SCIENTIFIC OPINION

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Creatine in combination with resistance training and improvement in muscle strength: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Abstract

Following an application from AlzChem AG, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Austria, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to creatine in combination with resistance training and improvement in muscle strength. The Panel considers that the food constituent, creatine, which is the subject of the health claim, is sufficiently characterised. The Panel considers that improvement in muscle strength is a beneficial physiological effect. A total of 21 human intervention studies and two meta-analyses were provided by the applicant as being pertinent to the claim. The Panel considers that no conclusions can be drawn from 11 studies and the meta-analyses cannot be used for the scientific substantiation of the claim. In weighing the evidence the Panel took into account that, overall, the human intervention studies submitted provide evidence for an effect of creatine, consumed at doses of at least 3 g/day in combination with regular resistance training (three times per week for several weeks) of moderate intensity, on muscle strength in adults over the age of 55, while no such effect was observed when similar doses of creatine on a weekly basis were given on training days only (three times per week). The Panel also took into account the plausible mechanism by which daily consumption of creatine in combination with resistance training could improve muscle strength. On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of creatine in combination with resistance training and improvement in muscle strength in adults over the age of 55.

Keywords: creatine, muscle strength, resistance training, health claims

Requestor: Competent Authority of Austria following an application by AlzChem AG

Question number: EFSA-Q-2015-00437

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Summary

Following an application from AlzChem AG, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Austria, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to creatine in combination with resistance training and improvement in muscle strength.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on the evaluation of Article 13.5 and 14 health claims[1] and the guidance on the scientific requirements for health claims related to physical performance.[2]

The food constituent, which is the subject of the health claim, is creatine. The Panel considers that the food constituent, creatine, is sufficiently characterised.

The claimed effect and the target population proposed by the applicant are 'improvement of muscle strength/muscle function in individuals above 55 years of age who regularly perform resistance training'. Noting that muscle strength is a specific aspect of muscle function, the Panel considers that this claim relates specifically to muscle strength, rather than to muscle function in general. The Panel considers that improvement in muscle strength is a beneficial physiological effect.

The applicant provided 21 human intervention studies and two meta-analyses as being pertinent to the claim.

The Panel considers that no conclusions can be drawn from 11 studies for the scientific substantiation of the claim owing to several reasons (e.g. no control group, absence of appropriate outcome measures for muscle strength). The Panel considers that the two meta-analyses provided, which include intervention studies from which conclusions cannot be drawn, cannot be used for the scientific substantiation of the claim.

From the remaining human intervention studies submitted the Panel considers that, overall, five studies, which investigated the effect of daily consumption of creatine in combination with resistance training on muscle strength, provide evidence for an effect of creatine at daily doses of 3–6 g in combination with regular resistance training (three times per week) of moderate intensity on muscle strength in adults over the age of 55, whereas one study did not show an effect of creatine at daily doses of 5 g for about 7 weeks in combination with resistance training on muscle strength. The Panel considers that four studies, in which creatine was consumed on training days only (three times per week, at doses of 5–7 g/day) in combination with resistance training, did not show an effect of creatine on muscle strength.

In relation to the mechanism by which creatine could exert the claimed effect, the Panel considers that an increase of the creatine phosphate pool in muscle cells following daily consumption of creatine can enhance the ATP regeneration rate after intense muscle contractions. Creatine consumption in combination with resistance training improves the muscle's ability to train at higher intensities and this leads to higher muscle strength.

In weighing the evidence, the Panel took into account that, overall, the human intervention studies submitted provide evidence for an effect of creatine, consumed at doses of at least 3 g/day in combination with regular resistance training (three times per week for several weeks) of moderate intensity, on muscle strength in adults over the age of 55, while no such effect was observed when similar doses of creatine on a weekly basis were given on training days only (three times per week). The Panel also took into account the plausible mechanism by which daily consumption of creatine in combination with resistance training could improve muscle strength.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of creatine in combination with resistance training and improvement in muscle strength.

The following wording reflects the scientific evidence: 'daily creatine consumption can enhance the effect of resistance training on muscle strength in adults over the age of 55'.

[1] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 20 pp. doi:10.2903/j.efsa.2016.4367. Available online: www.efsa.europa.eu/efsajournal

[2] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Guidance on the scientific requirements for health claims related to physical performance. EFSA Journal 2012;10(7):2817. Available online: www.efsa.europa.eu/efsajournal

In order to obtain the claimed effect, 3 g of creatine should be consumed daily in conjunction with a resistance training which allows an increase in the workload overtime. Resistance training should be performed at least three times per week for several weeks, at an intensity of at least 65–75% of one repetition maximum. The target population is adults over the age of 55, who are engaged in regular resistance training.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006[3] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction in disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

1.2. Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: creatine in combination with resistance training and improvement in muscle strength.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of creatine, a positive assessment of its safety, nor a decision on whether creatine is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

1.3. Additional information

A claim on creatine and increase in physical performance during short-term, high intensity, repeated exercise bouts has already been assessed by the Panel with a favourable outcome (EFSA NDA Panel, 2011).

