

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to soy isoflavones and maintenance of bone mineral density (ID 1655) pursuant to Article 13(1) of Regulation (EC) No 1924/2006¹

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

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to soy isoflavones and the maintenance of bone mineral density. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The food constituent that is the subject of the health claim is soy isoflavones. Soy isoflavones constitute a range of compounds of plant origin, which mainly comprise genistein, daidzein, and glycitein, among others. The Panel considers that soy isoflavones are sufficiently characterised.

The claimed effect is “bone health”. Bone health relates to bone mass, bone mineral density (BMD) and bone structure, which all contribute to bone strength. After menopause, an increased rate of bone loss and bone remodelling, and a decrease in BMD, are observed. The Panel considers that maintaining bone mineral density is beneficial to the health of post-menopausal women.

In weighing the evidence the Panel took into account that, although statistically significant effects on markers of bone turnover and/or on spine bone mineral density have been described in some short-term randomised trials (up to 12 weeks and up to 12 months, respectively) in relation to the dietary intake of soy isoflavones, longer-term interventions do not support a sustained effect of soy isoflavone intake on markers of bone health. The Panel also took into account the lack of a clear dose-response relationship between the dietary intake of soy isoflavones and the claimed effect, and the different results obtained depending on the source and nature of the isoflavones used.

1 On request from the European Commission, Question No EFSA-Q-2008-2391 adopted on 02 July 2009.

2 Panel members: Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

Correspondence: nda@efsa.europa.eu

For citation purposes: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to soy isoflavones and maintenance of bone mineral density (ID 1655) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9):1270. [14 pp.]. doi:10.2903/j.efsa.2009.1270. Available online: www.efsa.europa.eu

The Panel concludes that the evidence provided is not sufficient to establish a cause and effect relationship between the consumption of soy isoflavones and the maintenance of bone mineral density in post-menopausal women.

KEY WORDS

Soy isoflavones, genistein, daidzein, glycitein, soybean protein isolates, bone mineral density, post-menopausal women, health claims.

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ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank for the preparation of this opinion:

The members of the Working Group on claims Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

The members of the Claims Sub-Working Group on Bone/Teeth/Connective Tissue: Rikke Andersen, Olivier Bruyère, Albert Flynn, Ingegerd Johansson, Jukka Meurman and Hildegard Przyrembel.

INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006³ submitted by Member States contains main entry claims with corresponding conditions of use and literature from similar health claims. The information provided in the consolidated list for the health claims subject to this opinion is given in Table 1

Table 1. Main entry health claims related to soy isoflavones, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food component	Health Relationship	Proposed wording
1655	Soy isoflavones	Bone health and soy foods	- Maintenance of healthy bones/(natural)/support to bone health/contributes to the maintenance of normal bone strength in post-menopausal women.
	Conditions of use <ul style="list-style-type: none"> - 40 to 100 mg of soy isoflavones. - Erwachsene Frauen 20 – 100 Milligramm (mg). - Minimum 35 mg per day. - 100 mg täglich–Nahrungsergänzung. 		

ASSESSMENT

1. Characterisation of the food/constituent

The food constituents that are the subject of the health claim are soy isoflavones. Soy isoflavones constitute a wide range of compounds of plant origin, which mainly comprise genistein, daidzein, and glycitein, among others (Ma et al., 2008a and 2008b). Soy isoflavones could be consumed as soybean-protein isolates (SPI), as whole-soybean foods or extracts, as supplements or as pure compounds (Cassidy et al., 2006).

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

2. Relevance of the claimed effect to human health

The claimed effect is “bone health”. The Panel assumes that the target population is post-menopausal women.

Bone health relates to bone mass, bone mineral density (BMD) and bone structure, which all contribute to bone strength. Whereas bone structure and bone strength are not usually measured *in vivo*, BMD is a good indicator of bone health in the general population.

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.

