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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to glucosamine and maintenance of normal joint cartilage pursuant to Article 13(5) of Regulation (EC) No 1924/20061

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)2, 3

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Merck Consumer Healthcare, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to glucosamine, formulated as glucosamine sulphate or hydrochloride, and maintenance of normal joint cartilage. Glucosamine is sufficiently characterised. The claimed effect is “contributes to the maintenance of normal joint cartilage”. The target population as proposed by the applicant is the general population, and in particular people exposing their joints to high mechanical load and people with joint cartilage deterioration due to normal ageing. The Panel considers that the maintenance of normal joint cartilage is a beneficial physiological effect. The applicant provided references to studies in patients with osteoarthritis, in healthy subjects, in animals and in vitro as being pertinent to the health claim. In weighing the evidence, the Panel took into account that no human studies were provided from which conclusions could be drawn on the effect of dietary glucosamine on the maintenance of cartilage in individuals without osteoarthritis, and that the evidence provided in the in vitro and animal studies in support of the biological plausibility for a possible contribution of dietary glucosamine to the maintenance of joint cartilage in humans is weak. The Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine and maintenance of normal joint cartilage in individuals without osteoarthritis. © European Food Safety Authority, 2012

KEY WORDS
Glucosamine, joints, cartilage, health claims

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1 On request from the Competent Authority of Belgium following an application by Merck Consumer HealthCare, Question No EFSA-Q-2011-01113, adopted on 25 April 2012.
2 Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Laggiou, Martinus Lovik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhausser-Berthold, Hildegard Pryzembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. One member of the Panel did not participate in the discussion on the subject referred to above because of potential conflicts of interest identified in accordance with the EFSA policy on declarations of interests. Correspondence: nda@efs.europa.eu
3 Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Lovik, Ambroise Martin, Hildegard Pryzembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen for the preparatory work on this scientific opinion.


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SUMMARY

Following an application from Merck Consumer Healthcare, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to glucosamine and maintenance of normal joint cartilage.

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

The food constituent that is the subject of the health claim is glucosamine, formulated as glucosamine sulphate or hydrochloride. The Panel considers that glucosamine is sufficiently characterised.

The claimed effect is “contributes to the maintenance of normal joint cartilage”. The target population as proposed by the applicant is the general population, and in particular people exposing their joints to high mechanical load, for example through extensive sports activities or obesity, and people with joint cartilage deterioration due to normal ageing. From the information provided, the Panel notes that the claimed effect relates to the maintenance of joint cartilage. The Panel considers that the maintenance of normal joint cartilage is a beneficial physiological effect.

In the original application, the applicant identified a total of 61 references as being pertinent to the health claim. These references comprised 20 references describing 12 human intervention studies, 13 reviews on the effects of glucosamine supplementation on maintenance of joints, four animal studies on the effects of glucosamine on joints, 14 in vitro studies on the effects of glucosamine on cartilage cells/tissues, nine studies in humans and/or animals on the bioavailability of glucosamine, and one unpublished narrative review.

Nineteen references were provided that report on 11 human intervention studies. These studies addressed the effects of glucosamine sulphate or glucosamine hydrochloride on joint-related outcomes in patients with clinical diagnosis of degenerative osteoarthritis (OA), mainly of the knee. The applicant proposed that results from these studies in patients with OA could be extrapolated to subjects without OA on the assumption that cartilage degeneration occurs by the same metabolic pathways and mechanisms during progression of OA as in pre-arthritic conditions, and that glucosamine may be expected to have similar effects on joint tissues with and without OA.

The Panel notes that while a number of factors which may contribute to cartilage degeneration in the development (onset) and progression of OA have been identified, the term OA denotes a number of pathological degenerative processes of one or more joints of complex and variable aetiology for which no common pathological pathway has been described. The Panel also notes, in particular, that the pathobiology of the onset and early progression of OA is poorly defined. The evidence provided by consensus opinions/reports from authoritative bodies indicates that normal cells and tissues are genetically (gene expression) and functionally different from osteoarthritic cells and tissues and therefore may respond differently to intervention with exogenous substances. The Panel also notes that the evidence provided for the proposed mechanisms which would explain an effect of glucosamine on joint cartilage is weak. The Panel considers that results from studies in subjects with OA relating to the treatment of symptoms of this disease (e.g. erosion of articular cartilage, and reduced function of joints) with glucosamine cannot be extrapolated to the target population. Therefore, no scientific conclusions can be drawn from the studies on patients with OA for the substantiation of the claimed effect in subjects without OA.

