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Norwegian Scientific Committee for Food Safety

Assessment of creatine in sports products

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

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Assessment of creatine in sports products

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Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employers. 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 appointed an *ad hoc* group consisting of both VKM members and external experts to answer the request from the Norwegian Food Safety Authority. The members of the *ad hoc* group are acknowledged for their valuable work on this opinion. Thanks to Christine Helle for her valuable discussions in the initial face. She participated in two *ad hoc* group meetings.

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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) conducted an assessment of creatine in sports products (e.g. supplements). The evaluation has been performed by an *ad hoc* group, and assessed by the VKM Panel on nutrition, dietetic products, novel food and allergy.

The evaluation of safety and possible risks of creatine supplementation in this opinion is based on previous reports, 23 original papers and 14 reviews from literature searches.

Marketing and sales of sport products are increasing in the Nordic countries, with creatine supplements being one of four most common categories. In addition to be used by athletes, the use of creatine supplements seems to increase among general exercisers and young people. Creatine supplements are mainly used for their supposed effects on muscles mass and high intensity and short duration sport performances. Supplementation has been shown to result in higher concentration of creatine phosphate in the muscles, which is the limited substrate.

For athletes, it is recommended a loading dose of 10-20 g/day for 4-7 days and a maintenance dose of 2-5 g/day for weeks or months. Some athletes continue the maintenance dose for several years. It is well documented that creatine supplementation has positive effects on muscle mass combined with strength training and performance during maximal exercise. There are however large individual variation in the response, and there are responders and non-responders.

The new scientific literature, including long term studies, is in line with the EFSA (European Food Safety Authority) opinion from 2004.

VKM Panel on nutrition, dietetic products, novel food and allergy supports the EFSA conclusion that supplementation of creatine in doses below 3 g/day is unlikely to pose any risks if the purity of the creatine compound is adequate.

Scientific long-term studies with doses up to 5-10 g/day in adult athletes have shown no harmful effects, but there are no dose-response studies indicating a safe upper limit for creatine.

The potential negative effects (impaired kidney function, weight gain and gastrointestinal disturbances) which have been published in non scientific journals and anecdotal reports have not found support in controlled systematic studies on healthy subjects. It has been indicated that individuals with impaired kidney functions should refrain from creatine supplements.

Creatine-monohydrate is the most studied form of creatine supplements, and only creatine monohydrate has been included in the scientific investigations on adverse effects.

Norsk sammendrag

Vitenskapskomité for mattrygghet (VKM) har på oppdrag fra Mattilsynet gjennomført en vurdering av kreatin i sportsprodukter (for eksempel kosttilskudd). Vurderingen er utarbeidet av en *ad hoc*-gruppe, og godkjent i VKMs faggruppe for ernæring, dietetiske produkter, ny mat og allergi.

Denne risikovurderingen av kreatintilskudd er basert på tidligere rapporter og vurderinger samt 23 enkeltstudier og 14 oversiktsartikler fra litteratursøk. Den nye vitenskapelige litteraturen, som også inkluderer langtidsstudier, er i samsvar med EFSAs vurdering fra 2004.

Markedsføring og salg av sportsprodukter i de nordiske landene er økende, og kreatintilskudd er en av de fire mest vanlige typer tilskudd blant sportsproduktene. Bruk av kreatintilskudd synes å øke også blant mosjonister og ungdom.

Kreatintilskudd blir hovedsakelig benyttet på grunn av den antatte effekten på muskelmasse og ved idrettsaktiviteter av høy intensitet og kort varighet. Tilførsel av kreatin har vist å resultere i høyere konsentrasjon av kreatinfosfat i muskel – som er begrensende faktor for maksimal ytelse.

For idrettsutøvere anbefales en startdose på 10-20 g/dag i 4-7 dager, og deretter en vedlikeholdsdose på 2-5 g/dag i uker eller måneder. Enkelte utøvere fortsetter med vedlikeholdsdosen i flere år.

Det er godt dokumentert at kreatintilskudd har positiv effekt på muskelmasse og ved idrettsaktiviteter av høy intensitet og kort varighet. Det er imidlertid store individuelle variasjoner, og det er respondenter og ikke-respondenter.

VKMs faggruppe for ernæring, dietetiske produkter, ny mat og allergi støtter EFSAs konklusjon om at kreatin i doser under 3 g/dag sannsynligvis ikke vil medføre noen helserisiko forutsatt at renhet for kreatinforbindelsen er tilfredsstillende.

Vitenskapelige langtidsstudier med doser opp til 5-10 g/dag med voksne idrettsutøvere har ikke vist noen negative helseeffekter, men vi har ikke funnet dose-respons studier som indikerer en sikker øvre grense for kreatin.

De potensielle negative helseeffektene (nedsatt nyrefunksjon, vektøkning og gastrointestinale plager) som har blitt beskrevet i ikke vitenskapelige tidsskrifter og i anekdotiske rapporter er ikke dokumentert i kontrollerte systematiske studier med friske personer. Det har blitt antydet at personer med nedsatt nyrefunksjon bør unngå kreatintilskudd.

Kreatinmonohydrat er den mest studerte formen for kreatintilskudd, og bare kreatinmonohydrat inngår i studier som fokuserer på negative helseeffekter.

Contents

1 Background

Sports products (e.g. supplements) are classified and regulated as foods for particular nutritional uses. Creatine is not included in the list of substances that may be added to foods for particular nutritional uses (commission regulation No 953/2009). Substances other than those on the list may be added to foods for particular nutritional uses on the condition that they are safe and suitable.

According to a Nordic consumer survey[1], the marketing and sales of sport products are increasing in the Nordic countries. Grouped together, various creatine supplements are one of the four most common categories of sports products, with creatine capsules being the most common creatine supplement in Norway[2].

In Denmark, only creatine monohydrate in compliance with a national specification for DK, 126 creatine, is permitted on the market. The Danish Veterinary and Food Administration has also implemented regulations of permitted daily dose of this creatine compound with special labelling requirements.

Previous safety opinions and assessments have been valuable background documents in this VKM assessment. These previous assessments are:

- *Diet and nutrition in sport* from the Swedish Sport Confederation (Eva Blomstrand & William Apró, 2009)
- *Creatine monohydrate for use in foods for particular nutritional uses* (EFSA, 2004)
- *Food and performance – Dietary guidelines for athletes* (*Mat og prestasjon – Kostholdsanbefalinger for idrettsutøvere*) (Sosial- og helsedirektoratet, 2003)
- *Report of the Scientific Committee on Food on composition and specification of food intended to meet the expenditure of intense muscular effort, especially for sportsmen* (SCF, 2001)
- *Assessment of the risks of creatine on the consumer and of the veracity of the claims relating to sports performance and the increase of muscle mass* (AFSSA, 2001)

2 Terms of reference

The Norwegian Food Safety Authority has requested the following assessment of creatine in sports products[3].

