**DRAFT SCIENTIFIC OPINION**

# Draft guidance on the scientific requirements for health claims related to neurological and psychological functions[1]

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

European Food Safety Authority (EFSA), Parma, Italy

## SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products Nutrition and Allergies to draft guidance on scientific requirements for health claims related to neurological and psychological functions**.** This draft guidance has been drawn from scientific opinions of the NDA Panel on such health claims. Thus, this guidance represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas. It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures that are acceptable. Rather, it presents examples drawn from evaluations already carried out to illustrate the approach of the Panel, as well as some examples which are currently under consideration within ongoing evaluations. This draft guidance document was endorsed by the NDA Panel on 16 September 2011, and is released for public consultation from 17 October 2011 to 16 December 2011.

**Key words**

Health claims, scientific requirements, neurological function, psychological function.

[1] On request from EFSA, Question No EFSA-Q-2010-01185, endorsed for public consultation on 16 September 2011.

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## BACKGROUND AS PROVIDED BY EFSA

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. According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by EFSA.

EFSA and its NDA Panel has been engaging in consultation with stakeholders and has published guidance on scientific substantiation of health claims since 2007[5]. Most recently, a briefing document on scientific evaluation of health claims was published for consultation in April 2010, followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma, in June 2010[6].

Based on experiences gained with the evaluation of health claims and to further assist applicants in preparing and submitting their applications for the authorisation of health claims, the NDA Panel is asked to develop guidance documents on the scientific requirements for the substantiation of health claims in selected areas, in addition to the guidance for the scientific substantiation of health claims related to gut and immune function (EFSA-Q-2010-01139).

## TERMS OF REFERENCE AS PROVIDED BY EFSA

The NDA Panel is requested by EFSA to develop guidance documents on the scientific requirements for health claims in the following areas:

- Post-prandial blood glucose responses/blood glucose control
- Weight management, energy intake and satiety
- Protection against oxidative damage
- Cardiovascular health
- Bone, joint and oral health
- Neurological and psychological functions
- Physical performance

Specific issues to be addressed in this guidance include:

- which claimed effects are considered to be beneficial physiological effects?
- which studies/outcome measures are appropriate for the substantiation of function claims and disease risk reduction claims?

Each guidance document should be subject to public consultation and may be followed up as appropriate by scientific meetings with experts in the field.

Before the adoption of each guidance document by the NDA Panel, the draft guidance shall be revised taking into account the comments received during the public consultation. A report on the outcome of the public consultation for each guidance document shall be published. All guidance documents should be finalised by July 2012.

[4] 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.

[5] http://www.efsa.europa.eu/en/nda/ndaclaims.htm

[6] http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf

# ASSESSMENT

## 1. Introduction

To assist applicants in preparing and submitting their applications for the authorisation of health claims, EFSA and in particular its Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) has ongoing consultations with stakeholders and has published guidance on scientific substantiation of health claims since 2007[7]. In April 2010, a draft briefing document on scientific evaluation of health claims was published for consultation and was followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma, in June 2010. The draft briefing document has been transformed into a Panel output taking into account the questions/comments received. This document constitutes the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims and outlines the approach of the NDA Panel to the evaluation of health claims in general. In response to requests from industry, EFSA is engaged in further consultation with stakeholders and is developing additional guidance on specific types of claims.

The objective of the present public consultation is to discuss with scientific experts in the field the scientific requirements for the substantiation of health claims related to neurological and psychological functions. This consultation document will be revised to take into account the comments received, in order to provide additional guidance to applicants for the substantiation of health claims in these areas.

The consultation document focuses on two key issues related to substantiation of health claims related to neurological and psychological functions:

- claimed effects which are considered to be beneficial physiological effects;
- studies/outcome measures which are considered to be appropriate for the substantiation of health claims.

Issues which are related to substantiation that are common to health claims in general (e.g. characterisation of the food/constituent) are addressed in the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims[8].

This document has been drawn from scientific opinions of the NDA Panel on health claims related to the neurological and psychological functions. Thus, it represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas. The document should be read in conjunction with the briefing document for stakeholders on the evaluation of Article13.1, 13.5 and 14 health claims.

It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures which are acceptable. Rather it presents examples drawn from evaluations already carried out to illustrate the approach of the Panel as well as some examples which are currently under consideration within ongoing evaluations.

[7] http://www.efsa.europa.eu/en/nda/ndaclaims.htm

[8] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

## 2. General considerations

### 2.1. Beneficial physiological effect

According to the Regulation (EC) No 1924/2006, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect. For the purpose of this guidance document, physiological effects are broadly defined to encompass neurological, psychological, perceptual, psychomotor, and physiological regulatory effects. In assessing each claim, the NDA Panel makes a scientific judgement on whether the claimed effect is considered to be a beneficial physiological effect in the context of the specific claim as described in the information provided and taking into account the population group for whom the claim is intended. For function claims, a beneficial effect may relate to maintenance or improvement of a function.