One publication which reported on two studies (i.e. one observational cross-sectional study and one open-label intervention study) in subjects without osteoarthritis was provided. Both studies used urinary concentrations of type II collagen fragments as outcome measures. The authors stated that fragments of type II collagen were targeted as biomarkers of cartilage synthesis (C-terminal type II
Glucosamine and maintenance of normal joint cartilage

procollagen peptide, CPII) and breakdown (C-terminal crosslinking peptide, CTX-II; neoepitope C2C) since type II collagen is one of the major constituents of cartilage and represents 90-95% of the total collagen content in cartilage.

The cross-sectional study was performed to assess the validity of type II collagen fragments in urine as outcome measures of joint damage. Urinary concentrations of type II collagen fragments were assessed in 21 male soccer players and in 10 male college students who did not participate in any college athletics. Urinary concentrations of CTX-II, but not of C2C, were reported to be significantly higher in soccer players than in the control subjects (p<0.01), whereas urinary concentrations of CPII were not significantly different between the groups. The ratio of CTX-II/CPII in soccer players was significantly higher than that in controls (p<0.05). The Panel considers that the evidence provided does not establish that changes in urinary concentrations of type II collagen fragments can be used to predict joint cartilage degradation.

The open label intervention was conducted in the sample of soccer players, who received either 1.5 g (n=9) or 3 g (n=10) of glucosamine hydrochloride per day for three months. The Panel notes that no information was provided on the method used for allocating the subjects to either group, and also notes the absence of a placebo control group. Urine samples were collected at baseline, at the end of the 3-month intervention with glucosamine, and three months after glucosamine withdrawal. The endpoints of the study were urinary concentrations of CTX-II, C2C and CPII, and the CTX-II/CPII ratio. The Panel notes that only within-group comparisons between baseline, end of the intervention and follow up were reported, and that no statistical comparisons were made for baseline-adjusted changes in urinary analytes between the two glucosamine-treated groups. The Panel notes the methodological limitations of the study and considers that no conclusions can be drawn from this study with respect to the effects of glucosamine hydrochloride on urinary concentrations of type II collagen fragments. The Panel also notes that the evidence provided does not establish that changes in urinary CTX-II, C2C, CPII or the ratio of CTX-II/CPII over periods of three months can predict net changes in joint cartilage in the proposed target population. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of an effect of glucosamine on maintenance of joint cartilage.

The applicant also provided studies on the bioavailability of glucosamine in humans and animals. While these studies show that some dietary glucosamine is taken up into blood and synovial fluid, the Panel considers that uptake of glucosamine into cartilage cells would be very limited under in vivo conditions.

A number of references were provided on studies performed in animals and in vitro. The Panel considers that the evidence provided in the in vitro studies in support of the proposed mechanisms by which dietary glucosamine could contribute to the maintenance of joint cartilage in humans is weak, and that it was not established that results from animal studies could predict an effect of glucosamine on joint cartilage in humans.

In weighing the evidence, the Panel took into account that no human studies were provided from which conclusions could be drawn on the effect of dietary glucosamine on the maintenance of cartilage in individuals without osteoarthritis, and that the evidence provided in the in vitro and animal studies in support of the biological plausibility for a possible contribution of dietary glucosamine to the maintenance of joint cartilage in humans is weak.

The Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine and maintenance of normal joint cartilage in individuals without osteoarthritis.
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BACKGROUND

Regulation (EC) No 1924/2006\(^4\) 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 of 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).

STEPS TAKEN BY EFSA

- The application was received on 11/10/2011.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- On 27/10/2011, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- The applicant provided the missing information on 10/11/2011.
- The scientific evaluation procedure started on 20/11/2011.
- On 15/12/2011, 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 clock was stopped on 21/12/2011 and restarted on 05/01/2012, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 10/01/2012, EFSA received the requested information as submitted by the applicant.
- During its meeting on 25/04/2012, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to glucosamine and maintenance of normal joint cartilage.

