SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to ipriflavone and maintenance of bone mineral density (ID 1872) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

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 ipriflavone and 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 ipriflavone, a synthetic derivative of the natural isoflavone daidzein. Ipriflavone is chemically well characterised and is measurable by established methods. The Panel considers that ipriflavone is 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 maintenance of bone mineral density is beneficial to the health of post-menopausal women.

In weighing the evidence the Panel took into account that, although four small intervention studies suggest a role of ipriflavone in attenuating the loss of BMD at the lumbar spine in post-menopausal women by decreasing bone resorption, the largest randomised controlled trial with the highest number of subjects and the longest follow-up indicates that ipriflavone does not prevent bone loss or affect biochemical markers of bone turnover in post-menopausal women.

On the basis of the data available, the Panel concludes that a cause and effect relationship has not been established between the consumption of ipriflavone and maintenance of bone mineral density in post-menopausal women.

---

1 On request from the European Commission, Question No EFSA-Q-2008-2605 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 ipriflavone and maintenance of bone mineral density (ID 1872) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9):1267. [15 pp.]. doi:10.2903/j.efsa.2009.1267. Available online: www.efsa.europa.eu

KEY WORDS

Ipriflavone, bone, bone mineral density, post-menopausal women, health claims.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

EFSA DISCLAIMER

See Appendix B

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 1924/2006[3] 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 ipriflavone, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
1872	Ipriflavone	Bone health	- Exact wording of claim as it appears on product: Ipriflavone supresses bone resorption; - Examples of any alternative wording that may be used in relation to claim: Increases bone density/ prevents decreased bone mineral density/ prevents rapid bone loss/ total bone health/ Maintain healthy bones/ Maintain bone integrity/ Reduce bone loss/ Maintain adequate bone density/ support bone health/ contributes to bone health/ contributes to bone strength/ Beneficial effects on bone health/ increased bone mineral density/ Increased bone strength/ Helps reduce risk of bone loss - Is claim a picture: No
	Conditions of use - Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 600 miligram(s) Ipriflavone Weight of average daily food serving: 600 miligram(s) Daily amount to be consumed to produce claimed effect: 600 miligram(s) Number of food portions this equates to in everyday food portions: 3 Are there factors that could interfere with bioavailability: No Length of time after consumption for claimed effect to become apparent: 6 -12 months Is there a limit to the amount of food which should be consumed in order to avoid adverse health effects: No Other conditions for use: This beverage should be consumed as part of a varied, balanced, and healthy lifestyle. Three beverages are to be consumed daily in order to gain benefit. This product should be avoided by pregnant and lactating women, children, people with immune deficiencies, and people with ulcers.		

[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.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is ipriflavone (7-isopropoxy-isoflavone), a synthetic derivative of the natural isoflavone daidzein which is not naturally present in foods but is usually found in food supplements. Ipriflavone is chemically well characterised (7-isopropoxy-3-phenyl-4H-chromen-4-one) and it is measurable by established methods.

The Panel considers that the food constituent, ipriflavone, 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.

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 maintenance of bone mineral density is beneficial to the health of post-menopausal women.

3. Scientific substantiation of the claimed effect

Six references reporting results of intervention studies in humans on the effects of ipriflavone on bone mass and turnover (Gambacciani et al., 1994; Gennari et al., 1998; Ohta, 1999; Pagano et al., 1999; Sato et al., 1999; Somekawa et al., 2001), one review of randomised controlled trials (RCTs) (Agnusdei and Bufalino, 1997) and one review on the mechanisms of action of iproflavone on bone metabolism (Reginster, 1993) have been provided for the substantiation of the claimed effect. The Panel also considers that an additional reference reporting the results of a large multicentre RCT on the effects of ipriflavone on BMD and turnover in post-menopausal women is also relevant to the evaluation of the claim (Alexandersen et al., 2001).

Several *in vitro* studies suggest that ipriflavone (typically 200 mg orally 3 times per day) may inhibit bone resorption and increase bone formation, a mechanism by which ipriflavone could prevent bone loss in postmenopausal women (Reginster, 1993).

Four of the human intervention studies provided assessed the effects of ipriflavone on BMD and biochemical markers of bone turnover in patient populations with acute leukemia (Pagano et al., 1999), with stroke-induced hemiplegia (Sato et al., 1999), or with pharmacologically-induced hypogonadism caused by the administration a gonadotropin hormone-releasing hormone agonist (Gambacciani et al., 1994; Somekawa et al., 2001). The Panel notes that the evidence provided does not establish that these patient populations are representative of the general population with regard to bone status, or that results obtained in studies on such patients relating to the treatment of rapid bone loss can be extrapolated to the maintenance of bone mineral density in the general population of adults.

Three of the references provided report the results of four randomised controlled trials investigating the effects of ipriflavone consumption on BMD and/or bone turnover which have been conducted in post-menopausal women with either osteopenia or osteoporosis, which may be considered as representative of the target population for the claim.

One of the references (Agnusdei and Bufalino, 1997) was a review of two Italian multicentre studies performed in elderly women with established osteoporosis. Elderly women with diagnosis of osteoporosis and prevalent vertebral fractures were enrolled in seven centres. A total of 149 subjects entered the two studies, and 111 completed the 2-year intervention period. In both studies, the women were randomly allocated to receive either ipriflavone 600 mg/day or placebo for two years according to a double-blind, placebo-controlled, parallel design. In the first study, 14 women in the ipriflavone group and 13 in the placebo completed the 2-year treatment. Radial BMD significantly increased at years one (by 4%) and two (by 5%) of the intervention in the ipriflavone group compared with placebo. The urinary hydroxyproline/creatinine ratio decreased significantly in the ipriflavone group compared to placebo. In the second study, 41 women in the ipriflavone group and 43 in the placebo group completed the 2-year treatment. Radial BMD significantly increased at years one and two of the intervention in the ipriflavone group compared with placebo. The urinary hydroxyproline/creatinine ratio decreased significantly in the ipriflavone group compared to placebo. The Panel notes that the methodological weaknesses of these studies (i.e. small sample size, no intention-to-treat analysis, and high rate of drop outs in the first study) limit the conclusions that can be drawn in relation to the claimed effect.