1. Which adverse health effects have been reported due to intake of different forms of creatine (creatine compounds) (in food supplements/sports products)?
    - Can an upper safe limit for different forms of creatine (compounds) be given?

[1] Sport Nutrition Products. A Nordic Consumer Study; TemaNord 2009-531

[2] The Nordic Market for Sports Nutrition Products. A Market Analysis Using Norway as Case; TemaNord 2009-530

[3] Norsk mandat i Annex 1

- Is new scientific evidences published, or are the conclusions in the *Creatine monohydrate for use in foods for particular nutritional uses*; EFSA opinion from 2004 still valid? Does VKM support the conclusions in this EFSA opinion?
- Have certain groups in the population been identified that should avoid consumption of creatine in sports products?
- Have special risks been identified which can be connected to consumption of creatine in sports products in Norway?

2. Does creatine affect muscle mass? Have other beneficial effects from creatine supplements been identified?

3 Introduction

Creatine (N-(aminoiminomethyl)-N-methyl glycine) is a naturally occurring compound made in the liver, kidneys and pancreas from the essential amino acids arginine, glycine and methionine. In the human body approximately 95% of the total creatine pool is located in the skeletal muscle. Of this, approximately two-thirds exist as phosphocreatine (PCr) and one-third as free creatine. PCr serves a major role in energy metabolism.

The relative importance of PCr during exercise is dependent on the nature of the exercise. For most exercise situations, the demand for ATP is predominately provided through oxidative phosphorylation in the mitochondria

When energy demand increases, PCr donates its phosphate to ADP to produce ATP, providing energy at high rates for a few seconds until the PCr store is emptied. Theoretically, an increased PCr concentration should increase the energy reserve during maximum short term exercise, as PCr is a limiting factor for maintenance of ATP resynthesis during such exercise. In spite of the high concentration of creatine in the muscles, no creatine is synthesised in the muscles, but mainly in the liver, and are then being transported in blood to the muscles. In addition to the endogenously produced creatine, creatine is obtained through foods, mainly meat and fish, but also from food supplements. The daily turnover of creatine is estimated to approximately 2 gram with about 1 gram being produced in the body and 1 gram coming from foods. The main breakdown of creatine and phosphocreatine to creatinine takes place in the muscles by splitting off H_2O and phosphate, respectively. Creatinine is being excreted in the urine through the kidneys.

Creatine supplements are mainly used for their supposed effects on muscle mass and high intensity and short duration sports performances. Creatine phosphate in the muscle is the limiting substrate for maximum capacity during these exercises and supplementation has been shown to result in a higher concentration of creatine phosphate in the muscles (Harris *et al.*, 1992).

The possible ergogenic effect of creatine has led to its widespread use of supplementation in sport (LaBotz & Smith, 1999; Ronsen *et al.*, 1999; Greenwood *et al.*, 2000; Sheppard *et al.*, 2000; McGuine *et al.*, 2001; McGuine *et al.*, 2002). Ronsen *et al.* showed that 45% of Norwegian power sport athletes (boxers, weightlifters and track and field athletes) on National level were regular or occasional users of creatine. A later study determined the use of diet supplements in the total population of elite athletes in Norwegian National Teams (76 and 92% response rate in men and women, respectively) (Sundgot-Borgen *et al.*, 2003). It was found that 12% of men and 2% of female athletes used creatine, compared to 3% and 0% (men and women) in a randomly selected control group from the general population.

In addition to increased use by athletes, the use of creatine supplements seems to increase also among general exercisers and young people. Other population groups that might benefit from the claimed effects of creatine are elderly and individuals with decreased muscle mass (McMorris *et al.*, 2007; Gualano *et al.*, 2010a).

For athletes, it is commonly recommended a loading phase dose of 10-20 g/day for 4-7 days and a maintenance dose of 2-5 g/day for weeks or months. This supplementation-regime can according to the manufacturers be repeated. Some athletes continue this maintenance dose for several years (Poortmans & Francaux, 2000).

Previous reports (SCF, 2001; AFSSA, 2001; Eva Blomstrand & William Apró, 2009) conclude that there are positive effects of creatine supplementation in certain sports. Scientific studies published before and after these reports are in line with this conclusion. The focus in this VKM assessment will therefore be mainly on safety.

4 Data sources

Previous safety opinions and assessments that have been evaluated are listed in chapter 1 Background.

In addition, the following literature searches were performed in PubMed. The general creatine searches were limited to publications from 2004 and later, i.e., from the publication of the latest EFSA opinion. Furthermore, earlier dose-response studies have been evaluated because such studies have not been performed in the last years.

Search 1: Creatine supplementation in title or abstract: 481 articles in total; 197 articles from 2004 and later found. All abstract from the 197 papers published after 2004 was reviewed in order to look at main effects on performance and in order to identify papers dealing with safety aspects.

In addition to this search, the following searches were done in order to cover other papers on the safety issue:

Search 2: Creatine AND adverse OR safety OR risk OR high dose OR kidney OR renal OR side effects from 2004 and later: 46 (14 reviews and 32 original) articles found.

In addition, searches for other types of creatine than creatine monohydrate were conducted:

Search 3: Creatine pyruvate: 4 articles found.

Search 4: Creatine citrate: 6 articles found.

Finally, a last search was done to get all review papers on performance effects published in 2009 and 2010:

Search 5: Creatine supplementation in title OR abstract, review published 2009 or later: 8 review papers found.

All papers in search 2-4 was reviewed in full text and discussed together with the four reviews in search 5 dealing with performance aspects.

5 Identification and characterisation of creatine

5.1 Characteristics of creatine

Creatine N-(aminoiminomethyl)-N-methyl glycine is an amino acid derivative synthesised from arginine, glycine, and methionine mainly in the liver (approx 95%), but also in the kidneys, and pancreas. The synthesis rate is about 1–2 g/d (Walker, 1979).

Creatine can also be obtained through the diet, mainly from meat and fish (Table 1). The average daily intake from the diet is about 1 g creatine (Walker, 1979). Normal turnover rate of creatine is about 2 g/day. Consequently, endogenous synthesis and intake from the diet covers the daily turnover (Walker, 1979).