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: glucosamine and maintenance of normal joint cartilage.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of glucosamine, a positive assessment of its safety, nor a decision on whether glucosamine 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.
INFORMATION PROVIDED BY THE APPLICANT

Applicant’s name and address: Merck Consumer HealthCare n.v./s.a., Brusselsesteenweg 288, BE-3090 Overijse.

Food/constituent as stated by the applicant
According to the applicant, glucosamine, formulated as glucosamine sulphate or hydrochloride.

Health relationship as claimed by the applicant
According to the applicant, disturbance of tissue homeostasis due to overweight, high mechanical load, bad posture or previous injuries and normal aging can lead to cartilage deterioration, which is reflected by joint space narrowing and reduced joint functionality. Glucosamine is a major building block of joint cartilage tissue, and a physiological inducer of cartilage formation. Glucosamine helps to maintain the normal joint cartilage metabolism, which is required for the maintenance of normal joints and their appropriate structure and function.

Wording of the health claim as proposed by the applicant
The applicant proposed the following wording for the health claim: “Glucosamine contributes to the maintenance of normal joint cartilage”. Alternatively: “Glucosamine contributes to the maintenance of normal joints”.

Specific conditions of use as proposed by the applicant
The applicant proposed an intake of 500-1500 mg of glucosamine per day in usual dosage forms of food supplements, i.e. as capsules, tablets, powder or liquids. The indicated amount can be easily consumed in the form of food supplements as part of a balanced diet. The target population for this health claim is the general population, in particular people exposing their joints to high mechanical load, for example through extensive sports activities or obesity, and people with joint cartilage deterioration due to normal ageing.

ASSESSMENT

1. Characterisation of the food/constituent
The food constituent that is the subject of the health claim is glucosamine, formulated as glucosamine sulphate or hydrochloride.

Glucosamine is a well characterised amino monosaccharide where a hydroxyl group (-OH) is replaced with an amino group (-NH2) (2-amino-2-deoxy-D-glucose). Glucosamine is usually formulated as the hydrochloride or as glucosamine sulphate and can be quantified in foods by established methods.

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

2. Relevance of the claimed effect to human health
The claimed effect is “contributes to the maintenance of normal joint cartilage”. The target population as proposed by the applicant is the general population, and in particular people exposing their joints to
high mechanical load, for example through extensive sports activities or obesity, and people with joint cartilage deterioration due to normal ageing.

From the information provided, the Panel notes that the claimed effect relates to the maintenance of joint cartilage. For claims on the maintenance of joint cartilage, it is recognised that net loss of cartilage may lead to a general loss in joint function. Changes in joint cartilage structure leading to an improvement (or reduced loss) in joint function(s) can be considered beneficial physiological effects.

The Panel considers that the maintenance of normal joint cartilage is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The Panel has already issued an opinion on glucosamine hydrochloride and reduced rate of cartilage degeneration and reduced risk of development of osteoarthritis pursuant to Article 14 of Regulation (EC) No 1924/2006 with an unfavourable outcome (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009a). The Panel has also issued two opinions on glucosamine alone or in combination with chondroitin sulphate and maintenance of joints pursuant to Article 13(1) of Regulation (EC) No 1924/2006 (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009b) and pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011) with unfavourable outcomes.

The applicant performed a literature search (databases and search terms not specified) to identify human intervention studies (published in English or German) which investigated the effects of glucosamine at doses up to 1500 mg daily in healthy subjects or in patients with osteoarthritis (OA) on the following primary endpoints: joint space width, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne, cartilage degradation marker C-terminal crosslinking peptide-II (CTX-II), functional marker (e.g. walking test), percentage of joint replacement, and magnetic resonance imaging (MRI). Human intervention studies without a control group, without a detailed description of the methodology, using “non-validated” biomarkers, on patients with rheumatoid arthritis or other joint diseases, using supplementation of glucosamine in combination with other substances, assessing only joint pain by visual analogue scales (VAS), or with results obtained by post-hoc analysis were excluded.

Non-human studies were identified by hand search in PubMed using different combinations of the key words glucosamine, animal, study, cell-culture, in vitro, and chondrocyte.