2. Data and methodologies

2.1. Data

2.1.1. Information provided by the applicant

2.1.1.1. Food/constituent as stated by the applicant

According to the applicant, the food constituent which is the subject of the health claim is creatine (CAS-No. 57-00-1). The most common traded form of creatine is creatine monohydrate (CAS-No. 6020-87-7).

2.1.1.2. Health relationship as claimed by the applicant

Creatine helps to maintain muscle function in the elderly. Muscle function (i.e. strength) is assessed via upper and lower body strength testing by 1-repetition maximum (1-RM) bench press, leg press, knee extension and/or biceps curl. Supportive of the claimed effect, creatine helps to prevent/delay physiological loss of muscle mass. Body composition can be determined by dual body dual-energy X-ray absorptiometry and lean muscle mass can be calculated from the scan result. Motor functional

[3] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

performance, which was measured by certain tests like gait speed, timed-get-up-and-go test, stair climbing, was proposed by the applicant as supportive indicator of muscle function.

2.1.2. Mechanism by which the food/constituent exerts the claimed effect as proposed by the applicant

According to the applicant, the role of creatine in muscle energy homeostasis is well documented. Creatine is converted to creatine phosphate (CrP) by creatine kinase (CK; E.C.2.7.3.2) using ATP. In skeletal muscles, a large pool of CrP (25–40 mM) is available for immediate regeneration of ATP from ADP, as well as shuttling of high-energy phosphate from compartments of energy production to sites of energy utilisation. Besides temporal and spatial energy buffering of the CK/CrP system, CrP via the CK reaction functions as pH buffer, accounting for 50% of muscle buffer capacity. Increased concentrations of cellular creatine and CrP lead to an improved cellular CrP/ATP ratio energy status. According to the applicant, creatine supplementation may be able to promote muscle hypertrophy through a variety of molecular mechanisms (e.g. cell swelling; alteration to the expression of myogenic transcription factors; increase in satellite cell mitotic activity; improvement in the CrP/ATP energy ratio of cells).

2.1.2.1. Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'creatine contributes to the maintenance of muscle function in the elderly'.

2.1.2.2. Specific conditions of use as proposed by the applicant

The target population proposed by the applicant is elderly (i.e. ~ > 55 years of age) people of both sexes who are physically active. Physically active elderly engage regularly in low- and moderate-intensity exercises including muscle strengthening activities.

The applicant has proposed a daily intake of 3 g of creatine.

2.1.3. Data provided by the applicant

Health claim application on creatine in combination with resistance training and improvement in muscle strength pursuant to Article 13.5 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims.[4]

As outlined in the EFSA general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims,[5] it is the responsibility of the applicant to provide the totality of the available evidence.

2.2. Methodologies

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.[6]

The scientific requirements for health claims related to physical performance are outlined in a specific EFSA guidance.[7]

[4] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1). EFSA Journal 2011;9(5):2170, 36 pp. doi:10.2903/j.efsa.2011.2170

[5] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 20 pp. doi:10.2903/j.efsa.2016.4367. Available online: www.efsa.europa.eu/efsajournal

[6] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal 2011;9(4):2135, 24 pp. doi:10.2903/j.efsa.2011.2135. Available online: www.efsa.europa.eu/efsajournal

[7] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Guidance on the scientific requirements for health claims related to physical performance. EFSA Journal 2012;10(7):2817.

3. Assessment

3.1. Characterisation of the food/constituent

The food constituent, which is the subject of the health claim, is creatine.

Creatine is a non-essential nitrogenous organic acid that occurs in vertebrates, and it is also synthesised in the human body from L-arginine, glycine and L-methionine. Approximately 95% of the creatine pool in the body is located in skeletal muscle. The content of creatine in foods can be measured by established methods.

The Panel considers that the food constituent, creatine, which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is 'helps to maintain muscle function'. The target population proposed by the applicant is 'elderly (i.e. ~ > 55 years of age) people of both sexes who are physically active'.

The applicant has proposed the following outcome variables to assess muscle function (i.e. strength): 1-RM bench press, leg press, knee extension and/or biceps curl. Body composition and motor functional performance (e.g. gait speed, timed-get-up-and-go test, stair climbing) have been proposed by the applicant as supportive outcomes.

