UKNHCC

UK Nutrition & Health Claims Committee

SCIENTIFIC OPINION

Scientific Opinion for the substantiation of a health claim on creatine supplementation and improved cognitive function pursuant to Article 13(5) of retained Regulation (EC) No 1924/2006[1], as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020

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Application ID

004UKNHCC

Requestor

Alzchem Trostberg GmbH

UKNHCC members

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Declarations of interest

Read the UKNHCC register of interests containing all declarations of interests made by members.

UKNHCC secretariat

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Official observers[2]

[1] 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.

[2] The UKNHCC code of practice states that Official observers attend UKNHCC meetings to provide updates from their respective nations on science and policy matters of relevance whilst respecting UKNHCC independence.

Sarah Clarke (Welsh Government), Chika Edeh (Food Standards Scotland), Elliott Dews (Food Standards Agency Northern Ireland) and Margie Van Dijk (Department of Health and Social Care)

Suggested citation

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UKNHCC disclaimer

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of creatine supplementation, 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 retained Regulation (EC) No 1924/2006[1], as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020.

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 change, pending the outcome of the authorisation procedure foreseen in Article 18(4) of retained Regulation (EC) No 1924/2006[1] as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020.

Claim type

Article 13(5): Function claim based on a (non-essential) beneficial physiological effect.

Process undertaken by the UKNHCC

- The application was received by the UKNHCC on 26 March 2024, at which point the scientific evaluation process started.
- During its meeting on 2 May 2024, the UKNHCC evaluated the evidence submitted by the applicant.
- During its meeting on 9 July 2024, the UKNHCC discussed the draft scientific opinion.
- Following the meeting, the final scientific opinion was agreed via email correspondence and a drafting meeting on 30 July 2024.

Summary

An application was received from Alzchem Trostberg GmbH, submitted for authorisation of a health claim pursuant to Article 13(5) of retained Regulation (EC) No 1924/2006[1] as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020 to the Competent Authority of Great Britain. The United Kingdom Nutrition and Health Claims Committee (UKNHCC) was asked to deliver an opinion on the scientific substantiation of the proposed health claim that “Daily creatine supplementation can contribute to improved cognitive function”.

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

The food that is the subject of the health claim is creatine and the Committee considers that it is sufficiently characterised in relation to the proposed claimed effect.

The claimed effect proposed by the applicant is “daily creatine supplementation can contribute to improved cognitive function”. The quantity of the food required to obtain the claimed effect proposed by the applicant is 3g per day. The target population proposed by the applicant is the “general population, healthy individuals (i.e. individuals of and/or over 18 years of age) of both sexes”.

The applicant presented 10 randomised controlled trials (RCTs) as pertinent to the claim (Benton & Donohoe, 2011, Borchio et al, 2020, Cook et al, 2011, Van Cutsem et al, 2020, McMorris et al, 2007, Pires, 2020, Turner et al, 2015, Watanabe et al, 2002, Alves et al, 2013, Rawson et al, 2008). The Committee assessed each of the studies in relation to the following criteria: dose, target population and cognitive outcomes.

The Committee considers that eight studies are not pertinent to the proposed claim due to a dose of more than (>) 3g per day creatine (Benton & Donohoe, 2011, Borchio et al, 2020, Cook et al, 2011, Van Cutsem et al, 2020, McMorris et al, 2007, Turner et al, 2015, Watanabe et al, 2002, Alves et al, 2013).

One study (Pires, 2020) is not considered pertinent to the proposed claim as it had not been demonstrated that the results (in Muay Thai (Thai boxing) female athletes exercising to exhaustion) can be extrapolated to the target group (that is, the general population, healthy adults of both sexes).

The Committee considers one of the 10 submitted studies to be pertinent to the proposed claim (Rawson et al, 2008). This study included a dose of 2.2g creatine and a target population of healthy non-vegetarian participants. The study reported no difference between creatine supplementation and placebo groups for any cognitive outcome, at any time-point.

As such, in weighing the evidence, the Committee concludes a cause -and-effect relationship has not been established between the consumption of ≤3g per day creatine and improved cognitive function.