In the original application, the applicant identified a total of 61 references as being pertinent to the health claim. These comprised 20 references describing 12 human intervention studies (11 randomised controlled trials (RCT), one open label intervention study), 13 reviews on the effects of glucosamine supplementation on maintenance of joints, four animal studies on the effects of glucosamine on joints, 14 in vitro studies on the effects of glucosamine on cartilage cells/tissues, nine studies in humans and/or animals on the bioavailability of glucosamine, and one unpublished narrative review on putative mechanisms for cartilage degradation and development/progression of OA.

Human studies in patients with osteoarthritis

The applicant provided 19 references which reported on 11 human intervention studies. These studies addressed the effects of glucosamine sulphate (10 studies) or glucosamine hydrochloride (one study) on joint-related outcomes (e.g. joint space width in three studies, and joint function in eight studies) in patients with clinical diagnosis of degenerative OA, mainly of the knee (Bruyere et al., 2003, 2004, 2008; Christgau et al., 2004; Cibere et al., 2004; Clegg et al., 2006; Drovanti et al., 1980; Frestedt et al., 2008; Herrero-Beaumont et al., 2007; Houpt et al., 1999; Hughes and Carr, 2002; Kawasaki et al., 2008; McAlindon et al., 2004; Noack et al., 1994; Pavelka et al., 2002; Reginster et al., 2001;
Rozendaal et al., 2008; Usha and Naidu, 2004; Zenk et al., 2002). The applicant proposed that results from these studies in patients with OA could be extrapolated to subjects without OA on the assumption that cartilage degeneration occurs by the same metabolic pathways and mechanisms during progression of OA as in pre-arthritic conditions, and that glucosamine may be expected to have similar effects on joint tissues with and without OA (Alexander et al., 2010, unpublished).

The applicant was invited to comment on recent expert reviews which indicate that there is lack of agreement on the specific cellular and molecular mechanisms by which cartilage degeneration occurs in the development (onset) and progression of osteoarthritis. In reply, the applicant indicated that a very good consensus has been established concerning the various mechanisms and pathways contributing to cartilage deterioration and osteoarthritis development. The applicant provided several references to factors that are considered to contribute to cartilage metabolism as well as putative mechanisms for cartilage degradation associated with the onset of OA as a result of joint overloading, ageing and obesity, as well as for cartilage degradation associated with progression of OA (e.g. Bronner and Farach-Carson, 2007; Hunter, 2008, 2011; Lane et al., 2011; Malemud, 2010). The Panel notes that while a number of factors which may contribute to cartilage degeneration in the development (onset) and progression of OA have been identified, the term OA denotes a number of pathological degenerative processes of one or more joints of complex and variable aetiology for which no common pathological pathway has been described. The Panel also notes, in particular, that the pathobiology of the onset and early progression of OA is poorly defined. The evidence provided by consensus opinions/reports from authoritative bodies indicates that normal cells and tissues are genetically (gene expression) and functionally different from osteoarthritic cells and tissues, and therefore may respond differently to intervention with exogenous substances (FDA, 2004a, b; Jordan et al., 2011). The Panel also notes that the evidence provided for the proposed mechanisms which would explain an effect of glucosamine on joint cartilage is weak (see below). The Panel considers that results from studies in subjects with OA relating to the treatment of symptoms of this disease (e.g. erosion of articular cartilage, and reduced function of joints) with glucosamine cannot be extrapolated to the target population. Therefore, no scientific conclusions can be drawn from the studies on patients with OA for the substantiation of the claimed effect in subjects without OA.

**Human studies in subjects without osteoarthritis**

One publication (Yoshimura et al., 2009) reported on one observational cross-sectional study and one open-label intervention study which used urinary concentrations of type II collagen fragments as outcome measures. The authors stated that fragments of type II collagen were targeted as biomarkers of cartilage synthesis (C-terminal type II procollagen peptide, CPII) and breakdown (C-terminal crosslinking peptide, CTX-II; neoeptipeptide C2C) since type II collagen is one of the major constituents of cartilage and represents 90-95% of the total collagen content in cartilage.