For reduction of disease risk claims, 'beneficial' refers to whether the claimed effect relates to the reduction (or beneficial alteration) of a risk factor for the development of a human disease (not reduction of the risk of disease). A risk factor is a factor associated with the risk of a disease that may serve as a predictor of development of that disease. Whether or not the alteration of a factor is considered to be beneficial in the context of a reduction of disease risk claim, depends on the extent to which it is established that:

- The factor is an independent predictor of disease risk (such a predictor may be established from intervention and/or observational studies);
- The relationship of the factor to the development of the disease is biologically plausible.

Except for well established risk factors, the extent to which the reduction of a factor is beneficial in the context of a reduction of disease risk claim needs to be considered on a case-by-case basis.

The NDA Panel considers that the population group for which health claims are intended is the general (healthy) population or specific subgroups thereof, for example elderly people, physically active subjects, pregnant women. In its evaluation, the NDA Panel considers that where a health claim relates to a function/effect that may be associated with a disease, subjects with the disease are not the target population for the claim, for example Alzheimer disease patients. Applications for claims that specify target groups other than the general (healthy) population are the subject of ongoing discussions with the Commission and Member States with regard to their admissibility.

The NDA Panel also considers whether the claimed effect is sufficiently defined to establish that the studies identified for substantiation of the claim were performed with (an) appropriate outcome measure(s) of that claimed effect. Reference to general, non-specific benefits of the nutrient or food for overall good health or health-related well-being may only be made if accompanied by a specific health claim.

Claims referring to "mental performance", "mental health", "mental well-being", "emotional balance", "relaxation", "serenity" have been proposed. These terms are too general and cannot be assessed. Hence, the Panel considers that they are not sufficiently defined for a scientific evaluation.

### 2.2. Studies/outcome measures appropriate for substantiation of claims

As human studies are central for substantiation of health claims, the document focuses in particular on such studies. In considering whether the studies provided are pertinent (i.e. studies from which conclusions can be drawn for the scientific substantiation of the claim), the NDA Panel addresses a number of questions, including:

- Whether the studies have been carried out with the food/constituent for which the claim is made. This requirement means that there should be sufficient definition of the food/constituent for which the claim is made and of the food/constituent that has been investigated in the studies that have been provided for substantiation of the claim. The evaluation also considers how the conditions under which the human studies were performed relate to the conditions of use (e.g. quantity and pattern of consumption of the food/constituent) proposed for the claim.

- Whether the design and quality of the studies allow conclusions to be drawn for the scientific substantiation of the claim. The evaluation takes into account the hierarchy of evidence as described in the scientific and technical guidance of the NDA Panel[9], for example intervention studies generally provide stronger evidence than observational studies. Intervention studies should be appropriately conducted so as to minimise bias. In observational studies adequate control of confounders is important. Each health claim is assessed separately and there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim. In this regard, the reproducibility of the effect of the food/constituent as indicated by consistency between studies is an important consideration.

- Whether the studies have been carried out in a study group representative of the population group for which the claim is intended. Can the results obtained in the studied population be extrapolated to the target population? For studies in groups (e.g. subjects with a disease) other than the target group (e.g. general population) for a claim, the NDA Panel considers on a case-by-case basis, the extent to which it is established that extrapolation from the study group to the target group is biologically plausible.

- Whether the studies used (an) appropriate outcome measure(s) of the claimed effect. For this, the NDA Panel considers what is generally accepted in the relevant research fields and consults experts from various disciplines, as appropriate.

## 3. General claims on neurological and brain functions and development

General claims on neurological and brain functions have been proposed. Contribution to normal neurological and brain functions or improvement in neurological and brain functions are generally considered beneficial physiological effects. Except for some essential nutrients which have well-established roles across a wide range of neurological domains, the Panel considers that for other food constituents, maintenance or improvement of "neurological function", "brain function" or "psychological functions" (the latter encompass both cognitive and affective domains) *per se* are not sufficiently defined for a scientific evaluation. The specific aspect of the neurological/brain functions which is the subject of the claim must be identified. The substantiation of a range of claims relating to the maintenance or improvement of specific neurological/brain functions is discussed in the other sections of this document.

General claims on neurological and brain development have been proposed. Contribution to normal neurological and brain development is considered a beneficial physiological effect. The particular life stage to which the claim applies should be specified. As for general claims on neurological and brain functions, for food constituents other than essential nutrients, the specific aspect of neurological or brain development which is the subject of the claim must be identified. The substantiation of claims relating to cognitive and visual development is discussed in section 4.1 and 4.3 of this document, respectively.

