and histology have often not been identified. Therefore, based on available data from the previous risk assessments and the literature searches in the current report, VKM has not been able to find conclusive documentation that the doses tested of creatine supplementation adversely affect renal function.

Whether creatine use in high doses, will promote the formation of compounds with potential mutagenic/carcinogen effects, has not been clarified, but there is currently no available evidence to support the clinical relevance of this notion. Importantly, both EFSA (2004) and AESAN (2012) quoted murine studies showing no mutagenic effects or signs of renal dysfunction at doses of 50 to 2000 mg creatine/kg bw per day for use up to one month.

The highest dose tested in the animal experiments was a maintenance dose of 2 g/kg bw per day, and this was not associated with adverse outcomes when used for 8 weeks. This study and the results reported from the other included animal studies are in line with those obtained in the human studies and gave no cause of additional concern about the use of creatine. However, the animal studies mostly focused on renal function whereas other possible adverse effects were largely omitted from the analyses. Also, few doses were tested and the studies were not performed according to OECD guidelines or other approved standards. Moreover, as detailed in the description of the animal research assessed in the present report (see section 2.4.2), several limitations were noted for the individual studies, Therefore VKM has not used the results from the animal studies in the risk characterisation of the specified doses of creatine. Consequently the data from these animal studies did not change VKM's conclusion that doses above 3 g per day may represent a risk of adverse effects in humans.

There is no information about risk related to use of creatine supplements among healthy children/adolescents aged 10-17 years.

As a value for comparison in the risk characterisation of creatine, VKM will use 3.0 g/day corresponding to 43 mg/kg bw per day in a 70 kg adult. This value is based primarily on the SCF (2000) and supported by VKM (2010) and AESAN (2012) as well as the articles identified in the literature searches and stems from studies of healthy humans, and is supported by animals studies. VKM considers the evidence of absence of adverse effects from studies providing creatine doses higher than 3 g/day to be insufficient, as these studies were characterised by low sample sizes, short duration, markedly heterogeneous study populations and poor reporting of possible adverse effects.

3 Exposure / Intake

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

3.1 Food supplements

The Norwegian Food Safety Authority has requested a risk assessment of 3.0, 5.0, 10.0 and 24.0 g/day of creatine in food supplements for children 10 years and above, adolescents and adults. The default body weights (bw) determined by 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 creatine from specified doses in food supplements in children, adolescents and adults.

Groups	Daily doses	Body weight	Exposures (mg/kg bw per day)
Children (10 to <14years)	3.0, 5.0, 10.0 and 24.0 g	43.4	69, 115, 230 and 553
Adolescent (14 to <18 years)	3.0, 5.0, 10.0 and 24.0 g	61.3	49, 82, 163 and 392
Adults (≥ 18 years)	3.0, 5.0, 10.0 and 24.0 g	70.0	43, 71, 143 and 343

3.2 Other sources

Creatine can also be obtained through the diet, mainly from meat and fish. The average daily intake from the diet is about 1 g creatine, and the endogenous production also amounts to about 1 g/day (SCF, 2000).

4 Risk characterisation

The doses received from NFSA are 3.0, 5.0, 10.0 and 24.0 g/day creatine in food supplements, and the exposures for adults, children and adolescents are given in chapter 3.

The value for comparison used in this risk characterisation is 3 g/day (corresponding to 43 mg/kg bw/day in a 70 kg person).

The studies included in the previous risk assessments as well as those identified in the literature searches, are heterogeneous in terms of dosage, duration and study subjects. Moreover, few of the studies have primarily addressed adverse health effects following use of creatine supplementation.

Most of the studies report 3 g/day as an upper dose for safe use, although the choice of testing this particular dose of 3 g/day has not been explained.

No particular adverse effects were identified. In particular, there is no evidence that creatine in doses up to 3 g/day adversely affect renal function.

The data from the animal experiments support those found in the human studies in so far that no additional adverse effects were identified at doses used in the animal experiments compared with 43 mg/kg bw per day in a 70 kg person (the value of comparison in this risk assessment).

There are no relevant studies of vulnerable groups (e.g. fetuses, children, pregnant/lactating women and the elderly).

No tolerance level is set for L-creatine specifically for children or adolescents. There are no data indicating that children and adolescent are more vulnerable than adults for L-creatine. Assuming similar tolerance for these age groups as for adults, doses below 43 mg/kg bw per day in children and adolescents are considered to be unlikely to cause adverse health effects.

VKM considers that in adults (≥ 18 years), the specified dose of 3.0 g/day creatine in food supplements is unlikely to cause adverse health effects. While there are some studies with variable duration and small numbers in athletes indicating that higher doses (between 5 to 10 g/day), the evidence of absence of adverse health effects of doses 5.0, 10.0 and 24.0 g/day creatine in food supplements in the general population is limited. These doses may represent a risk of adverse health effects in adults.

In children (10-14 years) and adolescents (14-17 years) the specified doses of 3.0, 5.0, 10.0 and 24.0 g/day creatine in food supplements may represent a risk of adverse health effects.

5 Uncertainties

Most studies of creatine as supplements have not been specifically designed to address adverse health effects, in particular RCTs are missing, and some adverse effects might therefore not have been detected. In the human studies, the adverse effects reported are partly based on self-reporting, and partly on intermediate endpoints/surrogate biomarkers for negative health effects (e.g. serum creatinine concentration). Furthermore, in several studies there is no information on how the adverse effects have been examined.