The cross-sectional study was performed to assess the validity of type II collagen fragments in urine as outcome measures of joint damage (Yoshimura et al., 2009). Urinary concentrations of type II collagen fragments were assessed in 21 male soccer players (19-22 years of age) and in 10 male college students (controls, 20-27 years of age). Soccer players were training five times a week for about 2 h/day, whereas the control subjects did not participate in any college athletics, nor had experienced moderate or hard exercise for over one year. Urinary concentrations of CTX-II, neoeptipeptide C2C and CPII were measured in second void morning urine samples and were standardised for creatinine. Urinary concentrations of CTX-II, but not of C2C, were reported to be significantly higher in soccer players than in the control subjects (p<0.01), whereas urinary concentrations of CPII were not significantly different between the groups. The ratio of CTX-II/CPII in soccer players was significantly higher than that in controls (p<0.05).

The applicant was invited to provide justification for the validity of the biomarkers used in the study to assess the claimed effect, i.e. evidence that changes in the biomarkers used over periods of, for example, three months can predict net changes in joint cartilage in the proposed target population. In
reply, the applicant claimed that while it is not possible to establish a correlation between such biomarkers and net changes in joint cartilage, CTX-II is a well-established prognostic biomarker and independent risk factor of joint cartilage breakdown in the progression of osteoarthritis, and is a suitable surrogate indicator for chondroprotective effects of supplements and medicinal products, including glucosamine. A number of studies were provided by the applicant on the use of urinary concentrations of type II collagen fragments (mainly on urinary CTX-II) as markers for diagnosis of OA and for the progression of joint damage during development, progression and treatment of OA (Bay-Jensen et al., 2009; Cahué et al., 2007; Cheras et al., 2010; Christgau et al., 2001; Christgau et al., 2004; Cibere et al., 2009; Dam et al., 2009; Garnero et al., 2001, 2002, 2003; Iwamoto et al., 2010; Karsdal et al., 2010; Kummer et al., 2009; Mazieres et al., 2006; Reijsman et al., 2004; Scarpellini et al., 2008; Sharif et al., 2007; Sowers et al., 2009; Syversen et al., 2009; Tanishi et al., 2009; Watari et al., 2008), rheumatoid arthritis (Christensen et al., 2009; Garnero et al., 2002b; Hashimoto et al., 2009; van Tuyl et al., 2010) and other joint disorders (Jansen et al., 2009; Rousseau et al., 2010). The applicant also claimed that urinary CTX-II is a suitable early indicator of joint cartilage damage in healthy subjects, e.g. upon repetitive physical joint loading, as in sports (Yoshimura et al., 2009-cross-sectional study), and that increased urinary concentrations of CTX-II in menopausal women correlate with a higher prevalence of OA (Mourtizen et al., 2003). The Panel considers that while the studies provided by the applicant may indicate an association between urinary concentrations of type II collagen fragments and joint cartilage damage in certain population subgroups, the evidence provided does not establish that changes in urinary concentrations of type II collagen fragments can be used to predict joint cartilage degradation. This conclusion is in agreement with what is generally accepted by experts in the field, as indicated in a recent consensus report (Kraus et al., 2011).

The open label intervention (Yoshimura et al., 2009) was conducted in the sample of soccer players, who received either 1.5 g (n=9) or 3 g (n=10) of glucosamine hydrochloride per day for three months. The Panel notes that no information was provided on the method used for allocating the subjects to either group, and also notes the absence of a placebo control group. Second void morning urine samples were collected at baseline, at the end of the 3-month intervention with glucosamine, and three months after glucosamine withdrawal (follow-up). The endpoints of the study were urinary concentrations of CTX-II, C2C and CPII, all standardised for creatinine, and the CTX-II/CPII ratio. The Panel notes that only within-group comparisons between baseline, end of the intervention and follow up were reported, and that no statistical comparisons were made for baseline-adjusted changes in urinary analytes between the two glucosamine-treated groups. The Panel notes the methodological limitations of the study and considers that no conclusions can be drawn from this study with respect to the effects of glucosamine hydrochloride on urinary concentrations of type II collagen fragments. The Panel also notes that the evidence provided does not establish that changes in urinary CTX-II, C2C, CPII or the ratio of CTX-II/CPII over periods of three months can predict net changes in joint cartilage in the proposed target population. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of an effect of glucosamine on maintenance of joint cartilage.