[9] EFSA (European Food Safety Authority), 2011. Opinion of the Panel on dietetic products, nutrition and allergies (NDA) on a request from the Commission related to scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim (revision 1). EFSA Journal, 9(5):2170, 36 pp.

# 4. Claims on specific neurological and brain functions

## 4.1. Claims on cognitive function

Cognitive function encompasses several domains, including memory, attention (concentration), alertness, learning, intelligence, language and problem solving, which are well defined psychological constructs. The Panel considers that contribution to normal cognitive function and improvement of cognitive function are beneficial physiological effects.

The substantiation of a claim on a specific domain or sub-domain of cognitive function requires specific tests which have demonstrated validity and reliability for the particular domain that is the subject of the claim (see sections 4.1.1 to 4.1.3). The substantiation of a general claim on cognitive function requires a more comprehensive assessment using tests which assess several cognitive domains.

Effects on cognitive function can be objectively measured by standard psychometric tests (e.g. standard 'computerised' or 'paper-and-pencil' tests), validated for the relevant age group. Standardised cognitive test batteries allow a comprehensive assessment of different domains of cognitive function, using sets of tests (e.g. Wechsler intelligence scales, Cambridge automated neurological test battery (CANTAB)). Electrophysiological measures (e.g. change in electroencephalogram (EEG) frequency patterns) are not validated to date as functional markers of cognition.

The consistency of the effects or the associations observed and the repeatability of the results are important considerations when reviewing the evidence. Training effects should be considered in the study design.

Some claims have referred to the long-term maintenance of cognitive function. A reduced rate of cognitive decline in older people is considered a beneficial physiological effect. In addition to the use of validated psychometric tests, evidence for an effect of the consumption of the food/constituent on the incidence of age-related cognitive decline, using validated clinical diagnosis tools, could be used for the substantiation of a claim on the maintenance of cognitive function.

Claims on the cognitive development of infants and small children have been proposed. Contribution to normal cognitive development of infant and small children is considered a beneficial physiological effect. The particular life stage to which the claim applies should be specified. Validated neurodevelopmental tests, which are appropriate for the age group, are considered adequate outcome measures. Examples include Bayley scales of infant development, Fagan test of infant intelligence, Peabody picture vocabulary test, clinical linguistic and auditory milestone scale, Kaufman assessment battery for children.

The extrapolation of results obtained from patients with diagnosed cognitive impairment to the target population (e.g. general population) requires evidence that the mechanism by which the food constituent exerts an effect on cognition is similar in disease and health. Where appropriate, the confounding role of medication should be considered. A rationale for the extent to which results obtained in individuals with psychological or neurological disorders can be extrapolated to the target population for the claim should be provided and considered on a case-by-case basis.

### 4.1.1. Claims on alertness

Alertness refers to a state of enhanced arousal and readiness to receive and process information and to respond. The Panel considers that increased alertness might be a beneficial physiological effect.

Changes in alertness can be measured using validated psychometric tests, which determine reaction time and/or speed of response to standardised tasks (e.g. measures of reaction time on simple reaction time, choice reaction time or standard vigilance tests measuring speed of reactions).

Self-rating scales of alertness (e.g. mood, alertness and physical sensations scales (MAPSS)) cannot be used to substantiate a claim on alertness.

### 4.1.2. Claims on attention

Attention (concentration) refers to the ability to attend, select and use incoming sensory information. There are two broad categories of attention. Selective attention is the ability to concentrate on one task or source of information to the exclusion of others. Sustained attention (vigilance) is the ability to concentrate over a period of time. The Panel considers that increased attention is a beneficial physiological effect.

Changes in selective attention can be measured using validated psychometric tests (e.g. visual selective search test, Stroop test and categoric search attention test) and appropriate Event Related Potential (ERP) measures. Changes in sustained attention can be measured using validated psychometric tests (e.g. continuous performance task, rapid visual information processing task, and visual or auditory vigilance tasks).

Standardised attention test batteries allow a comprehensive assessment of the full spectrum of attention by using sets of tests (e.g. test of everyday attention (TEA), CANTAB sub-tests of attention).

With respect to the study population, extrapolation of results obtained from children with attention disorders, such as attention deficit hyperactivity disorders (ADHD), to the target population (e.g. general population of children) requires evidence that the mechanism by which the food constituent exerts an effect on attention is similar in disease and health. Where appropriate, the confounding role of medication should be considered. A rationale for the extent to which results obtained from individuals with psychological or neurological disorders can be extrapolated to the target population for the claim should be provided and considered on a case-by-case basis.