Information provided by the applicant

Applicant name and address

Alzchem Trostberg GmbH, Dr.-Albert-Frank-Str. 32, 83308 Trostberg, Germany

Food/constituent as stated by the applicant

“The health claim is intended for creatine (CAS-No. 57-00-1). The most common traded form of creatine is creatine monohydrate (CAS-No. 6020-87-7; abbreviated as CrM throughout the text). The brand name of creatine monohydrate with a purity of ≥99.9 % produced by the applicant is Creavitalis® (Creavitalis_TDS)”.

Health relationship as claimed by the applicant

According to the applicant, “There is evidence that creatine is involved in relevant physiological processes in the brain”. “Creatine plays a central role in energy homeostasis, suggesting that increased supply of creatine may similarly boost brain activity and brain metabolism in humans.” “In line with this hypothesis, CrM supplementation resulted in significant increases in creatine and phosphocreatine concentrations in the human brain leading to changes in cerebral haemoglobin oxygenation. Also, brain ATP levels increased following creatine supplementation. In addition, there is evidence that creatine supplementation significantly increases energy supply to neurons”. "Pre-treatment with creatine showed a protective effect against anoxic and ischemic cell damage in vitro, providing enhanced intracellular PCr [phosphocreatine] concentrations, protection against ATP depletion, delayed membrane depolarization, and reduced structural damage". “By virtue of its function, creatine contributes to improved cognitive performance”.

Wording of the health claim as proposed by the applicant

“Daily creatine supplementation can contribute to improved cognitive function”.

Specific conditions of use as proposed by the applicant

"Creatine should be ingested in an amount of 3g per day”. “The target population for the health claim is the general population, healthy adults of both sexes, thus no other restrictions of use apply”.

The applicant noted that creatine can be consumed in the form of capsules, chewable or effervescent tablets, dissolved in a liquid or incorporated in a food matrix.

The applicant noted the following potential risk to health if the food that is the subject of the claim is consumed in excess “consumption of excess creatine as bolus (single dose >5g) may lead to gastrointestinal distress”.

Documentation provided

Health claim application on daily creatine supplementation and its contribution to improved cognitive function pursuant to Article 13(5) of retained Regulation (EC) No 1924/2006[1], as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations

2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020. Application ID: 004UKNHCC. Submitted by Alzchem Trostberg GmbH.

Assessment

1. Characterisation of the food/constituent

1.1. The food that is the subject of the proposed claim is creatine, a single food constituent. The most common form of creatine is creatine monohydrate (CrM) (CAS-No. 6020-87-7).

1.2. Creatine is a nitrogenous organic acid occurring in vertebrates, and is synthesized endogenously from arginine, glycine, and methionine. In muscle, brain and other tissues creatine is phosphorylated to phosphorylcreatine which in turn supplies high-energy phosphate to adenosine diphosphate yielding adenosine triphosphate thus playing an important role in energy metabolism. Creatine is naturally present in animal derived food, in particular meat and fish. Creatine can be measured by established methods (EFSA Panel on Dietetic Products & Allergies, 2011). Besides the occurrence of creatine in food, creatine can be derived from chemical synthesis and consumed as a food ingredient or as a dietary/food supplement.

1.3. Details of the manufacturing process, quality control and stability were not provided by the applicant. The applicant stated that details were not provided as the food that is the subject of the claim is creatine (not solely CrM). The applicant noted that CrM can be synthesized by several established methods.

1.4. The Committee considers that the food, creatine, which is the subject of the health claim, is sufficiently characterised in relation to the proposed claimed effect.

2. Relevance of the claimed effect to human health

2.1. The claimed effect proposed by the applicant is improved cognitive function. The target population proposed by the applicant is the general population, healthy adults of both sexes.

2.2. The applicant proposed that 3g per day of creatine should be consumed in order to achieve the claimed effect. The applicant noted that “studies of different duration often apply a so-called loading phase for the first 5 to 7 days of supplementation, involving a high dose of creatine between 20 and 25g per day (Hammett et al, 2010). However, an efficient uptake of creatine into target tissue can be achieved by constant low dose ingestion of 2 to 3g per day as well (Hultman et al, 1996, EFSA Panel on Dietetic Products & Allergies, 2011).”

2.3. The applicant proposed that the body function that is the subject of the claimed effect is “cognition/cognitive function, comprising mental processes in the brain”.