Creatine levels in the body will affect both the absorption in the intestines, uptake in tissues and clearance from the kidneys. When skeletal muscle stores become saturated, which is the case with repeated doses, the bioavailability of creatine decreases. Components like protein and carbohydrates in the food may also affect bioavailability (Bemben & Lamont, 2005; Buford *et al.*, 2007).

Creatine monohydrate is the most studied form of creatine supplements, but also creatine pyruvate (4 studies), creatine citrate (6 studies), and polyethylene glycosylated creatine (1 study) have been studied. In addition, creatine in the form of Kre-Alkalyn is reported in some non-scientific papers (see below).

In Denmark creatine monohydrate (N-(aminoiminomethyl)-N-methyl glycine) is the only form of creatine accepted for use after approval[4]. The reference for control of the specification is *Guide to JECFA Specification*, FAO Food and Nutrition, Paper no. 5, revision 2 from 1991.

The Danish Veterinary and Food Administration has accepted the use of creatine monohydrate in a daily dose of 2-3 g/day. It is expressed specifically that the products should only be used by athletes during short dynamic disciplines. The Danish reference for use of creatine monohydrate is the EFSA opinion (EFSA, 2004).

Another product of creatine which has been submitted for approval in Denmark is Kre-Alkalyn. The work on the approval for this product has not been concluded.

Some work has been performed on Kre-Alkalyn by a Bulgarian research team with commercial interests in this compound. No health effects have been observed with this compound, and they claim that the stability of Kre-Alkalyn is superior to creatine monohydrate. It is however important to stress that these reports have not been published in scientific journals.

5.2 Absorption and bioavailability

Uptake of creatine in the intestines occurs via transporters (McCall & Persky, 2007). These transporters have been identified in ileum and jejunum (in rodents) and both on the apical and basolateral membrane of enterocytes. A study of Persky *et al*. indicates two peaks in the concentration-time curve after a single dose of creatine, which may suggest more than one uptake mechanism (Persky *et al.*, 2003). At the present, only limited scientific research is available to determine mechanisms for absorption of creatine in the human intestine.

It is not known which form of creatine delivers the largest fraction of the administered dose, but in solid form creatine may be incompletely dissolved in the intestines and thus not be

[4] Specification for DK 126 Creatin, Fødevarestyrelsen 1. november 2004

absorbed. Furthermore, the bioavailability of supraphysiological doses of creatine is unknown.

Harris *et al*. compared the relative bioavailability of 2 g creatine in different forms. Results of plasma peak concentration showed that solution > suspension = pills > meat. Little difference was found in time to peak concentration, but the shape of the concentration-time curves varied for the different creatine forms, suggesting differences in absorption kinetics (Harris *et al.*, 2002).

In a study of Jager *et al*. the bioavailability of three forms of creatine supplements (creatine pyruvate, creatine monohydrate and creatine citrate was tested according to the increase in creatine plasma values after oral intake of 4.4 g (Jager *et al.*, 2007). Mean area under the curve (AUC) for plasma creatine values was higher after the creatine pyruvate intake than after the creatine monohydrate and creatine citrate intake (14-17% higher AUC). However, no significant differences between creatine forms were found for estimated velocity for absorption or elimination. Because creatine monohydrate already is reported to be absorbed close to 100% (Deldicque *et al.*, 2008), the authors concluded that the bioavailability of these three forms of creatine are similar and that the small differences found in kinetics are unlikely to have any significant effects on the availability to increase muscle creatine levels during loading phases.

The polyethylene glycosylated form of creatine was shown to have similar effects as creatine monohydrate on strength and high intensity exercise performance in one study, despite the fact that creatine in the polyethylene glycosylated form of creatine was administered in lower doses than in the creatine monohydrate form (1.25 or 2.5 g vs. 5 g creatine per day) (Herda *et al.*, 2009). It is therefore concluded in this study that creatine in the polyethylene glycosylated form has comparable ergogenic effects to creatine monohydrate, and consequently the bioavailability of creatine should also be comparable.

Several studies (Green *et al.*, 1996a; Green *et al.*, 1996b; Steenge *et al.*, 2000) have indicated an enhanced absorption of creatine in the muscles when carbohydrates and/or protein are consumed together with creatine. Also physical activity seems to increase the uptake of creatine in the muscles (Harris *et al.*, 1992; Robinson *et al.*, 1999).

In conclusion, the bioavailability of different creatine forms seems to be high, and there seems to be no major differences between creatine monohydrate and the other forms tested.

5.3 Creatine distribution

Creatine is distributed in many tissues, especially those with high energy demands, e.g., brain, eyes, cardiac muscle, skeletal muscle, testes and kidneys (Walker, 1979; Wyss & Schulze, 2002). More than 95% is found in skeletal muscle. Distribution volume of creatine is close to that of total body water (approx 45 l). Creatine is transported in plasma in unbound form, but a small fraction (<10%) may be associated/bound to plasma protein.

Creatine disposition is mainly studied in skeletal muscle. Uptake into muscle fibres is predominately by way of a sodium-chloride dependent creatine transporter (Persky *et al.*, 2003). A variety of mechanisms can regulate the transporter and thus creatine uptake rates, e.g., phosphorylation and glycosylation, in addition to changes in extra- and intracellular creatine content. Ingesting creatine with a carbohydrate source may enhance uptake, primarily through the effect of insulin stimulation of the receptor (Harris *et al.*, 1992; Green *et al.*, 1996a). Thus, glucose is a more potent stimulant than fructose.

The normal concentration of total creatine in skeletal muscle is about 120 mmol/kg (dry mass) (Harris *et al.*, 1992; Hultman *et al.*, 1996), whereas the upper limit appears to be about 150–160 mmol/kg, and in this way muscle stores of creatine will be saturated. One possible mechanism for this is down regulation of creatine transporter function or number, but there is little evidence to support this at the present. Interestingly, no saturation of creatine accumulation in brain has been found, but similar doses of creatine intake leads to a lower increase in brain creatine compared to muscle creatine (McCall & Persky, 2007).

In humans, the Km for plasma membrane transport is in the order of 20-100 µM. Plasma concentration is 25-50 µM under normal conditions, which is in the range of the Km of the transporter. This kinetics keeps interstitial concentrations at approximately 40% of plasma concentrations (Persky *et al.*, 2003). Under normal conditions, creatine kinase reaction is at equilibrium with about 2/3 of cytosolic creatine being in the phosphorylated form (Meyer *et al.*, 1984).