Upon a request by EFSA for clarification on the claimed effect and the target population, the applicant indicated that the claim relates to the improvement of muscle strength/muscle function in individuals above 55 years of age who regularly perform resistance training of moderate intensity two to three times a week (approximately 60 min per session). The applicant indicated that resistance training of intensity between 65% and 75% of the maximum amount of weight that can be lifted is generally recommended for adults older than 65 years of age (ACSM, online).

Noting that muscle strength is a specific aspect of muscle function, the Panel considers that this claim relates specifically to muscle strength, rather than to muscle function in general. The Panel considers that the following outcome variables proposed by the applicant are appropriate to assess muscle strength in human studies: 1-RM and isometric strength tests.

Outcomes variables related to motor functional performance (e.g. gait speed, timed-get-up-and-go test, stair climbing) and body composition are not direct measures of muscle strength.

The Panel considers that improvement in muscle strength is a beneficial physiological effect.

3.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed and SciFinder using the search terms 'creatine monohydrate', '57-00-1', '6020-87-7', and 'supplementation', 'treatment', 'intake', 'human', 'age', 'older', 'elderly', '*menopausal', 'geriatric', 'mature'. Only publications in English were included. Publications related to people younger than 45 years of age, non-healthy people, or referring to creatine as metabolite or as diagnostic tool (e.g.CK) were excluded.

The applicant provided 20 human intervention studies and two meta-analyses as being pertinent to the claim. The Panel notes that the two meta-analyses include one additional human intervention study which is relevant to the substantiation of the claim (Candow et al., 2008).

Among the human intervention studies provided by the applicant, one (Candow et al., 2014b) lacked a control group; four studies (Gotshalk et al., 2002, 2008; Eijnde et al., 2003; Stout et al., 2007) were designed as placebo-controlled, double-blind, parallel interventions but the results were analysed as changes within groups from baseline, and a statistical analysis of between-group differences for the outcome variables of interest was not provided; five studies (Smith et al., 1998; Rawson et al., 1999; Jakobi et al., 2001; Canete et al., 2006; Eliot et al., 2008) lacked appropriate outcome measures for muscle strength, but rather assessed body composition and/or motor functional performance only; and one study (Neves et al., 2011) was conducted in women with knee osteoarthritis, the results of which cannot be extrapolated to the target population for the claim (subjects without knee osteoarthritis) because knee osteoarthritis may lead to functional impairment and limit the extent and intensity of resistance training. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

3.3.1. Human intervention studies on the effect of creatine plus resistance training on muscle strength

A total of 10 studies investigated the effect of creatine plus resistance training on muscle strength. Creatine was given daily throughout the intervention period in six studies (Bermon et al., 1998; Chrusch et al., 2001; Brose et al., 2003; Rogers et al., 2006; Aguiar et al., 2013; Gualano et al., 2014). In the remaining four studies (Carter et al., 2005; Candow et al., 2008; Bemben et al., 2010; Cooke et al., 2014), creatine was administered only on training days (three times per week).

3.3.1.1. Studies in which creatine was consumed daily through the intervention

In the placebo-controlled, double-blind, parallel intervention study by Aguiar et al. (2013), 18 healthy women above 60 years of age performed an initial 12-week resistance training programme without supplementation (three training days per week, run-in). Subsequently, participants were matched according to their age, body weight (bw) and 1-RM tests and randomised to consume either 5 g/day of creatine (n = 9; mean age: 64 ± 4 years) or placebo (n = 9; mean age: 65 ± 6 years) for an additional 12 weeks. During the study, participants followed a resistance training programme (3 days/week; two sets of 10–15 repetitions). The training load was adjusted weekly, based on the number of repetitions performed at the end of the second set of each exercise. Specifically, 1 kg-load was added every one (lower extremity) or two (upper extremity) repetitions that exceeded the 15 repetitions of the second set of each exercise. The training volume was progressively increased throughout the training programme.

Before and after resistance training, participants completed a battery of 1-RM tests, which consisted of bench press, knee extension, and biceps curl exercises. Repeated-measures analysis of variance (ANOVA) and the Bonferroni test were used to analyse differences in 1-RM strength changes between groups.

One-RM strength for bench press (creatine group: 14.3 ± 6.7% vs placebo group: 4.7 ± 1.8%; $p < 0.05$), knee extension (creatine group: 8.6 ± 2.7% vs placebo 4.7 ± 1.8%; $p < 0.05$), and biceps curl (creatine group: 22.3 ± 7.1% vs placebo group: 13.5 ± 3.9%; $p < 0.05$) increased significantly more in the creatine group compared to the placebo group. Training volume increased significantly more in the creatine group than in the placebo group (294.1 ± 85.8% vs 129.9 ± 52.4%, respectively; $p < 0.01$). Noting that the number of sets and repetitions were similar between the two groups, the authors indicated that such a difference was due to a difference in the weight lifted by the two groups (i.e. participants in the creatine group were able to lift more weight than the placebo group).