2.4. The applicant noted that “Cognitive function is a broad term that refers to mental processes involved in the acquisition of knowledge, manipulation of information, and reasoning. Cognitive functions include the domains of perception, memory, learning, attention, decision making, and language”.

2.5. The applicant stated that “cognitive performance can be measured by a variety of specifically developed cognitive tests, depending on the specific cognitive function”. The applicant provided details of the cognitive tests used to substantiate the claim, in line with the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) guidance (EFSA Panel on Dietetic Products & Allergies, 2012).

2.6. The Committee notes the relevant EFSA guidance (EFSA Panel on Dietetic Products & Allergies, 2012) that “cognitive function encompasses several domains, including memory, attention (concentration), alertness, learning, intelligence, language, and problem solving, which are well defined psychological constructs. An increase, maintenance, or reduced loss of cognitive function in one or more of its domains is a beneficial physiological effect”.

2.7. The Committee notes the relevant EFSA guidance (EFSA Panel on Dietetic Products & Allergies, 2012) that “the scientific evidence for the substantiation of health claims related to one or more specific domains of cognitive function can be obtained from human intervention studies showing an effect on objective measures of the specific domain(s) by using standard psychometric tests (e.g. standard ‘computerised’ or ‘paper-and-pencil’ tests), established test batteries, or valid and reliable tests for the specific domain(s) that is/are the subject of the claim”.

2.8. The Committee considers that:

- an effect on one or more cognitive domains is a beneficial physiological effect for the general population
- the standard psychometric tests presented by the applicant may be suitable outcome measures for the scientific substantiation of claims related to cognitive function
- not all of the tests used in the studies submitted were validated cognitive or psychometric tests
- limited evidence was provided by the applicant that the psychometric tests or other tests used in submitted studies were appropriate for the

objective assessment of cognitive endpoints in the study population of interest.

2.9. The Committee had some concerns that 'general cognitive function' is broad and ideally evidence for a range of domains (including memory, attention (concentration), alertness, learning, intelligence, language, and problem solving) that fall within the definition of cognitive function should be provided.

3. Scientific substantiation of the claimed effect

3.1. The applicant noted that a claim was also submitted on the E-Submission Food Chain Platform of the European Commission (EC) via the member state Austria on 22 December 2023. The Health Claim application number is HC-2023-19270 and the EFSA Question Number is EFSA-Q-2024-00106.

3.2. The scientific risk assessment was conducted in line with the UKNHCC Framework for the evaluation of evidence submitted for the substantiation of nutrition and health claims (UKNHCC, 2023).

3.3. In assessing the application, the Committee discussed and agreed that further information was not required via the stop the clock process.

3.4. In assessing the application and proposed conditions of use, the Committee considers:

- the claim relates to both creatine and CrM. The Committee notes that there is a difference in the molecular weight of creatine compared with CrM; however, it would have a negligible impact on doses of creatine-based supplements given in studies
- studies should show an effect at ≤3g creatine per day in order to meet the conditions of use
- study populations should include healthy adults (aged 18 and over) to allow results to be applied to the general population
- that exhaustive exercise, sleep deprivation and hypoxia as mental challenges in the study populations presented may not be appropriate to the conditions of use
- that creatine levels may be lower in vegetarian and vegan populations compared with omnivores, and that any impact of creatine supplementation on cognitive function may be more pronounced in these groups compared with supplementation in healthy adults.

3.5. The applicant performed literature searches in databases CA and Medline on 14 February 2023 using the following search terms and syntax:

- creatine monohydrate [6020-87-7] OR creatine [57-00-1]

- AND supplementation OR treatment OR intake lutein
- AND human
- AND cognition OR cognitive function OR behaviour OR mental OR brain function OR memory OR mental fatigue OR psychological OR Psychomotor OR perceptual OR attention OR learning OR intelligence OR attention OR mood OR affect OR depression OR anxiety OR sleep.

The search was limited to articles published in English and German, no patents, and by publication year, 1990 and onwards. The inclusion and exclusion criteria applied to select the pertinent publications were reported. The applicant included RCTs on healthy human subjects with no risk of creatine deficiency due to health issues. Cognitive outcome measures included diverse tests such as standardised cognitive tests assessing memory, verbal fluency, reaction times, skill performance, memory recall and mathematical processing.