5.4 Removal from circulation

In healthy individuals, creatine is cleared from the blood by both kidneys and muscles (since muscles irreversibly trap and use creatine). The proportion of contribution from the two tissues probably depends on dosage of intake and dose frequency. Creatine clearance in muscles may be affected by the same factors that affect the transporters, including insulin, IGF-1, catecholamine, exercise and intracellular creatine concentrations. Since large muscle mass probably corresponds to a higher number of transporters and larger storage capacity, it seems more correct to scale the dosing to body mass or lean body mass. Findings of creatine transporters in the kidneys support that creatine can be reabsorbed from preurine (Nash *et al.*, 1994). In unsupplemented condition, the renal clearance of creatine is 0.3-0.8 l/ h which is much less than the glomerular filtration rate (GFR) (approx 7 l/h) (Poortmans *et al.*, 1997; Poortmans *et al.*, 2005). Clearance increases to 9-22 l/h under supplemented conditions. This is higher than the glomerular filtration rate and implies secretion of creatine from the blood into renal tubules.

6 Evaluation of documentation - effect on performance

The evaluation of the effects on performance from creatine supplementation is based on the previous reports (SCF, 2001; Eva Blomstrand & William Apró, 2009) and the literature search in PubMed limited to reviews from 2009/2010 (after the Swedish report), as described in chapter 4 (Data sources).

6.1 Summary from the Swedish report “Diet and nutrition within sports” regarding creatine supplements for athletes – effect on performance

Eva Blomstrand, Associate Professor in physiology and lecturer at The Swedish School of Sport and Health Sciences was given the task by the Swedish Sports Confederation to make a survey of the published scientific studies concerning diet and athletics. The report *Diet and nutrition in sport* was published in December 2009 (Eva Blomstrand & William Apró, 2009). In this report a chapter about the use of creatine monohydrate supplement is included. This section is a résumé of the creatine chapter.

According to the Swedish report, supplementation with creatine has been shown to result in higher concentrations of creatine phosphate in the muscles and an improvement of explosive performances of short durations, especially with repeated maximum performances. The mechanism behind the enhanced exercise capacity is based on the fact that creatine phosphate is the limiting substrate for maximum capacity. Normally the storage of creatine is sufficient for 5-8 seconds maximum performance (Newsholme & Leech, 1983), but with increased levels in the muscles the performance can be maintained for a longer period. In the majority of the studies showing enhanced performance, the exercise is of high intensity and short duration.

The Swedish report further states that creatine supplementation has also shown enhanced effects in relation to strength performances. The scientific literature supports that supplementation with creatine in combination with strength training over longer periods results in increased maximum strength, increased ability for high intensity performance and also increased muscle mass compared with strength training without creatine supplementation.

According to the Swedish report, creatine supplementation generally results in increased levels of creatine in the muscles, but with large individual variation (Harris *et al.*, 1992; Greenhaff *et al.*, 1994). The reason for the large variation in response is not fully understood, but the initial level of creatine in the muscles before supplementation seems to be of importance (Burke *et al.*, 2003). The enhancement of the performance also shows large differences between individuals, possibly explained by variations in the uptake of creatine (Harris *et al.*, 1992).

6.2 Summary from report of the Scientific Committee on Food on composition and specification of food intended to meet the expenditure of intense muscular effort, especially for sportsmen – effect on performance

In 2001 the Scientific Committee on Food (SCF) reviewed the scientific literature in the area of sport nutrition as well as a number of consensus reports prepared by various sport organisations (SCF, 2001). SCF concluded that the concept of a well-balanced diet is the basic requirement for athletes. Nevertheless, taking into consideration the aspects of intense muscular exercise such as intensity, duration, frequency, time and convenience, it was suggested that individuals can benefit from particular foods or food ingredients beyond the recommendations for the general population. In this aspect creatine has been mentioned separately.

SCF states that creatine ingestion increases the total creatine content in human muscles by approximately 15-20% (mean value). Similar to the Swedish report, they also stress that the increase is rather variable between subjects, ranging from zero to 40%, showing that there are responders and non-responders.

6.3 Reviews and other studies

In 2009/2010 a total of nine new reviews on creatine supplementation were published. However, eight of these reviews have a clinical approach and do therefore not discuss effects on sports performance. These reviews do therefore not add to the information summarised in the Swedish report. The last review focuses on the possible effects of creatine

supplementation on heat tolerance and hydration status (Lopez *et al.*, 2009). The conclusion in this review is that creatine supplementation does not hinder the body's ability to dissipate heat or negatively affect the athlete's body fluid balance.

6.4 Discussion effect on performance

It is well documented that creatine supplementation can increase high intensity short duration exercise performance due to the elevated levels of creatine phosphate found after supplementation. It is also well documented that creatine supplementation during strength training can enhance the increase in muscle strength and muscle mass. However, it is important to note the large individual variations in the response. Consequently, there are both responders and non-responders to the normal creatine supplementation regimens. In some studies, it is estimated that 20-30% of a normal population will be non-responders. Furthermore, already high levels of muscle creatine phosphate may be the main explanation for why some people do not increase creatine levels in response to creatine supplementation.

Most studies on the effect of creatine supplementation on sports performance include intervention periods lasting up till 16 weeks. The long-term effect of creatine supplementation on exercise performance is therefore less studied. Furthermore, several athletes use creatine repeatedly with some weeks or months between each supplementation period. So far the effect of this cycling on and off creatine supplementation has not been extensively studied.

6.5 Conclusion evaluation of documentation for effect on performance

Supplementation with creatine has been shown to result in a higher concentration of creatine phosphate in the muscles. In most studies, a loading phase of 20 g/day for 5-7 days is followed by a maintenance period (weeks-months) where the intake is reduced to 2-5 g/day. The majority of studies have shown that creatine supplementation enhances performance in high intensity and short duration sport activities, especially if high intensity exercise is repeated with short recovery time (< 1 min) between the intense exercise bouts.

Enhanced effect has also been shown in relation to strength performance. When combined with strength training, creatine supplementation may also increase muscle mass.

It is important to underline that there are individual variations, and that there are responders and non-responders.

7 Evaluation of safety

The evaluation of safety and possible risks related to creatine supplementation is based on the previous reports (SCF, 2001; AFSSA, 2001; EFSA, 2004; Eva Blomstrand & William Apró, 2009), 23 original papers, and 14 reviews from the literature searches in PubMed, described in chapter 4 (Data sources).