In addition, no dose-response related to adverse effects have been observed, hence the documentation supporting a daily dose of 3.0 g is limited. The data for potential adverse health effects from long term use are not well documented.

The studies have often included a low number of participants. In some studies various patient groups have been included, with or without impaired renal function, making comparisons between studies difficult. Athletes have been studied because of their relatively high intake of creatine supplements, however the term "athlete" has not been defined, and we do not know if an extrapolation of data from athletes to the general adult population can be justified in all cases. No studies on creatine have been identified in healthy children or adolescents.

Most of the studies (including the RCTs) have concluded that doses up to 3 g/day for shorter periods (1-4 weeks) are safe. There is a lack of studies testing doses above 3 g/day and for longer durations. Notably, the studies based on long term exposure (i.e. 1-5 years) and/or with daily creatine intake above 3 g often (i) involved few and highly trained individuals of whom some took high daily loading doses of creatine for a short period (usually < 1 week), and (ii) were designed to test clinical benefit without emphasis on adverse effects, in particular firm clinical endpoints, i.e. information about possible organ dysfunctions, are lacking.

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 creatine in food supplements at the following doses: 3.0, 5.0, 10.0 and 24.0 g/day for the general population, ages 10 years and above.

Available documentation suggests that use of creatine in doses up to 3 g/day supplemental creatine is unlikely to cause adverse health effects.

Studies with daily creatine intake above 3 g were performed with few and highly trained individuals of whom some took high daily loading doses of creatine for a short period and they were mostly designed to test clinical benefit without emphasis on adverse effects. Overall therefore, the documentation for absence of adverse health effects of doses > 3 g per day of creatine in food supplements in the general population is limited and these doses may therefore represent a risk of adverse health effects in adults.

No relevant information about adverse health effects of creatine supplements among putative vulnerable groups such as fetuses, children, pregnant women and the elderly have been identified.

VKM concludes that:

- In adults (\geq 18 years) a daily dose of 3.0 g/day creatine in food supplements is unlikely to cause adverse health effects. Doses of 5.0, 10.0 and 24.0 g/day creatine in food supplements may represent a risk of adverse health effects.
- In children (10-14 years) and adolescents (14-17 years) the specified doses of 3.0, 5.0, 10.0 and 24.0 g/day creatine in food supplements may represent a risk of adverse health effects.

An overview of the conclusions is presented in Table 6-1.

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

	Creatine			
Doses	3 g/day	5 g/day	10 g/day	24 g/day
Age groups				
Children (10 to <14 years)	Red	Red	Red	Red
Adolescents (14 to <18 years)	Red	Red	Red	Red
Adults (≥18 years)	Green	Red	Red	Red

7 Data gaps

There is lack of both short- and long term studies in humans of creatine with adverse health effects as the primary outcome that are of sufficient quality. Usually intake of creatine supplements is limited to a few weeks or days, often related to participation in exercise activities. However, we lack information about the safety in a longer-term perspective.

Data are lacking to draw any conclusion regarding whether the doses 5.0, 10.0 and 24.0 g/day creatine in food supplements may represent a risk of adverse health effects in adults.

There are few if any relevant studies on adverse health effects related to creatine in fetuses, children and adolescents, as well as in pregnant/lactating women and the elderly.

Identification of more biomarkers with a direct link to creatine metabolism is also called for.

In order to determine possible mechanisms for adverse effects, well-designed animal studies may yield important information.

8 References

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Appendix 1

Search strategies for this risk assessment

Search strategy for human studies

Database: Embase <1974 to 2016 May 24>, Ovid MEDLINE(R) In-Process & Other Non-Indexed

1. creatine*.ti. (18667)
2. creatine kinase.ti. (10220)
3. 1 not 2 (8447)
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. (9928737)
5. 3 and 4 (925)
6. (conference abstract* or letter* or editorial*).pt. (4995370)
7. 5 not 6 (862)
8. limit 7 to (danish or english or norwegian or swedish) (797)
9. limit 8 to human (545)
10. limit 9 to yr="2009-Current" (181)
11. remove duplicates from 10 (106)

Search strategy for studies in children and adolescents

Database: Ovid MEDLINE(R) <1946 to June Week 1 2015>, Embase <1974 to 2015 June 04>

1. creatine*.ti. (17940)
2. creatine kinase.ti. (10019)
3. 1 not 2 (7921)
4. (child* or adolescent* or teenage* or college*).tw. (2739571)
5. 3 and 4 (296)
6. (conference abstract* or letter* or editorial*).pt. (4465372)
7. 5 not 6 (275)
8. limit 7 to (danish or english or norwegian or swedish) (226)
9. limit 8 to human (201)
10. remove duplicates from 9 (143)

Search Strategy for animal studies

Database: Embase <1974 to 2015 September 10>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>

1. creatine*.ti. (18513)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (9460797)
3. 1 and 2 (2219)
4. (conference abstract* or letter* or editorial*).pt. (4714936)
5. 3 not 4 (2094)
6. limit 5 to (danish or english or norwegian or swedish) (1940)
7. limit 6 to yr="2000 -Current" (1208)
8. remove duplicates from 7 (654)
9. limit 8 to animal studies [Limit not valid in Ovid OLDMEDLINE(R),Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process; records were retained] (603)