SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to manganese and protection of DNA, proteins and lipids from oxidative damage (ID 309), maintenance of bone (ID 310), energy-yielding metabolism (ID 311), and cognitive function (ID 340) 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 manganese and the following claimed effects: protection of DNA, proteins and lipids from oxidative damage, maintenance of bone, energy-yielding metabolism, and cognitive function. 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 claims is manganese, which is a well recognised nutrient and is measurable in foods by established methods. The Panel considers that manganese is sufficiently characterised.

The Panel concludes that a cause and effect relationship has been established between the dietary intake of manganese and the protection of DNA, proteins and lipids from oxidative damage, the maintenance of normal bone, and normal energy-yielding metabolism.

The evidence provided does not establish that inadequate intake of manganese leading to impaired functions of the above-mentioned health relationships occurs in the general EU population.

The Panel considers that, in order to bear the claims, a food should be at least a source of manganese as per Annex to Regulation 1924/2006. Such amounts can be easily consumed as part of a balanced diet. The target population is the general population.

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1 On request from the European Commission, Question No EFSA-Q-2008-1096, EFSA-Q-2008-1097, EFSA-Q-2008-1098, EFSA-Q-2008-1127 adopted on 02 July 2009.

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The Panel concludes that a cause and effect relationship has not been established between the dietary intake of manganese and normal cognitive function.

KEY WORDS

Manganese, bone, energy-yielding metabolism, oxidative damage, cognitive function, health claims.

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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 tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is manganese, which is a well recognised nutrient and is measurable in foods by established methods.

Manganese occurs naturally in foods and is authorised for addition to foods (Annex I of Regulation (EC) No 1925/2006[4] and Annex I of Directive 2002/46/EC[5]). This evaluation applies to manganese naturally present in foods and those forms authorised for addition to foods (Annex II of Regulation (EC) No 1925/2006 and Annex II of Directive 2002/46/EC).

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

2. Relevance of the claimed effect to human health

2.1. Protection of DNA, proteins and lipids from oxidative damage (ID 309)

The claimed effects are "protection of body tissues and cells from oxidative damage" and "antioxidant activity". The Panel assumes that the target population is the general population.

Reactive oxygen species (ROS) including several kinds of radicals are generated in biochemical processes (e.g. respiratory chain) and as a consequence of exposure to exogenous agents (e.g. radiation, pollutants). These reactive intermediates can cause oxidative damage to biologically important molecules such as DNA, proteins and lipids if they are not intercepted by the antioxidant defence system which includes free radical scavengers like antioxidant nutrients.

The Panel considers that the protection of DNA, proteins and lipids from oxidative damage is beneficial to human health.

2.2. Maintenance of bone (ID 310)

The claimed effect is "bone formation". The Panel assumes that the target population is the general population.

In the context of the proposed wording, the Panel notes that the claimed effect relates to the maintenance of normal bone.

The Panel considers that the maintenance of normal bone is beneficial to human health.

[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.
[4] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.
[5] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

2.3. Energy-yielding metabolism (ID 311)

The claimed effect is "energy metabolism". The Panel assumes that the target population is the general population.

In the context of the proposed wordings, the Panel notes that the claimed effect relates to the conversion of energy from foods into energy in the form of ATP which may be readily used by the body.

The Panel considers that normal energy-yielding metabolism is beneficial to human health.

2.4. Cognitive function (ID 340)

The claimed effect is "mental state and performance". The Panel assumes that the target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect relates to cognitive function.

The Panel considers that normal cognitive function is beneficial to human health.

3. Scientific substantiation of the claimed effect

Manganese is essential as a cofactor for the metalloenzymes superoxide dismutase (SOD), xanthine oxidase, arginase, galactosyltransferase and pyruvate carboxylase. Manganese also activates a number of other enzymes such as various decarboxylases, glutamine synthetase, hydrolases, kinases and transferases, such us glycosyltranferases. Manganese is not essential for the activity of most of these enzyme systems, which can also be activated by other metals, with the exception of glycosyltransferases (JHCI, 2003; Buchman, 2006).

3.1. Protection of DNA, proteins and lipids from oxidative damage (ID 309)

SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide, and, as such, it is an important antioxidant defence in nearly all cells exposed to oxygen. SOD2 (Mn-SOD) is the isoenzyme of SOD present in mitochondria. Its synthesis is regulated by manganese by a mechanism of gene activation and reduced activity of the enzyme has been shown in manganese deficiency in mice. Mice lacking SOD2 die a few days after birth owing to massive oxidative stress. Tissue Mn-SOD activity increases after exposure to environmental factors inducing an increase of free radicals in animal cells (JHCI, 2003; Buchman, 2006).