3.6. The applicant identified a total of 10 RCTs as being pertinent to the proposed claim (Benton & Donohoe, 2011, Borchio et al, 2020, Cook et al, 2011, Van Cutsem et al, 2020, McMorris et al, 2007, Pires, 2020, Turner et al, 2015, Watanabe et al, 2002, Alves et al, 2013, Rawson et al, 2008). The Committee assessed each of these studies in relation to dose, target population and cognitive outcomes.

3.7. The Committee considers 9 out of 10 studies as not pertinent to the proposed claim.

- Eight studies due to a dose of > 3g per day creatine (Benton & Donohoe, 2011, Borchio et al, 2020, Cook et al, 2011, Van Cutsem et al, 2020, McMorris et al, 2007, Turner et al, 2015, Watanabe et al, 2002, Alves et al, 2013), of these:
    - 6 studies used a loading dose of 20g per day creatine (Benton & Donohoe, 2011, Borchio et al, 2020, Van Cutsem et al, 2020, McMorris et al, 2007, Turner et al, 2015, Alves et al, 2013)
    - one study (Watanabe et al, 2002) used a dose of 8g per day creatine
    - one study (Cook et al, 2011) used doses of 4.5g and 9g per day creatine.
- One study (Pires, 2020) as it had not been demonstrated that the results (in Muay Thai (Thai boxing) female athletes exercising to exhaustion) can be extrapolated to the target group (ie the general population, healthy adults of both sexes).

3.8. The Committee notes further concerns in relation to the cognitive tests used in many of the studies are not pertinent to the claim based on the conditions of use. This includes the cognitive tests being undertaken on participants after a mental challenge (for example, exhaustive exercise, sleep deprivation or hypoxia) or the use of non-validated cognitive tests (for example, rugby passing skill test).

3.9. The Committee considers one study as pertinent to the claim (Rawson et al, 2008). This was a double-blind placebo-controlled study in which 22 participants were randomly assigned to 2.2g (0.03g per kilogram of body weight per day) of encapsulated creatine supplements or placebo for 6 weeks. Participants completed a battery of neurocognitive tests pre- and post-supplementation. Cognitive tests included simple reaction time, logical reasoning, mathematical processing, running memory, memory recall and code substitution (immediate and delayed). Authors reported estimating that 10 participants in each group would be sufficient to detect a significant effect. A repeated measures ANOVA with a grouping factor was used to assess the pattern of change between groups from pre- to post-supplementation (group x time interaction term). Significance was set a priori at $p \leq 0.05$. Authors reported that there was no significant effect of group, no significant effect of time and no significant effect of group by time interaction for any of the reported tests (simple reaction time, logical reasoning, mathematical processing, running memory, memory recall and code substitution (immediate and delayed). As such, the Committee considers that Rawson et al. (2008) does not provide evidence of a difference between creatine and placebo supplemented groups for any cognitive outcomes at any time-point. The Committee also notes that there is no registered protocol or trial registration for this study.

4. Weighing the evidence

4.1. On the basis of the evidence presented, the Committee identified only one randomised controlled trial (RCT) (Rawson et al, 2008) from which conclusions could be drawn. The RCT reported no difference between creatine and placebo supplemented groups in relation to any of the reported cognitive tests.

4.2. The Committee concludes that a cause-and-effect relationship has not been established between the consumption of ≤3g per day creatine and improved cognitive function.

Conclusions

On the basis of the data presented by the applicant, the Committee concludes that:

- the food, creatine, which is the subject of the health claim, is sufficiently characterised in relation to the claimed effect.

- the claimed effect relates to cognitive function. Improved cognitive function is a beneficial physiological effect. The target population is healthy adults.

- a cause-and-effect relationship has not been established between the consumption of ≤3g per day creatine and improved cognitive function.

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Abbreviations

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
CrM	Creatine monohydrate
EC	European Commission
EFSA	European Food Safety Authority
NDA	Panel on Dietetic Products, Nutrition and Allergies
RCT	Randomised Controlled Trial
UKNHCC	United Kingdom Nutrition and Health Claims Committee