7.1 Summary from the Swedish report “Diet and nutrition within sports” regarding creatine supplements for athletes – safety

This section is a résumé of the safety aspect in the creatine chapter in the Swedish report. According to the Swedish report (2009) the use of creatine has been widely discussed after

being introduced on the market, and has been claimed to be both dangerous and unnecessary (Buford *et al.*, 2007). The potential negative effects claimed in non scientific journals, have not found support in systematic studies in healthy subjects (Terjung *et al.*, 2000; Bemben & Lamont, 2005; Buford *et al.*, 2007).

Concerns have particularly been related to a proposed negative effect on renal function, as the creatine ingested is removed by the kidneys and excreted through the urine. The main reference in this regard is a case study based on one person with an already existing kidney problem (Pritchard & Kalra, 1998). Other scientific studies have not found any negative effects of creatine supplementation on kidney function or other health parameters. (Poortmans & Francaux, 1999; Greenwood *et al.*, 2003; Poortmans *et al.*, 2005; Pline & Smith, 2005; Gualano *et al.*, 2008).

In the Swedish report it is underlined that it is important to be aware of the fact that long-term studies (more that 5 years) on creatine's possible health effects are missing.

The report further claims that individuals with reduced kidney function should refrain from creatine supplementation.

In this report no safe upper level for intake of creatine is given.

7.2 Summary of the EFSA opinion 2004 "Creatine monohydrate for use in foods for particular nutritional uses" - safety

The SCF from 2001 expressed that the evidence is insufficient to provide reassurance about safety of creatine supplementation involving high loading doses. This report also pointed out that little information exists on long term safety of creatine and that adequate quality control and specifications for food grade materials should be developed.

In the EFSA opinion from 2004 only creatine monohydrate with high purity (minimum 99.95%) is considered (EFSA, 2004).

This EFSA panel underline, however, that little information exits both on the short-term and long-term safety of creatine and adequate quality control of the commercially marked creatine is lacking.

They also stress that even if trials have studied the effects of creatine, large scale well-controlled studies are lacking, and that available results observed in highly trained athletes cannot necessary be extrapolated to the general public.

The EFSA opinion says that although no important adverse effects have been reported in the efficacy trials, such evidence is insufficient to provide reassurance about the safety of creatine supplementation involving high loading doses. Among others, there are doubts about safety in relation to kidney function.

The EFSA panel endorses the previous opinion of the SCF that high loading doses of creatine should be avoided. The EFSA Panel considers that consumption of doses up to 3 g/day is unlikely to pose any risk.

The petitioner reports that the acute toxicity of creatine monohydrate is low and not mutagenic in the Ames test. This has been tested in a 28-day rat study with doses up to 2 g/kg bw/day.

A human study indicates that creatine monohydrate supplementation for up to 21 months does not appear to adversely affect markers of health status in athletes (Kreider *et al.*, 2003).

In this study the subjects were given 15.75 g/day of creatine monohydrate for 5 days and an average of 5 g/day thereafter in 5-10 g/day doses.

No specific assessment of exposure of creatine monohydrate was considered necessary provided the intake of creatine is within the amounts judged unlikely to pose any risk (2-3 g/day).

7.3 Summary from "Report of the Scientific Committee on Food on composition and specification of food intended to meet the expenditure of intense muscular effort, especially for sportsmen" 2001 - safety

In spite of numerous anecdotal reports of creatine supplementation causing gastrointestinal, cardiovascular and muscular problems, no scientific evidence support these reports.

Even if creatine supplementation increases urinary creatine and creatine excretion, the SCF report claims that there is no a priori reason to expect that acute and long-term creatine ingestion impairs kidney function in healthy individuals.

The SCF could, however, not conclude that creatine supplementation is free from health risks as documentation was lacking or incomplete.

7.4 Assessment of the AFSSA-report "Risks of creatine on the consumer and of the veracity of the claims relating to sports performance and the increase of muscle mass" 2001 - safety

A 2001 report by the Food Safety Agency of France (AFSSA) (http://www.afssa.fr/) raised questions about creatine supplements possibly putting users at risk for cancer, particularly if supplements are taken for long periods of time (AFSSA, 2001). However, the European Commission and the Council for Responsible Nutrition in the United States both determined that AFSSA's claims were unsubstantiated and not based on any scientific evidence of connection between creatine and cancer. All three organisations do agree,that risks of long-term use of creatine are not known.

7.5 Reviews and other studies-safety

A total of 23 original papers and 14 reviews/meta analyses discussing the safety of creatine supplementation are published after 2004, according to PubMed. The use of creatine evaluated in most studies includes a loading phase of 20 g/day for 4-7 days followed by a maintenance phase of 2-5 g/day. The total supplementation period varies from 1 week to 6 months in most studies.

The findings in the 23 original papers are summarised in annex 2. The investigated possible adverse effects are mostly related to renal function, liver function, gastrointestinal problems and risk factors for cardiovascular disease (Bizzarini & De, 2004; Bemben & Lamont, 2005; Francaux & Poortmans, 2006; Persky & Rawson, 2007). Further, two reviews focus on possible side effects related to acclimatization to the heat (Dalbo *et al.*, 2008; Lopez *et al.*, 2009). The suggested possible adverse effect of taking creatine supplements in a warm climate is not supported in these reviews.

One review is focusing on the use of creatine in paediatrics (Evangeliou *et al.*, 2009). In this review positive effects of creatine supplementation are listed for a number of diseases and no

adverse effects are mentioned. The use of creatine supplementation in healthy children is, however, not discussed.

In the short term studies (5-14 days) high doses of creatine were administered throughout the intervention period (~ 20 g/day, (Santos *et al.*, 2004; Poortmans *et al.*, 2005; Ahmun *et al.*, 2005; Hile *et al.*, 2006; Armentano *et al.*, 2007; Gotshalk *et al.*, 2008)). Except for increased serum levels of creatine and/or creatinine, no adverse effects were reported in these studies. In line with the findings in the acute studies, no adverse effects were reported in the studies on healthy men and women taking creatine supplement for 4-12 weeks (Cancela *et al.*, 2008; Gualano *et al.*, 2008; Ostojic & Ahmetovic, 2008). The longest well controlled study lasted for 310 days and was performed on patients with the neurodegenerative disease amyotrophic lateral sclerosis (Groeneveld *et al.*, 2005).The patients were administered either 10 g creatine per day or a placebo. During the intervention period selected adverse effects were measured by questionnaire and in blood and urine samples. No differences between groups were observed for nausea, gastrointestinal discomfort, plasma urea levels or micro-albuminuria. However, oedematous limbs were seen more often in subjects using creatine, probably due to water retention.