The Panel considers that this study shows an effect of daily consumption of 5 g of creatine for 12 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Rogers et al. (2006), 45 adults aged 55–84 years (n = 21 male) were randomised to consume either creatine (3 g/day; n = 15), creatine plus a botanical extract (n = 15) or placebo (n = 15) for 12 weeks. Randomisation was stratified by age and sex. During the study, participants performed a strength training programme (3 days a week for 12 weeks), which consisted of sets of upper or lower body exercises. The initial resistance, which was set at 70% of 1-RM, was increased individually during the training.

At baseline and after training, participants performed a 1-RM exercise twice (separated by 2–3 days) for bilateral knee extension, bilateral knee flexion, bench press, leg press, lat pulldown and bilateral arm curl. The greater of the two 1-RM measurements was used for analysis. Repeated-measures ANOVA and Tukey's test were used in the statistical analysis.

At baseline, there were no significant differences between groups for the outcomes investigated. One participant in the creatine group withdrew from the study. The study reported a greater increase in all 1-RM tests, except for bench press, in the creatine group as compared with the placebo group ($p < 0.05$): in the creatine and placebo groups leg press improved 59% and 45%; knee extension improved 62% and 28%; knee flexion improved 55% and 40%; lat pull-down improved 41% and 31%; and arm curl improved 25% and 8%, respectively.

The Panel considers that this study shows an effect of daily consumption of 3 g of creatine for 12 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Chrusch et al. (2001), 33 men (aged between 60 and 84 years) were randomised to consume daily either creatine (n = 17; mean age: 70.4 ± 1.6 years) or placebo (n = 16; mean age: 71.1 ± 1.8 years) for 11 weeks. After 5 days of loading dose (0.3 g/kg bw), participants consumed daily 0.07 g/kg bw of either creatine or placebo.

Participants were engaged in a 12-week resistance training programme (three sessions per week) and started consuming the study products at the beginning of the second week of resistance training. Participants started performing exercises at levels ≤ 50% of 1-RM. Training volumes for hip and back exercises were progressed throughout the study at equal levels for all participants. For all other exercises, the resistance was individually progressed.

One-RM for leg press, knee extension and bench press were performed before, in the middle and at the end of the resistance training. Training volume was calculated as kg of weights lifted multiplied by the number of repetitions.

ANCOVA with baseline measurements as a covariate was used to analyse results on 1-RM bench press, as significant differences were observed between groups at baseline for this variable. The ANOVA test was used for the other 1-RM measurements and the Tukey's test was used to analyse differences between groups. Unpaired *t*-test was used to analyse training volume.

One participant in the creatine group and two in the placebo group withdrew owing to reoccurrence of chronic degenerative knee or back injuries which prevented adherence to the protocol. At baseline, no significant differences between groups were observed in muscular strength or training volume, but bench press strength was higher in the creatine group relative to placebo ($p = 0.05$). Compared with placebo, the creatine group showed higher increases in leg press 1-RM (creatine, + 50.1 kg; placebo, + 31.3 kg; $p < 0.03$) and knee extension 1-RM (creatine, + 14.9 kg; placebo, + 10.7 kg; $p = 0.05$), but not in bench press 1-RM. Training volume was 31% greater in the creatine group than in the placebo group ($p = 0.05$).

The Panel considers that this study shows an effect of daily consumption 0.07 g/kg bw (i.e. about 6 g) of creatine for 11 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Gualano et al. (2014), 74 women above 60 years of age were randomised into four groups: creatine (n = 18; mean age: 66.1 ± 4.8 years), creatine plus resistance training (n = 19; mean age: 67.1 ± 5.6 years), placebo (n = 18; mean age: 66.3 ± 6.0 years) and placebo plus resistance training (n = 19 groups, mean age: 63.6 ± 3.6 years). All participants were classified as having osteopenia (T-score from −1 to −2.5) or osteoporosis (T-score ≤ −2.5) and being 'apparently vulnerable' (i.e. people who commonly complain of being 'slowed up' or have disease symptoms), according to the Canadian Study of Health and Aging clinical frailty scale (Rockwood et al., 2005). After the initial 5 days of loading dose (20 g/day), participants consumed 5 g/day of creatine or placebo for the following 23 weeks. While consuming the study products, half of the participants (n = 38) undertook a resistance training programme twice a week for 24 weeks. The resistance training programme consisted of leg press, leg extension, squat, seated row, bench press, lat-pull down and sit-up exercises. Participants were required to perform three sets of 8–12 RM, except during the first week, when a reduced volume of two sets of 15–20 RM for each exercise was performed. From the second week on, progression in the absolute exercise load was implemented when the subject could perform more than 12 repetitions on a given exercise set.