After menopause, an increased rate of bone loss and bone remodelling, and a decrease in BMD, are observed. These changes have been associated with an increased risk of bone fractures. Bone metabolism can be measured by assessing biochemical markers of bone turnover. BMD, a relevant factor for the assessment of bone health, can also be measured by established methods.

The Panel considers that maintaining bone mineral density is beneficial to the health of post-menopausal women.

3. Scientific substantiation of the claimed effect

Publications on the health effects of phytoestrogens in general, or on the effects of soy isoflavones on health outcomes unrelated to bone status, were not considered pertinent to the evaluation of this claim.

Two meta-analyses and one systematic review were presented investigating the effects of soy isoflavones on bone parameters in post-menopausal women (Cassidy et al., 2006; Ma et al., 2008a and 2008b). These studies deal with the effect of soy isoflavones on BMD and/or on biochemical markers of bone turnover. All the individual studies presented have been considered in these publications.

The systematic review only included placebo-controlled double-blind randomised clinical trials (RCTs) conducted in healthy women >1 year post-menopausal with a duration from six months up to one year (Cassidy et al., 2006). Six studies investigating the effects of soybean phyto-oestrogens on BMD, bone turnover, or both, met the inclusion criteria. Three of these studies used pure compounds or extracts and three studies provided foods containing soybean protein or SPI (Gallagher et al., 2004; Potter et al., 1998; Kreijkamp-Kaspers et al., 2004). Of the three studies that used soybean isoflavone extracts or pure genistein, two are suggestive of an effect on BMD at doses ranging from 35 to 54 mg/d aglycone equivalents (Clifton-Bligh et al., 2001; Morabito et al., 2002). Only one of the three studies performed with SPI showed an effect on BMD at a dose of 56 mg/d aglycone equivalents (Potter et al., 1998), while the two other studies show no effect with doses ranging from 4 to 103 mg/d aglycone equivalents (Gallagher et al., 2004; Kreijkamp-Kaspers et al., 2004). Only three of the studies included biomarkers of bone formation or bone resorption. One study using SPI (Gallagher et al., 2004) and one study using red clover extract (Clifton-Bligh et al., 2001), showed no effect of the intervention on markers of bone turnover, whereas the study using genistein (54 mg/d) showed an increase in bone formation and a reduction in bone resorption biomarkers (Morabito et al., 2002).

The first meta-analysis (search dates 1966 – April 2006) selected nine RCTs including 432 peri- (two studies, total of 66 subjects) and post-menopausal women and investigating the effects of soy isoflavones on markers of bone turnover (Ma et al., 2008a). The duration of the intervention varied widely among studies (from 4 to 48 weeks), with only three of them lasting longer than 12 weeks. Soy isoflavone intake varied between 37 and 118 mg/d in the various intervention groups. Soy isoflavone intake was associated with a significant increase in bone-specific alkaline phosphatase (a marker of bone formation) and with a significant decrease in urinary deoxypyridinoline (a marker of bone resorption) compared to placebo. Differences between intervention and control groups were not significant when only the three RCTs lasting >12 weeks were taken into account. The Panel notes that meaningful changes in bone resorption and bone formation markers in response to an intervention can only be expected after 12 and 24 weeks, respectively (Prentice et al., 2003). The Panel also notes these markers alone cannot be considered as primary indicators of bone health.

The second meta-analysis (search dates 1966 – September 2006) selected 10 RCTs including 608 peri- (two studies, total of 66 subjects) and post-menopausal women and investigating the effects of soy isoflavones on BMD (Ma et al., 2008b). The duration of the intervention varied widely among studies (from 3 to 24 months), with only four of them lasting longer than one year. Soy isoflavone intake varied between 4.4 and 150 mg/d in the various intervention groups. When all the studies were combined, soy isoflavone intake significantly increased spine BMD compared to placebo. However,

these results were not significant when the analysis was restricted to the four studies with at least one year of duration. The Panel notes that at least 6–12 months are needed to evaluate the short-term impact of an intervention on BMD, and that 2–3 years are necessary to evaluate the long-term effects.