Gennari et al. (1998) randomised 56 post-menopausal women with low vertebral BMD and postmenopausal age less than five years to receive either ipriflavone (200 mg three times daily) or placebo for two years. All subjects received also 1,000 mg/d of calcium. A statistically significant lower decrease in vertebral BMD was observed in the ipriflavone group compared with placebo at one and two years (-0.4% and -4.9% in the iproflavone and placebo groups at two years, respectively). At the end of the study, urine hydroxyproline/creatinine excretion, a marker of bone resorption, was significantly higher in the placebo group than in the ipriflavone group.

In the study by Ohta (1999), for which only the abstract was available, 60 women with postmenopausal osteopenia or osteoporosis were randomly assigned to receive either 600 mg/d ipriflavone or 0.8 g/d calcium lactate for one year. The rate of the decrease in L2-4 BMD was significantly greater in the calcium lactate group than in the ipriflavone group. Median urinary deoxypyridinoline concentrations significantly decreased in the ipriflavone group after one year compared to baseline, whereas no changes were observed in the control group. No statistical comparison between ipriflavone and control groups was reported for this marker of bone resorption.

Finally, in a large prospective, randomised, double-blind, placebo-controlled trial including 474 postmenopausal Caucasian women aged 45 to 75 years with osteopenia or osteoporosis (Alexandersen et al., 2001), subjects were randomly assigned to receive either ipriflavone (200 mg 3 times per day, n = 234) or placebo (n = 240) for three years in addition to 500 mg/d of calcium. Based on an intention-to-treat analysis, the annual percent change from baseline in BMD at the lumbar spine or at any of the other sites measured did not differ significantly between the ipriflavone and the placebo groups after 36 months of treatment. The response of biochemical markers of bone turnover did not differ between groups. The number of women with new vertebral fractures was not different between the intervention and control groups after three years of follow-up.

In weighing the evidence the Panel took into account that, although four small intervention studies suggest a role of ipriflavone in attenuating the loss of BMD at the lumbar spine in post-menopausal women by decreasing bone resorption, the largest RCT with the highest number of subjects and the longest follow-up indicates that ipriflavone does not prevent bone loss or affect biochemical markers of bone turnover in post-menopausal women.

The Panel concludes that a cause and effect relationship has not been established between the consumption of ipriflavone and maintenance of bone mineral density in post-menopausal women.

CONCLUSIONS

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

- The food constituent, ipriflavone, 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.
- A cause and effect relationship has not been established between the consumption of ipriflavone and 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-2008-2605). The scientific substantiation is based on the information provided by the Members 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

Agnusdei D and Bufalino L, 1997. Efficacy of ipriflavone in established osteoporosis and long-term safety. Calcified Tissue International, 61, S23-S27.

Alexandersen P, Toussaint A, Christiansen C, Devogelaer JP, Roux C, Fechtenbaum J, Gennari C, Reginster JY; Ipriflavone multicenter european fracture study, 2001. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. JAMA, 285, 1482-1488.

Gambacciani M, Spinetti A, Piaggesi L, Cappagli B, Taponeco F, Manetti P, Weiss C, Teti GC, Lacommare P, Facchini V, 1994. Ipriflavone prevents the bone mass reduction in premenopausal women treated with gonadotropin hormone-releasing hormone agonists. Bone and Mineral, 26, 19-26.

Gennari C, Agnusdei D, Crepaldi G, Isaia G, Mazzuoli G, Ortolani S, Bufalino L, Passeri M, 1998. Effect of ipriflavone - a synthetic derivative of natural isoflavones - on bone mass loss in the early years after menopause. Menopause, 5, 9-15.

Ohta H, Komukai S, Makita K, Masuzawa T, Nozawa S, 1999. Effects of 1-year ipriflavone treatment on lumbar bone mineral density and bone metabolic markers in postmenopausalwomen with low bone mass. Logo, 51, 178-183.

Pagano L, Teofili L, Mele L, Piantelli M, Ranelletti FO, Equitani F, Larocca LM, Leone G, 1999. Oral ipriflavone (7-isopropoxy-isoflavone) treatment for elderly patients with resistant acute leukemias. Ann. Oncol., 10, 124-125.

Reginster JY, 1993. Ipriflavone: pharmacological properties and usefulness in postmenopausal osteoporosis. Bone Miner., 23, 223-232.

Sato Y, Kuno H, Kaji M, Saruwatari N, Oizumi K, 1999. Effect of ipriflavone on bone in elderly hemiplegic stroke patients with hypovitaminosis D. Am. J. Phys. Med. Rehabil., 78, 457-463.

Somekawa Y, Chiguchi M, Ishibashi T, Wakana K, Aso T, 2001. Efficacy of ipriflavone in preventing adverse effects of leuprolide. J. Clin. Endocrinol. Metab., 86, 3202-3206.

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 foods[4] (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 FOOD[5]

Foods are commonly involved in many different functions[6] 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

[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).

functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

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 DISCAIMER

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
RCT	Randomised controlled trial