Muscle strength (primary outcome) was measured by 1-RM leg press and bench press tests at baseline and at week 24. Based on data from a previous study (Gotshalk et al., 2008) and the G-Power software, a sample size of 56 subjects was determined in order to provide 95% power ($\alpha = 0.05$; estimated effect size of 0.59) for muscle strength. In order to account for withdrawals, 74 women were randomised. One-way ANOVA and Tukey's test were used to analyse the delta scores (i.e. post–pre values) of the outcomes investigated.

Fourteen participants withdrew due to personal reasons (n = 3 in each group not performing resistance training and n = 4 in each group performing resistance training). Therefore, 60 subjects completed the 24-week intervention period and were analysed (n = 15 per group). The 1-RM bench press increased significantly more in the creatine plus resistance training group compared to the placebo plus resistance training group ($p < 0.05$), whereas no significant differences were observed for the 1-RM leg press. No significant differences were reported for changes in 1-RM leg press or bench press between the creatine and placebo groups which did not perform resistance training.

The Panel considers that this study does not show a consistent effect of daily consumption of 5 g of creatine for 23 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Brose et al. (2003), 30 healthy adults (> 65 years of age; mean age for men: 67.8 ± 4.0 years; mean age for women: 69.3 ± 6.3 years) were randomised to consume either 5 g/day of creatine monohydrate (n = 16; n = 8 men) or placebo (n = 14; n = 7 men) for 14 weeks. During the study, participants performed strength training three times a week on non-consecutive days. This training progressed from one set of exercise at 50% of the initial 1-RM strength to three sets at 80% of 1-RM over the training period.

Before and after training, participants performed 1-RM of four different exercises (upright chest press, leg press, arm flexion, knee extension) and three maximal voluntary contractions for handgrip, ankle dorsiflexion, and knee extension. Three-way (with group, time and gender as factors) repeated-measures ANOVA and Tukey's test were used for data analysis.

Two women in the creatine group withdrew from the study due to personal reasons unrelated to the training or supplementation. At baseline, the creatine and placebo groups were not significantly different as regards 1-RM for the four exercises (except for arm flexion in men), handgrip, ankle dorsiflexion, and knee extensor strength. After the training, no significant differences between groups were observed in any of the four 1-RM exercises. The knee extensor strength increased significantly more in the creatine group than in the placebo group (46.2 $\pm$ 22.5% vs 22.5 $\pm$ 14.4%, respectively; $p < 0.05$) for both genders. There was a significant increase in the ankle dorsiflexion strength in the creatine group as compared to placebo in men (17.8 $\pm$ 11.6% vs 2.2 $\pm$ 5.6%, respectively; $p < 0.05$), but not in women. No statistically significant differences between groups were reported for handgrip strength.

The Panel notes that this study reports an effect of creatine on two (i.e. ankle dorsiflexion, knee extensor strength only in men) of the outcomes investigated, but not in others (i.e. four 1-RM tests). The Panel considers that this study does not show a consistent effect of daily consumption of 5 g of creatine for 14 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Bermon et al. (1998), 32 adults (aged 67–80 years) were randomised into four groups (four men and four women per group): creatine, creatine plus resistance training, placebo (glucose), placebo plus resistance training. After 5 days of loading dose (20 g/day), participants consumed 5 g/day of creatine or placebo for the following 47 days. The exercise training lasted 7 weeks (three times per week).

At the beginning and end of the study, all participants performed 1-RM and 12-RM tests (leg press, chest press and leg extension). Three-way repeated-measures ANOVA (with supplementation, training and time as factors) and adjusted paired *t*-test (two-tailed) were used for data analysis. No statistically significant differences were observed between groups for changes in 1-RM leg press, chest press or leg extension.

The Panel considers that this study does not show an effect of daily consumption of 5 g of creatine over a period of 47 days, in combination with resistance training, on muscle strength.