In one study, professional basketball players consuming 5 g creatine per day were followed through three competition seasons (total of 3 years) (Schroder *et al.*, 2005).Within each season, a total of 5 blood samples were drawn and analysed, and between seasons there was a 2 month off-season without creatine supplementation. Amongst the 16 health-variables measured, only the levels of creatinine and creatine kinase increased to values higher than the clinical reference values. Increased level of creatine kinase is normally seen after high intensity exercise and is therefore probably not related to the supplementation. Furthermore, increased plasma creatinine level is often reported with creatine supplementation and this elevation is not related to impaired renal function, but simply reflects the increased conversion of creatine to creatinine with increased creatine intake.

The ratio of dihydrotestosterone/testosterone was found to be increased after creatine supplementation in one study (Van Der Merwe *et al.*, 2009). It is however not possible to conclude whether this change in dihydrotestosterone/testosterone ratio is an adverse effect of creatine supplementation and the authors speculate whether this change in testosterone metabolism could be one cause behind the observed positive effects on muscle mass.

The longest reported follow-up on possible adverse effects of creatine supplementation is 5 years (Poortmans & Francaux, 1999). In this study athletes reporting self administration of creatine supplements were compared with matched controls for several markers of renal function. The creatine users had taken creatine for 10 months up to 5 years and the daily doses ranged from 1 g/day up to 80 g/day. The main result in this study was that glomerular filtration rate, tubular reabsorption, and glomerular membrane permeability were normal in both groups. Consequently, the authors concluded that neither short-term, medium-term, nor long-term oral creatine supplements induce detrimental effects on kidneys in healthy individuals.

The effect of creatine supplementation in different patient populations has been studied for various durations ranging from 4 days to 2 years (Braegger *et al.*, 2003; Taes *et al.*, 2004; Roitman *et al.*, 2007; Taes *et al.*, 2008; Bender *et al.*, 2008; Jahangir *et al.*, 2009; Gualano *et al.*, 2010b). In the study of Jahangir it was reported that creatine supplementation in patients with coronary artery disease (21 g/day for four days) significantly increased the concentration of plasma total homocysteine, which could be a risk factor for cardiovascular disease. The clinical relevance of increased homocystein is still under discussion. Except for this effect and

one patient reporting muscle pain and increased serum levels of creatinine in two other studies, no adverse effect of the creatine supplementation was reported.

In addition to the reported placebo-controlled trials reported, two case-reports were also included in this evaluation. In one case, a unilateral nephrectomised patient followed a normal creatine supplementation regimen (20 g/day for 5 days followed by 5 g/day for 30 days) without any signs of adverse effects on kidney function (Gualano *et al.*, 2010b). In the other case report, a male bodybuilder who experienced acute renal failure was characterised (Thorsteinsdottir *et al.*, 2006). The bodybuilder reported a use of 15 g creatine per day for the last 6 months. In addition, several other supplements were used in this period and it was not possible to establish a cause-effect relation between the creatine use and the acute renal failure.

In general, no strong scientific evidence for adverse effects is found, but some studies remark that the issue of long-term use (several years) has not been properly addressed. In addition, possible risks for patients with renal disorders are mentioned in one of the reviews (Francaux & Poortmans, 2006).

No literature comparing safety and purity in different creatine compounds were found.

7.6 Special groups

No studies have been found on possible adverse effects of creatine supplementation on healthy children or adolescents. The effect of creatine supplementation in young patient groups has been discussed in a review paper (Evangeliou *et al.*, 2009), but possible adverse effects were not in focus. Consequently, it is not possible to conclude on eventual adverse effects of creatine supplementation in children.

7.7 Summary and conclusion adverse events related to creatine

The EFSA opinion concludes that the safety and bioavailability of creatine and creatine monohydrate in foods for particular nutritional uses, is not a matter of concern provided that there is adequate control of the purity of the source of creatine with respect to dicyandiamide and dihydro-1,3,5-triazine derivatives (EFSA, 2004).

The EFSA Panel endorses the previous opinion of the SCF that high loading doses of creatine should be avoided. Provided high purity creatine monohydrate is used in foods for particular nutritional uses, the EFSA Panel agrees with the opinion of the SCF that the consumption of doses of up to 3g/day of supplemental creatine, similar to the daily turnover rate of creatine, is unlikely to pose any health risk.

It is also stated in the EFSA opinion that although many efficacy trials have studied the effects of creatine, large-scale, well-controlled studies of potential adverse effects are lacking. They also underline that available results observed in highly trained athletes cannot necessarily be extrapolated to the general public.

The Swedish report underlines that individuals with reduced kidney function should refrain from supplementation of creatine (Eva Blomstrand & William Apró, 2009).

Only creatine monohydrate has been included in the scientific investigations on adverse effects. Among the reviews found in the literature no adverse health effects have been reported.

VKM Panel on nutrition, dietetic products, novel food and allergy supports the EFSA conclusion that supplementation with creatine up to 3 g/day (close to turnover rate) is unlikely to pose any health risks. Scientific long-term studies with doses up to 5-10 g/day in adult athletes have shown no harmful effects.

In most studies, athletes or physically active subjects are investigated. Consequently, these results do not give reassurance about potential long-term effects of high doses of creatine in people who are not highly trained or belong to other population subgroups. However, the longest controlled trial was performed in a patient group, and a growing number of studies in patients and elderly support the findings from the studies in athletes.

8 Exposure

8.1 Duration of use of creatine supplements

Most studies investigating performance or health related aspects of creatine supplementation have been of 4-12 weeks duration. Supplementation often starts with a loading phase of 20 g/day for 4-7 days. This loading phase is followed by a maintenance phase of 2-5 g/day. In addition to these well controlled short term studies, there are some long-term studies, but most of these are less controlled.

The longest well controlled study lasted for 310 days and was performed on patients with the neurodegenerative disease amyotrophic lateral sclerosis (Groeneveld *et al.*, 2005).The patients were administered either 10 g creatine per day or a placebo.

In one study, professional basketball players consuming 5 g creatine per day were followed through three competition seasons (total of 3 years) (Schroder *et al.*, 2005)

The longest reported follow-up on possible adverse effects of creatine supplementation is 5 years (Poortmans & Francaux, 1999).