**Mechanistic studies**

The applicant provided data on the bioavailability of glucosamine in support of the biological plausibility of the claim (Akarasereenont et al., 2009; Block et al., 2010; Meulyzer et al., 2009; Oegema et al., 2002; Persiani et al., 2005, 2007; Setnikar et al., 1986, 1993; Setnikar and Rovati, 2001; Zhang et al., 2006; Zhu et al., 2009). A review by Block et al. (2010) concluded that the concentrations of glucosamine in the blood of subjects receiving 1500 mg of glucosamine per day reaches a maximum of about 10 µM between 1 and 4 h after ingestion, followed by a significant decline by about 6-8 h. Results were similar for glucosamine hydrochloride and sulphate. The mean concentration of glucosamine achieved in the synovial fluid 3 h after administration is around 80% of the mean blood concentration (Persiani et al., 2007). No information was provided on the uptake of exogenous glucosamine into joint cartilage cells (e.g. chondrocytes). However, the Panel notes that cellular uptake of exogenous glucosamine at extracellular concentrations of 10 µM would be very
limited in vivo owing to competition with much higher concentrations (about 5 mM) of glucose (Block et al., 2010).

The applicant proposed a number of mechanisms by which dietary glucosamine could contribute to the maintenance of joint cartilage. These include: (1) oral glucosamine is an exogenous source of glucosamine for glycosaminoglycan (GAG) synthesis, (2) oral glucosamine supports cartilage homeostasis, e.g. by inhibiting the gene expression of matrix metalloproteases in chondrocytes and synovial fibroblasts, or up-regulating the expression of TGF-β1 in chondrocytes, (3) glucosamine prevents joint degeneration owing to its anti-inflammatory properties.

A number of in vitro studies on the effect of glucosamine on cartilage formation/degradation were provided (Byron et al., 2008; Chan et al., 2005; Derfoul et al., 2007; Dodge and Jimenez, 2003; Largo et al., 2003; Lin et al., 2008; Lippiello, 2007; Lu et al., 2008; Sandy et al., 1999; Shikhman et al., 2001; Toegel et al., 2008; Uitterlinden et al., 2008; Varghese et al., 2007; Wei and Haut, 2009). The applicant was invited to provide a rationale on why any effects of glucosamine in vitro could predict effects in vivo in humans, taking into consideration the experimental conditions for these studies, e.g. concentrations of glucosamine used compared to concentrations of glucosamine achievable in vivo with a dietary intake of 1.5 g/d. The applicant did not address the question regarding the experimental conditions of these studies directly. Regarding a possible contribution of dietary glucosamine to GAG synthesis, the evidence provided included references on in vitro effects of glucosamine on cartilage tissue explants and chondrocytes in culture, including effects of glucosamine on the synthesis of cartilage components such as glycosaminoglycans (Bassleer et al., 1998; Byron et al., 2008; Derfoul et al., 2007; Toegel et al., 2008; Uitterlinden et al., 2008; Varghese et al., 2007). In almost all of these studies the concentrations of glucosamine at which effects were observed considerably exceeded those that are achieved in blood and synovial fluid in humans with a daily intake of 1500 mg of glucosamine. The Panel notes that no evidence was provided that endogenous synthesis of glucosamine from glucose and glutamine is insufficient for the maintenance of normal cartilage in subjects without OA. A contribution of dietary glucosamine to the synthesis of cartilage components (GAG) requires exogenous glucosamine to be taken up by chondrocytes in sufficient quantities. At achievable concentrations (~10 μM) in synovial fluid with a daily intake of 1500 mg glucosamine, two reviews concluded that the contribution of dietary glucosamine to the synthesis of GAG would be negligible (Silbert, 2009; Block et al., 2010). This conclusion takes into account the competition of glucosamine with much higher concentrations of glucose for uptake into cartilage cells, and the large excess of endogenously produced glucosamine for incorporation into GAG.