The Panel notes that three of the studies provided (Chrusch et al., 2001; Rogers et al., 2006; Aguiar et al., 2013) showed an effect of daily consumption of creatine at doses of about 3–6 g for 11–12 weeks in combination with regular resistance training of moderate intensity (three times per week) on muscle strength in adults over the age of 55; that two studies showed an effect of daily consumption of creatine at doses of 5 g for 14 (Brose et al., 2003) and 23 weeks (Gualano et al., 2014), respectively, in combination with resistance training (three times per week and twice per week, respectively) on some measures of muscle strength, but not on others; and that one study (Bermon et al., 1998) did not show an effect of daily consumption of creatine at doses of 5 g for about 7 weeks, in combination with resistance training on muscle strength. The Panel notes that the latter study had shorter duration of the intervention.

The Panel considers that, overall, the above-mentioned studies provide evidence for an effect of daily creatine consumption at doses of 3–6 g in combination with regular resistance training (three times per week) of moderate intensity on muscle strength in adults over the age of 55.

3.3.1.2. Studies in which creatine was consumed on training days only (three times per week)

In the placebo-controlled, double-blind, parallel intervention study by Cooke et al. (2014), 20 males (aged 55–70 years) were matched by lower body 1-RM strength, age and fat-free mass, and were randomised to receive either creatine or placebo (n = 10 per group; mean age: 61.4 $\pm$ 5.0 years in the creatine group; mean age: 60.7 $\pm$ 5.4 years in the placebo group). Participants were engaged in a high-intensity resistance training programme (3 days/week) for 12 weeks. After the initial week of loading dose (20 g/day on training days), participants consumed either 0.1 g/kg bw per day of creatine or placebo for 11 weeks on training days.

At baseline, at 4, 8 and 12 weeks, participants performed 1-RM leg press and bench press. Mixed design factorial multivariate analysis of variance (MANOVA), ANOVA and Bonferroni test were used for data analysis. No significant differences were observed between groups on 1-RM bench press and leg press.

The Panel considers that this study does not show an effect of creatine consumed at doses of 0.1 g/kg bw per day (i.e. about 7 g/day) on training days (three times per week) over a period of 12 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Bemben et al. (2010), 42 men aged 48–72 years were randomised to one of the four following groups: placebo (n = 10; mean age: 56.1 ± 1.4 years), creatine (n = 10; mean age: 56.1 ± 1.8 years), whey protein (n = 11; mean age: 58.2 ± 2.0 years), or creatine plus whey protein (n = 11; mean age: 57.2 ± 2.2 years). All participants performed a 14-week resistance training, which was individually set, with training loads fixed. After 2 weeks of a loading dose (7 g/day, 3 days/week), participants consumed either 5 g of creatine, 5 g of creatine plus 35 g of whey protein, 35 g of whey protein, or placebo after each resistance training session (three times per week) for 14 weeks.

Prior to resistance training and at weeks 5, 10 and 14 of the study, participants performed upper and lower body 1-RM exercises. Two-way ANOVA with repeated measures and Bonferroni tests were used for data analysis. No significant differences in muscle strength were observed between groups.

The Panel notes that, in this study, the training load was fixed throughout the intervention and that any potential effect of the study products on muscle recovery could therefore not result in increased training load. The Panel considers that this study, in which the training load was fixed, does not show an effect of creatine consumed at doses of 5 g/day on training days (three times per week) over a period of 14 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Candow et al. (2008), 40 men (aged 59–77 years) were randomised to consume creatine (n = 13; mean age: 65.5 ± 2.7 years), creatine plus protein (n = 10; mean age: 67.3 ± 3.1 years) or placebo (n = 12; mean age: 64.1 ± 3.1 years) on training days (3 days/week) for 10 weeks. A daily amount of 0.1 g/kg bw of creatine was consumed. Resistance training started with exercises at 70% 1-RM and it was increased once participants were able to complete the required number of repetitions.

One-RM leg press and bench press were measured at baseline and at the end of the study. A one-factor ANOVA was used for data analysis. Changes in 1-RM leg press, 1-RM bench press or in the average training volume per session were not significantly different between groups.

The Panel considers that this study does not show an effect of creatine consumed at doses of 0.1 g/kg bw (about 7 g/day) on training days (three times per week) over a period of 10 weeks, in combination with resistance training, on muscle strength.

In the placebo-controlled, double-blind, parallel intervention study by Carter et al. (2005), 42 males (aged 48–72 years) were randomly allocated to one of the four groups: creatine (n = 10; mean age: 56.1 ± 1.8 years), creatine plus whey protein (n = 11; mean age: 57.2 ± 2.2 years), whey protein (n = 11; mean age: 58.2 ± 2.0 years) or placebo (n = 10; mean age: 56.1 ± 1.4 years). All participants performed resistance training for (3 days/week, for 16 weeks). After 1 week of loading dose (7 g/day for 3 days) prior to resistance training, participants consumed 5 g/day of creatine, 35 g of whey protein, 5 g of creatine plus 35 g of whey protein, or placebo, after each resistance training session, for 16 weeks.