8.2 Content of creatine in some foods

Creatine is endogenously produced mainly in the liver. The synthesis rate is about 1–2 g/day (Walker, 1979). Creatine can also be obtained through the diet, mainly from meat and fish (Table 1). The average daily intake from the diet is about 1 g creatine, whereas it may be less for vegetarians. Normal turnover rate of creatine is about 2 g/day. Consequently endogenous synthesis and intake from the diet equals the daily turnover.

Table 1 (source: http://www.creapure.com/index.php?id=47): Creatine content of different foods (unprocessed)

Food		Creatine content g/kg
Fish	Herring	6.5-10
	Salmon	4.5
	Tuna	4
	Cod	3

Food		Creatine content g/kg
	Plaice	2
Meat	Pork	5
	Beef	4.5
Other	Breastmilk	0.1
	Vegetables	Trace Amounts
	Fruit	Trace Amounts

9 Data gaps

The risks related to long-term use and repeated doses of creatine are not known at this time. Few studies have investigated the safety of creatine in less trained adults and in children or adolescents. The risks related to creatine supplementation in individuals with reduced kidney function or renal diseases have not been clarified. It is likely that some (athletes) use creatine in combination with anabolic steroids. The impact of this combination has not been studied.

More studies is required to confirm whether short term or long-term creatine supplementation in healthy individuals may increase the concentration of plasma total homocysteine.

It is also necessary with more studies concerning the increased ratio of dihydrotestosterone /testosterone after creatine supplementation and the mechanisms underlying this change.

No literature comparing safety and purity in different creatine compounds were found.

10 Answer to the terms of reference

The Norwegian Food Safety Authority has requested an assessment of creatine in sports products.

1. Which adverse health effects have been reported due to intake of different forms of creatine (creatine compounds) (in food supplements/sports products)?

   No adverse effects from intake of creatine in doses below 3 g/day have been reported in well controlled systematic studies. The potential negative effects which have been published in non scientific journals and anecdotal reports, have not found support in systematic studies on healthy subjects. These negative effects include impaired kidney function, weight gain and gastrointestinal disturbances. All studies investigating adverse effects have used creatine monohydrate. Other creatine compounds have not been investigated for adverse effects.

   - Can an upper safe limit for different forms of creatine (compounds) be given?

     There are no dose-response studies indicating a scientifically or toxicologically based upper safe limit for creatine. As mentioned above, only creatine

monohydrate has been included in scientific literature investigating adverse effects. VKM Panel on nutrition, dietetic products, novel food and allergy supports the EFSA conclusion that supplementation with creatine up to 3 g/day is unlikely to pose any risks if the purity of the creatine compound is adequate.

- Is new scientific evidence published, or are the conclusions in the *Creatine monohydrate for use in foods for particular nutritional uses*; EFSA opinion from 2004 still valid? Does VKM support the conclusions in this EFSA opinion?

  New scientific literature is in line with the EFSA opinion and supported by new long-term studies. VKM Panel on nutrition, dietetic products, novel food and allergy supports the EFSA conclusion that supplementation with creatine up to 3 g/day is unlikely to pose any risks if the purity of the creatine compound is adequate. It should also be mentioned that scientific long-term studies with doses up to 5-10 g/day in adult athletes have shown no harmful effects.

- Have certain groups in the population been identified that should avoid consumption of creatine in sports products?

  It has been indicated that individuals with impaired kidney function should refrain from creatine supplements.

- Have special risks been identified which could be connected to consumption of creatine in sports products in Norway?

  No special risks have been identified which could be connected to consumption of creatine supplements in Norway

2. Does creatine affect muscle mass? Have other beneficial effects from creatine been identified?

   Supplementation with creatine has been shown to result in a higher concentration of creatine phosphate in the muscles. The majority of studies have shown an enhanced performance in high intensity and short duration sport activities from creatine supplementation.

   Enhanced effect has also been shown in relation to strength performance. Combined with strength training, creatine supplementation has also been shown to increase muscle mass.

   It is important to underline that there are individual variations, and that there are responders and non-responders.

   Other beneficial effects have been reported in some special patient groups. These findings range from improved muscle function in muscle diseases, improved well-being in cystic fibrosis patients and better glycemic control in type 2 diabetes patients when combined with resistance training. The strongest

evidence so far is the beneficial effects of creatine supplementation in neurodegenerative and muscular diseases.

Annex 1

Mattilsynet ber VKM om en vurdering om bruk av kreatin.

1. Hvilke negative helsemessige effekter kan foreligge ved inntak av ulike former for kreatin i næringsmidler?
    - Kan det settes en øvre trygg grense for de ulike formene for kreatin?
    - Mattilsynet ber om at faggruppen i denne sammenheng vurderer EFSAs rapport om kreatinmonohydrat publisert i 2004 (vedlegg 2), - har det skjedd endringer i kunnskapsstatus siden vurderingen ble foretatt eller kan konklusjonene i rapporten støttes?
    - Er det spesielle grupper i befolkningen som ikke bør spise produkter med kreatin?
    - Kan det foreligge spesielle farer knyttet til inntak av kreatin i Norge?

2. Har kreatin effekt på muskelmasse? Har kreatin eventuelle andre positive effekter?

Annex 2

Table of 23 studies discussing safety of creatine supplementation published after 2004

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Gualano *et al*., Am J Kidney Dis, 2010	Case-report		n=1, age=20, Unilateral nephrectomy, mildly decreased GFR, without kidney damage	20 g/d for 5 days, 5 g/d for 30 days	Renal function; Cr-EDTA clearance, proteinuria, albuminuria, serum urea, GFR	Not measured	No change	
Armentano *et al*., Mil Med, 2007	Double-blind randomised placebo-controlled clinical trial	Performance and safety	35 healthy men and women, age=22-36	20 g/d for 7 days	Performance and safety; Push-ups, serum creatinine, blood pressure and renal function	Not measured	Increased serum creatinine	No
Cancela *et al*., Br J Sports Med, 2008	Double-blind randomised placebo-controlled trial	Safety	14 healthy soccer players	15 g/d for 7 days 3 g/d 49 days	Renal and hepatic function markers	Not measured	No change	
Ferreira *et al*., Med Sci Sports Exerc, 2005	4 groups: 1) Cr, 2) Cr + exerc, 3) Exerc, 4) Control	Safety and body composition	Rats	2 g/kg food for 10 weeks	Renal function and body composition; GFR and renal plasma flow		Inulin and paraaminohippurate clearance reduced	