The Panel concludes that a cause and effect relationship has been established between the dietary intake of manganese and the protection of DNA, proteins and lipids from oxidative damage. However, the evidence provided does not establish that inadequate intake of manganese leading to impaired protection of DNA, proteins and lipids from oxidative damage occurs in the general EU population.

3.2. Maintenance of bone (ID 310)

Glycosyltranferases and xylosyltransferases are important for proteoglycan synthesis and thus bone formation and are sensitive to manganese intake and status in animals (JHCI, 2003; IoM, 2001; Buchman, 2006). Manganese deficiency interferes with normal skeletal development in various animal species (Combs et al., 1942; Leach and Muenster, 1962; Tsai and Everson, 1967). The very few cases reported of manganese deficiency in humans (induced in experimental conditions) also point towards an impairment of growth and development of bone. However, manganese deficiency has not been well documented in humans (Buchman, 2006).

The Panel concludes that a cause and effect relationship has been established between the dietary intake of manganese and the maintenance normal bone. However, the evidence provided does not

establish that intake of manganese inadequate for the maintenance of normal bone occurs in the general EU population.

3.3. Energy-yielding metabolism (ID 311)

Manganese is a cofactor of many enzymes involved in amino acid, carbohydrate and cholesterol metabolism. Deficiency signs of manganese in animals and in humans include alterations in carbohydrate and lipid metabolism (JHCI, 2003), albeit clinical manifestations of manganese deficiency regarding macronutrient metabolism in humans have not been well documented (Buchman, 2006).

The Panel concludes that a cause and effect relationship has been established between the dietary intake of manganese and normal energy-yielding metabolism. However, the evidence provided does not establish that inadequate intake of manganese leading to impaired energy-yielding metabolism occurs in the general EU population.

3.4. Cognitive function (ID 340)

A total of six references were provided in the consolidated list to support this claim (Takeda, 2003 and 2004; Bourre, 2004; Wedler, 1993; Shils et al., 1994; Buchman, 2006; Mason, 2001).

Glutamine synthetase, which catalyzes the conversion of glutamate to glutamine, is a manganese metalloprotein and accounts for approximately 80% of total manganese in the brain. Manganese-deficient rats are more susceptible to seizures induced by electroshock than control rats fed a manganese-adequate diet and ataxia has been reported in offspring from manganese-deprived rats (Takeda, 2003). Manganese deficiency has not been well documented and does not occur readily in humans. An impairment in neurological function is not among the signs and symptoms of manganese deficiency described in humans (Buchman, 2006). Although lower plasma concentrations of manganese have been found in sub-groups of patients with psychiatric diseases as compared to healthy controls (Takeda, 2003), it has not been shown that these conditions respond to increased manganese intake. No data have been provided on the effects of manganese supplementation on cognitive function or mental performance.

The Panel concludes that a cause and effect relationship has not been established between the dietary intake of manganese and normal cognitive function. However, the evidence provided does not establish that inadequate intake of manganese leading to impaired cognitive function occurs in the general EU population.

4. Panel's comments on the proposed wording

4.1. Protection of DNA, proteins and lipids from oxidative damage (ID 309)

The Panel considers that the following wording reflects the scientific evidence: "Manganese contributes to the protection of cell constituents from oxidative damage".

4.2. Maintenance of bone (ID 310)

The Panel considers that the following wording reflects the scientific evidence: "Manganese contributes to the maintenance of normal bone".

4.3. Energy-yielding metabolism (ID 311)

The Panel considers that the following wording reflects the scientific evidence: "Manganese contributes to normal energy-yielding metabolism".

5. Conditions and possible restrictions of use

The Panel considers that in order to bear the claims a food should be at least a source of manganese as per Annex to Regulation (EC) No 1924/2006. Such amounts can be easily consumed as part of a

balanced diet. The target population is the general population. Although adverse health effects of excess intake of manganese have been reported, Tolerable Upper Intake Levels (UL) have not been established owing to lack of data on dose response (SCF, 2000).

CONCLUSIONS

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

- The food constituent, manganese, that is the subject of the health claims, is sufficiently characterised.

Protection of DNA, proteins and lipids from oxidative damage (ID 309)

- The claimed effect is "protection of body tissues and cells from oxidative damage" and "antioxidant activity". The target population is assumed to be the general population. Protection of DNA, proteins and lipids from oxidative damage is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of manganese and the protection of DNA, proteins and lipids from oxidative damage.
- The evidence provided does not establish that inadequate intake of manganese leading to impaired protection of DNA, proteins and lipids from oxidative damage occurs in the general EU population.
- The following wording reflects the scientific evidence: "Manganese contributes to the protection of body cells from oxidative damage".