Isokinetic muscle function at three speeds for knee extensors and flexors as well as isokinetic muscle endurance test for knee extensor were measured 1 week before commencing the resistance training, at mid- and at the end of the resistance training. Repeated-measures ANOVA and Bonferroni test were used in the statistical analysis.

Five subjects withdrew from the study because of their inability to maintain a satisfactory attendance record, either because of personal schedules (n = 3) or non-training-related illnesses (n = 2). There were no statistically significant differences in isokinetic knee extension and flexion measurements between groups.

The Panel considers that this study does not show an effect of creatine consumed at doses of 5 g/day on training days only (three times per week) over a period of 16 weeks, in combination with resistance training, on muscle strength.

The Panel notes that the four human intervention studies in which creatine was consumed (doses 5–7 g/day) on training days only (three times per week), in combination with resistance training, did not show an effect of creatine on muscle strength.

3.3.2. Meta-analyses of intervention studies

The meta-analysis by Devries and Phillips (2014) includes some intervention studies which have been considered by the Panel as pertinent to the claim in this opinion (Bermon et al., 1998; Chrusch et al.,

2001; Brose et al., 2003; Carter et al., 2005; Candow et al., 2008; Bemben et al., 2010; Aguiar et al., 2013), but not others (Rogers et al., 2006; Cooke et al., 2014; Gualano et al., 2014). In addition, one of the studies included in the meta-analysis (Neves et al., 2011) was conducted in women with knee osteoarthritis, the results of which cannot be extrapolated to the target population for the claim. The Panel notes that this meta-analysis cannot be used for the scientific substantiation of the claim.

The meta-analysis by Candow et al. (2014a) includes some studies considered by the Panel as pertinent to the claim in this opinion (Bermon et al., 1998; Chrusch et al., 2001; Brose et al., 2003; Candow et al., 2008; Bemben et al., 2010; Aguiar et al., 2013) plus one intervention study in patients suffering from Parkinson disease (Hass et al., 2007), one study on creatine in combination with other substances (Tarnopolsky et al., 2007) and one study in women with knee osteoarthritis (Neves et al., 2011). The Panel notes that no conclusions can be drawn from the last three studies for the substantiation of the claim and considers that this meta-analysis cannot be used for the scientific substantiation of the claim.

3.3.3. Studies on the mechanism by which creatine could exert the claimed effect

The applicant indicated that the effect of creatine supplementation on muscle strength may be attributed to an increased capacity to regenerate ATP from ADP in skeletal muscles linked to a larger CrP pool in the myocytes. The applicant also indicated that creatine may promote muscle hypertrophy through a variety of molecular mechanisms (e.g. cell swelling; alteration in the expression of myogenic transcription factors; increase in satellite cell mitotic activity; improvement in the CrP/ATP energy ratio of cells).

To support the mechanism of action, the applicant provided 29 references: 16 human studies, two animal studies, five *in vitro* studies and six reviews.

The human studies reported on muscle concentrations of creatine, CrP and ATP; on type II skeletal muscle fibres, expression of myogenic transcription factors, and body composition (Sahlin, 1978; Möller et al., 1980; Sipila et al., 1981; Coggan et al., 1990; McCully et al., 1993; Greenhaff et al., 1994; Smith et al., 1998; Berneis et al., 1999; Campbell et al., 1999; Hespel et al., 2001; Parise et al., 2001; Willoughby and Rosene, 2001, 2003; Olsen et al., 2006; Candow et al., 2008; Larsen et al., 2012). The two animal studies investigated the effect of creatine supplementation on satellite cell mitotic activity, muscle creatine and plasma markers of oxidative stress in rats (Dangott et al., 2000; Deminice and Jordao, 2012). The *in vitro* studies investigated the effect of creatine or CrP on RNA-damage, synthesis of myosin and actin, myoblast fusion, and interactions with phospholipids of cell membranes (Ingwall, 1976; Young and Denome, 1984; O'Connor et al., 2008; Fimognari et al., 2009; Tokarska-Schlattner et al., 2012).

The reviews provided relate to creatine and skeletal muscle morphology, metabolism and antioxidant activity, as well as to physiological adaptations during resistance training (Wyss and Kaddurah-Daouk, 2000; Faulkner et al., 2007; Dalbo et al., 2009; Sestili et al., 2011; Candow et al., 2012; Cherniack, 2012). The applicant also provided 18 references on the bioavailability of creatine.