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Gotshalk *et al*., Eur J Appl Physiol, 2008	Double-blind randomised placebo-controlled trial	Performance	30 healthy women, age=58-71	0.3 g/kg/day for 7 days		No AE observed		
Poortmans e*t al*., Med Sci Sports Exerc, 2005	Prospective cohort	Safety	20 young healthy men	21 g/d for 14 days	Renal function; Plasma and urine levels of defined compounds	Not measured	Increased serum and urine creatine, no change in creatinine or urinary albumin	
Taes *et al*., Kidney Int, 2004	Double-blind randomised placebo-controlled trial	Improved homocysteine levels in hemodialysis patients	45 hemodialysis patients	2 g/d for 4 weeks	Homocysteine levels; Plasma homocysteine levels (tHcy)	Not measured	No change	
Gualano *et al*., Eur J Appl Physiol, 2008	Double-blind randomised placebo-controlled trial	Safety (renal function)	18 healthy men, age=18-35	10 g/d for 3 months	Renal function; Serum creatinine, urinary sodium and potassium and cystatin C (GFR)	Not measured	Decreased cystatin C in both groups (increased GFR because of training?)	
Taes *et al*., Nephrol Dial Transpl, 2008	Double-blind randomised placebo-controlled trial	Safety	20 male hemodialysis patients	2 g/d for 4 weeks	Plasma guanodine compounds	Not measured		

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Thorsteinsdottir *et al*., J Ren Nutr, 2006	Case-report	Renal failure	1 male with acute renal failure, 24 years	15 g/week for 6 months	Renal failure			
Bender *et al*., Nutr Research, 2008	Double-blind randomised placebo-controlled trial	Safety, particularly kidney function	60 men and women with early Parkinson disease, age=60±10	20 g/d for 6 days, 2 g/d for 6 months, 4 g/d for 1.5 yrs	Side effects; Questionnaires and a broad range of blood and urine tests	Significant increase in GI complaints after 2 yrs therapy	α(1)- and ß(2)-microglobulin, cystatin C, creatinine, total protein content, albumin, erythrocytes in the urine	None
Braegger *et al*., J Cystic Fibrosis, 2003	Open-label pilot study	Effect on muscle strength, lung function and CF transmembrane conductance regulator (CFTR) channel activity	18 men and women with cystic fibrosis, age=8-18	12 g/d for one week, 6 g/d for 11 weeks (also tested after 12-24 weeks post-treatment)	CFTR-related pathological symptoms, muscle strength, lung function, general well-being; Questionnaires and Isometric muscle strength, lung function, blood samples			One patient with transient muscle pain.

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Groeneveld *et al*., Nutrition, 2004	Double-blind randomised placebo-controlled trial	Disease progression, survival	175 subjects with amyotrophic lateral sclerosis, age=58±11	10 g/d (5gx2) for 310 days	Adverse events and renal function; Questionnaires and blood and urine samples	NS, but severe diarrhoea in 2 and severe nausea in 1 subject made them stop intake	Urinary creatine and albumin, plasma urea	Oedematous limbs higher in CR at 2 months, not other time points
Jahangir *et al*., Vasc Med, 2009	Double-blind randomised placebo-controlled trial	Effect of creatine and arginine on vascular function and homocysteine level	26-29 per group, CAD-patients, age creatine group: 60±11, placebo: 58±12	21 g/day (7gx3) for 4 days	Cr increased homocysteine content (not attributed to worsened renal function); Brachial artery flow-mediated dilation, plasma guanidinoacetate	NA	Increase in cystatin C w reduction in GFR with combination of Arg and Cr	None
Roitman *et al*., Bipolar Disord, 2007	Open, clinical add-on trial	Effect on depression	10 patients (8 unipolar and 2 bipolar), age=49±10	3 g/d for one week, 5 g/d for 3 weeks	Depression, anxiety; Depression and anxiety scales, clinical global impression scores	None	NA	None

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Vorgerd *et a*l. Acta Myol, 2007		Effect on muscle symptoms and performance in McArdle's patients	Patients with McArdle disease		Clinical scores; Muscle symptomatic and performance	NA	NA	NA
Ahmun *et al*., J Strength Cond Res, 2005		Performance	Healthy rugby-players	20 g/d for 5 days, 28 days wash-out	Repeated Wingate test, repeated sprint test	Not measured	Not measured	NA
Hile *et al*., J Athl Train, 2006		Effect on compartment pressure	11 healthy well-trained men, age=22±2	21.6 g/d for 7 days	Compartment pressure; Pressure and pain	Not measured	Not measured	Transient increased compartment pressure
Ostojic *et al*., Res Sports Med, 2008		Dose-response in relation to GI-distress	59 healthy top level soccer players	2x5 g/d or 1x10 g/d for 28 days	Perceived side effects on GI system; Questionnaire	Episodes of diarrhoea: placebo: 35%; C5: 28%; C10: 55% (P<0.05 vs other groups)	Not measured	Not reported

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Santos *et al*., Life Sci, 2004		Effect on inflammation and muscle soreness after 30 km running	Healthy marathon runners	20 g/d (4x5 g) for 5 days	Inflammation, muscle damage, muscle soreness; Creatine kinase, LDH, PGE2, TNF-alpha in blood	Diarrhoea	Not measured	
Schroder *et al*., Eur J Nutr, 2005		Risk assessment, long-term creatine supplementation in athletes	18 healthy professional basket players, age=24±4	5 g/d, 10 months/year for 3 years	Blood levels of 16 clinical markers; Minerals, lipids, serum enzymes, creatinine, urea, uric acid			Creatinine and creatine kinase above reference values
van der Merwe *et al*., Clin J Sport Med, 2009		Effect on dihydrotestosterone to testosterone ratio	20 healthy rugby players, age=18-19	25 g/d for 7 days, 5 g/d for 14 days	Dihydrotestosterone (DHT)/testosterone ratio; Concentrations in blood of dihydrotestosterone and testosterone	Not measured	Not measured	

Study	Study design	Objective	Subjects (n), age years	Dose (g/d) and duration	Primary outcome; measures, analysis	GI symptoms	Renal/ renal biomarkers	Other AE
Gualano *et al*., Eur J Appl Physiol, 2010		Safety and renal function	25 patients with type 2 diabetes, age=45-70	5 g/d for 12 weeks	Kidney function; Cr-EDTA clearance, proteinuria, albuminuria, serum urea, GFR	Not measured	No change	

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