Regarding other proposed mechanisms, the evidence provided included references on in vitro effects of glucosamine on cartilage tissue explants and chondrocytes in culture, including effects of glucosamine on pro-inflammatory cytokines (Chan et al., 2005; Derfoul et al., 2007; Largo et al., 2003; Lin et al., 2008; Lu et al., 2008; Sandy et al., 1999; Shikhman et al., 2001; Toegel et al., 2008), and degradative enzymes (Derfoul et al., 2007; Dodge and Jimenez, 2003; Lin et al., 2008; Lu et al., 2008; Varghese et al., 2007). The Panel notes that the concentrations of glucosamine used in almost all of these studies considerably exceeded those that are achieved in blood and synovial fluid in humans with a daily intake of 1500 mg glucosamine.

The Panel considers that the evidence provided in the in vitro studies in support of the proposed mechanisms by which dietary glucosamine could contribute to the maintenance of joint cartilage in humans is weak.

The applicant also provided studies in animals on the effect of glucosamine on cartilage formation/degradation (Chen et al., 2010; Meulzyzer et al., 2009; Naito et al., 2010; Oegema et al., 2002; Taniguchi et al., 2012). Four studies were provided in animal models of OA, i.e. in rats and rabbits with OA induced surgically or enzymatically (Chen et al., 2010; Naito et al., 2010; Oegema et al., 2002) and in Hartley guinea pigs susceptible to spontaneous OA (Taniguchi et al., 2012). One study was provided on the effect of glucosamine on induced (by injection of lipopolysaccharides from
*E. coli* inflammation of joints in horses (Meulyzer et al., 2009). The applicant was invited to justify the validity of the animal models in the context of the claimed effect, i.e. reasons why any effect of glucosamine in those animal studies could predict an effect on joint cartilage in the target population. The applicant did not address the question regarding the validity of these animal models directly. The Panel notes the lack of justification for the validity of these models. The Panel considers that the evidence provided does not establish that results from animal studies could predict an effect of glucosamine on joint cartilage in humans.

The Panel considers that the evidence provided in the *in vitro* and animal studies in support of the biological plausibility for a possible contribution of dietary glucosamine to the maintenance of joint cartilage in humans is weak.

In weighing the evidence, the Panel took into account that no human studies were provided from which conclusions could be drawn on the effect of dietary glucosamine on the maintenance of cartilage in individuals without osteoarthritis, and that the evidence provided in the *in vitro* and animal studies in support of the biological plausibility for a possible contribution of dietary glucosamine to the maintenance of joint cartilage in humans is weak.

The Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine and maintenance of normal joint cartilage in individuals without osteoarthritis.

**CONCLUSIONS**

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

- The food constituent, glucosamine, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “contributes to the maintenance of normal joint cartilage”. The target population as proposed by the applicant is the general population, and in particular people exposing their joints to high mechanical load, for example through extensive sports activities or obesity, and people with joint cartilage deterioration due to normal ageing. Maintenance of normal joint cartilage is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of glucosamine and maintenance of normal joint cartilage in individuals without osteoarthritis.

**DOCUMENTATION PROVIDED TO EFSA**


**REFERENCES**


cartilage protecting effects of glucosamine sulphate. Clinical and Experimental Rheumatology, 22, 36-42.


EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009b. Scientific Opinion on the substantiation of health claims related to glucosamine alone or in combination with chondroitin sulphate and maintenance of joints (ID 1561, 1562, 1563, 1564, 1565) and reduction of inflammation (ID 1869) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 7(9):1264, 17 pp.


FDA (U.S. Food and Drug Administration), 2004b. Letter Regarding the Relationship Between the Consumption of Glucosamine and/or Chondroitin Sulfate and a Reduced Risk of: Osteoarthritis; Osteoarthritis related Joint pain, Joint Tenderness and Joint Swelling; Joint Degeneration; and Cartilage Deterioration (Docket No. 2004P-0059).


**GLOSSARY / ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CPII</td>
<td>C-terminal type II procollagen peptide</td>
</tr>
<tr>
<td>CTX-II</td>
<td>C-terminal crosslinking peptide</td>
</tr>
<tr>
<td>GAG</td>
<td>glycosaminoglycan</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>OA</td>
<td>osteoarthritis</td>
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<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
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<tr>
<td>TGF-β1</td>
<td>transforming growth factor beta 1</td>
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<tr>
<td>VAS</td>
<td>visual analogue scales</td>
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<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Osteoarthritis Index</td>
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