The Panel has previously evaluated a claim on creatine and increase in physical performance during short-term, high intensity, repeated exercise bouts with a favourable opinion (EFSA NDA Panel, 2011). The Panel indicated that ingestion of creatine, which is readily absorbed, at the doses proposed by the applicant (i.e. 3 g/day), increases the intramyocellular content of CrP pool which can enhance the rate by which ATP may be regenerated after intense muscle contractions. The Panel also indicated that the combination of creatine consumption with resistance training appears to increase the normal physiological adaptations to a training program, which include increased muscle strength. Increase in muscle strength may be the result of an improved ability to perform high-intensity exercise via increased CrP availability (Terjung et al., 2000; SCF, 2001; Buford et al., 2007).

The Panel notes that, in this opinion, the studies which show a consistent effect of creatine on muscle strength (Chrusch et al., 2001; Rogers et al., 2006; Aguiar et al., 2013) have a design that allows for an increase in the workload with training duration (e.g. by 31% in Chrusch et al., 2001). Under these conditions, creatine consumption improves the muscle's ability to train at higher intensities and this leads to higher muscle strength. In addition, considering the short half-life of creatine in plasma (1–2 h) and the limited rate at which creatine can be incorporated to the myocellular CrP pool, it is plausible that maintenance of a high CrP pool requires daily creatine consumption. This is supported by the fact that, in the studies where creatine was provided on training days only (three times per week) (Carter et al., 2005; Candow et al., 2008; Bemben et al., 2010; Cooke et al., 2014),

no additional effect of creatine was observed on muscle strength, even if the creatine doses on a weekly basis were comparable to the studies in which creatine was consumed daily.

The Panel considers that there is evidence for a biologically plausible mechanism by which daily creatine consumption could increase muscle strength in combination with resistance training.

3.3.4. Weighing of the evidence

In weighing the evidence, the Panel took into account that, overall, the human intervention studies submitted provide evidence for an effect of creatine, consumed at doses of at least 3 g/day in combination with regular resistance training (three times per week for several weeks) of moderate intensity, on muscle strength in adults over the age of 55, while no such effect was observed when similar doses of creatine on a weekly basis were given on training days only (three times per week). The Panel also took into account the plausible mechanism by which daily consumption of creatine in combination with resistance training could improve muscle strength.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of creatine in combination with resistance training and improvement in muscle strength.

3.4. Panel's comments on the proposed wording

The Panel considers that the following wording reflects the scientific evidence: 'daily creatine consumption can enhance the effect of resistance training on muscle strength in adults over the age of 55'.

3.5. Conditions and restrictions of use

The Panel considers that, in order to obtain the claimed effect, 3 g of creatine should be consumed daily in conjunction with a resistance training which allows an increase in the workload overtime. Resistance training should be performed at least three times per week for several weeks, at an intensity of at least 65–75% of one repetition maximum. The target population is adults over the age of 55, who are engaged in regular resistance training.

4. Conclusions

On the basis of the data presented, the Panel concludes that:

- The food constituent creatine, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect and the target population proposed by the applicant are 'improvement of muscle strength/muscle function in individuals above 55 years of age who regularly perform resistance training'. Improvement in muscle strength is a beneficial physiological effect
- A cause and effect relationship has been established between the consumption of creatine in combination with resistance training and improvement in muscle strength.
- The following wording reflects the scientific evidence: 'daily creatine consumption can enhance the effect of resistance training on muscle strength in adults over the age of 55'.
- In order to obtain the claimed effect, 3 g of creatine should be consumed daily in conjunction with a resistance training which allows an increase in the workload overtime. Resistance training should be performed at least three times per week for several weeks, at an intensity of at least 65–75% of one repetition maximum. The target population is adults over the age of 55, who are engaged in regular resistance training.

Steps taken by EFSA

1) Health claim application on 'creatine contributes to the maintenance of muscle function in the elderly' pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 00437_AT). Submitted by AlzChem - AG Dr. Albert-Frank-Strasse 32, D-83338 Trostberg, Germany.
2) This application was received by EFSA on 13 July 2015.

3) The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
4) On 12 August 2015, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
5) On 19 August 2015, EFSA received the missing information as submitted by the applicant.
6) The scientific evaluation procedure started on 27 August 2015.
7) On 7 October 2015, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The scientific evaluation was suspended on 15 October 2015, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
8) On 27 October 2015, EFSA received the applicant's reply and the scientific evaluation was restarted.
9) During its meeting on 2 February 2016, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to creatine in combination with resistance training and improvement in muscle strength.

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Abbreviations

1-RM	1-repetition maximum
ADP	adenosine diphosphate
ATP	adenosine triphosphate
bw	body weight
CK	creatine kinase
CrP	creatine phosphate
NDA Panel	EFSA Panel on Dietetic Products, Nutrition and Allergies