Maintenance of normal of bone (ID 310)

- The claimed effect is "bone formation". The target population is assumed to be the general population. Maintenance of normal bone is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of manganese and the maintenance of normal bone.
- The evidence provided does not establish that intake of manganese inadequate for the maintenance of normal bone occurs in the general EU population.
- The following wording reflects the scientific evidence: "Manganese contributes to the maintenance of normal bone".

Energy-yielding metabolism (ID 311)

- The claimed effect is "energy metabolism". The target population is assumed to be the general population. Normal energy-yielding metabolism is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of manganese and normal energy-yielding metabolism.
- The evidence provided does not establish that inadequate intake of manganese leading to impaired energy-yielding metabolism occurs in the general EU population.
- The following wording reflects the scientific evidence: "Manganese contributes to normal energy-yielding metabolism".

Cognitive function (ID 340)

- The claimed effect is "mental state and performance". The target population is assumed to be the general population. Normal cognitive function is beneficial to human health.
- A cause and effect relationship has not been established between the dietary intake of manganese and normal cognitive function.

Conditions and possible restrictions of use

- In order to bear the claims a food should be at least a source of manganese as per Annex to Regulation (EC) No 1924/2006. Such amounts can be easily consumed as part of a balanced diet. The target population is the general population.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1096, EFSA-Q-2008-1097, EFSA-Q-2008-1098, EFSA-Q-2008-1127). 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.

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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[6] (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[7]

Foods are commonly involved in many different functions[8] 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.

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

[6] OJ L12, 18/01/2007

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

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

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.

APPENDIX C

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

ID	Food or Food component	Health Relationship	Proposed wording
309	Manganese	Protection of body tissues and cells from oxidative damage; Antioxidant activity	-Manganese is necessary for cells' protection; -Manganese helps scavenging free radicals.
	Conditions of use - Food supplement with 1-2mg of manganese in the daily dose - MUST AT LEAST BE A SOURCE OF MINERAL/S AS PER ANNEX TO REGULATION 1924/2006 Agency guidance for supplements is that products >0.5mg managanese should carry the following label advisory statement: 'Long term intake [of this amount of manganese] may lead to muscle pain and fatigue. Applicable to both children and adults		
	Food or Food component	**Health Relationship**	**Proposed wording**
310	Manganese	Bone formation	-Manganese helps maintain strong bones. -Manganese is needed for the structure of strong/healthy bones
	Conditions of use - MUST AT LEAST BE A SOURCE OF MINERAL/S AS PER ANNEX TO REGULATION 1924/2006 Agency guidance for supplements is that products containing > 0.5mg managanese should carry the following label advisory statement: 'Long term intake [of this amount of manganese] may lead to muscle pain and fatigue. Applicable to both children and adults - Tagesdosis:–2-5 mg Mangan als Mangangluconat–Erwachsene——Diabetiker–Tagesdosis: 5 mg Mangan als Mangangluconat - Jugendliche, Erwachsene 2 Milligramm (mg) max 5 Milligramm (mg) - MINDESTENS 15 % RDA JE 100 G ODER 100 ML ODER JE PORTION GEMÄß 90/496/EWG - 2,3 mg per day		
	Food or Food component	**Health Relationship**	**Proposed wording**
311	Manganese	Energy metabolism	The body needs manganese to produce energy.
	Conditions of use - MINDESTENS 15 % RDA JE 100 G ODER 100 ML ODER JE PORTION GEMÄß 90/496/EWG - Es werden nur die Nährstoffe beworben, die lt. Nährwertkennzeichnungs-verordnung (Anlage 1) mindestens 15 Prozent der empfohlenen Tagesdosis in 100 g oder 100 ml enthalten. - MUST AT LEAST BE A SOURCE OF MINERAL/S AS PER ANNEX TO REGULATION 1924/2006 Agency guidance for supplements is that 0.5mg managanese should carry the following label advisory statement: 'Long term intake [of this amount of manganese] may lead to muscle pain and fatigue. Applicable to both children and adults		
	Food or Food component	**Health Relationship**	**Proposed wording**
340	Manganese	Mental state and performance	Important for brain functioning. Protects the

			brain. Regulates nerve impulse progression
	Conditions of use - Food supplement with 1-2mg of manganese in the daily dose		