In weighing the evidence the Panel took into account that, although statistically significant effects on markers of bone turnover and/or on spine BMD have been described in some short-term RCTs (up to 12 weeks and up to 12 months, respectively) in relation to the dietary intake of soy isoflavones, longer-term interventions do not support a sustained effect of soy isoflavone intake on markers of bone health (Ma et al., 2008a and 2008b). The Panel also took into account the lack of a clear dose-response relationship between the dietary intake of soy isoflavones and the claimed effect, and the different results obtained depending on the source and nature of the isoflavones used (Cassidy et al., 2006; Weaver and Cheong, 2005).

The Panel concludes that the evidence provided is not sufficient to establish a cause and effect relationship between the consumption of soy isoflavones and the maintenance of bone mineral density in post-menopausal women.

CONCLUSIONS

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

- The food constituent, soy isoflavones, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “bone health”. The target population is assumed to be post-menopausal women. Maintenance of bone mineral density is beneficial to the health of post-menopausal women.
- The evidence provided is not sufficient to establish a cause and effect relationship between the consumption of soy isoflavones and the maintenance of bone mineral density in post-menopausal women.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-2391). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: <http://www.efsa.europa.eu/panels/nda/claims/article13.htm>

REFERENCES

- Cassidy A, Albertazzi P, Lise Nielsen I, Hall W, Williamson G, Tetens I, Atkins S, Cross H, Manios Y, Wolk A, Steiner, C, Branca F, 2006. Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women. *Proc. Nutr. Soc.* 65, 76-92.
- Cassidy A, Bingham S, Setchell K, 1995. Biological effects of isoflavones in young women: importance of the chemical composition of soyabean products. *Br. J. Nutr.* 74, 587-601.
- Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery ML, Moreton T, 2001. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. *Menopause* 8, 259-265.

- Gallagher JC, Satpathy R, Rafferty K, Haynatzka V, 2004. The effect of soy protein isolate on bone metabolism. *Menopause* 11, 290-298.
- Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, Lampe JW, van der Schouw YT, 2004. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 292, 65-74.
- Ma DF, Qin LQ, Wang PY, Katoh R, 2008a. Soy isoflavone intake inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials. *Eur. J. Clin. Nutr.* 62, 155-161.
- Ma DF, Qin LQ, Wang PY, Katoh R, 2008b. Soy isoflavone intake increases bone mineral density in the spine of menopausal women: meta-analysis of randomized controlled trials. *Clin. Nutr.* 27, 57-64.
- Morabito N, Crisafulli A, Vergara C, Gaudio A, Lasco A, Frisina N, D'Anna R, Corrado F, Pizzoleo MA, Cincotta M, Altavilla D, Ientile R, Squadrito F, 2002. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. *J. Bone Miner. Res.* 17, 1904-1912.
- Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman JW, Jr., 1998. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *Am. J. Clin. Nutr.* 68, 1375S-1379S.
- Prentice A, Bonjour JP, Branca F, Cooper C, Flynn A, Garabedian M, Müller D, Pannemans D, Weber P, 2003. PASSCLAIM – Bone health and osteoporosis. *Eur J Nutr* 42, I28-I49.
- Weaver CM and Cheong JM, 2005. Soy isoflavones and bone health: the relationship is still unclear. *J Nutr* 135, 1243-1247.

APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods⁴ (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

- a) the role of a nutrient or other substance in growth, development and the functions of the body; or
- b) psychological and behavioural functions; or
- c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

- (i) based on generally accepted scientific evidence; and
- (ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD⁵

Foods are commonly involved in many different functions⁶ of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

⁴ OJ L12, 18/01/2007

⁵ The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.

⁶ The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

- (a) the claimed effect of the food is beneficial for human health,
- (b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),
- (c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,
- (d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.
- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.
- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.

- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.
- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. 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 wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

GLOSSARY / ABBREVIATIONS

BMD	Bone mineral density
RCTs	Randomised clinical trials
SPI	Soybean-protein isolates