### 4.1.3. Claims on memory

Memory is the cognitive ability to maintain previously learned information, so that it may be accessed and used at a later time. The Panel considers that the improvement of memory is a beneficial physiological effect. Memory is not a unitary construct but instead reflects a number of distinct cognitive processes. Claims may focus on a certain aspect of memory (e.g. working memory, explicit memory, implicit memory).

Changes in memory can be measured using validated psychometric tests (e.g. for working memory: backward digit span test).

## 4.2. Claims on mood/affect

Affect encompasses defined states or traits such as positive (characterised by e.g. enthusiasm, calmness) or negative (characterised by e.g. confusion, depression, fatigue, tension) mood. The Panel considers that enhancement of mood/affect (i.e. increased positive affect, decreased negative affect) might be a beneficial physiological effect.

Affect can be measured by standard psychometric tests, including validated self-rating adjective checklists (e.g. profile of mood state (POMS), multiple affect adjective checklist (MAACL), positive

and negative affect schedule (PANAS)) or visual analogue mood scales (e.g. Bond-Lader visual analogue mood scales (VAMS)).

The substantiation of a claim on a specific aspect of mood/affect (e.g. calmness) requires specific tests which have demonstrated validity and reliability for the particular domain that is the subject of the claim. The substantiation of a general claim on enhancement of mood/affect requires a more comprehensive assessment using tests which assess several mood/affect domains.

Evidence of an effect of the consumption of the food/constituent on the incidence of depressed mood, using validated clinical diagnosis tools (e.g. Beck depression inventory, hospital anxiety and depression scale), could be used for the substantiation of a claim on the enhancement of mood.

The extrapolation of results obtained from patients with diagnosed affective disorders (e.g. depressed patients) to the target population (e.g. general population) requires evidence that the mechanism by which the food constituent exerts an effect on affect is similar in disease and health. Where appropriate, the confounding role of medication should be considered. A rationale for the extent to which results obtained in individuals with psychological or neurological disorders can be extrapolated to the target population for the claim should be provided and considered on a case-by-case basis.

### 4.2.1. Claims on psychological stress

In the psychological domain, "stress" is a defined subjective construct which refers to a particular emotional state characterised by psychological distress or tension, resulting from external stressors. Psychological stress may be experienced acutely (temporarily) or chronically (sustained). The Panel considers that the alleviation of psychological stress might be a beneficial physiological effect.

Standard psychometric outcome measures of psychological stress include validated visual analogue scales or self-report scales (e.g. perceived stress scale (PSS), stress sub-scale of depression, anxiety, and stress scales (DASS)). Measures of anxiety could be considered among appropriate endpoints for a claim on psychological stress, but are not sufficient on their own.

Concomitant changes in biological parameters associated with acute psychological stress responses (e.g. cortisol, heart rate, salivary IgA) may only be used as supportive evidence to the subjective assessment.

Studies using experimentally induced stress 'challenges' have been proposed for the substantiation of claims related to psychological stress. A rationale for the extent to which results obtained in these particular experimental conditions can be extrapolated to 'real world' should be provided and considered on a case-by-case basis.

### 4.2.2. Claims on anxiety

Anxiety is an affective state characterised by the apprehensive anticipation of perceived danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension. Anxiety may be experienced acutely (temporarily) or chronically (sustained). The Panel considers that reduction of anxiety might be a beneficial physiological effect.

Standard psychometric outcome measures of anxiety include validated visual-analog scales or self-report scales (e.g. hospital anxiety and depression scale (anxiety sub-scale), state trait anxiety inventory (STAI), Hamilton anxiety rating scale).

### 4.3. Claims on vision

Vision is a defined function of the eye. The Panel considers that the maintenance of normal vision is a beneficial physiological effect. Claims may focus on vision under specific light conditions, for instance, improvement of visual adaptation to dark.

Standard measures of visual function include valid tests of visual acuity and contrast sensitivity (e.g. measures of contrast acuity thresholds, distance and near-visual acuity tests).

Claims on the visual development of infants and small children have been proposed. Contribution to normal visual development of infants and small children is considered a beneficial physiological effect. The particular life stage to which the claim applies should be specified. Visual development, i.e. retinal and visual pathway maturation, can be estimated by objective methods, such as visual evoked potential (VEP) acuity testing (e.g. sweep VEP acuity), electroretinogram (ERG), and subjective, standardised behavioural measures of visual acuity (e.g. Teller acuity cards).

Some claims have referred to the long-term maintenance of vision. Age-related macular degeneration and age-related lens opacities (cataracts) are associated with the impairment of vision. The long-term maintenance of vision is considered to be a beneficial physiological effect. Evidence of effect from the consumption of the food/constituent on the incidence of these conditions could be used for the substantiation of a claim on the maintenance of normal vision.

It has not been established that high macular pigment density confers a protective effect in age-related macular degeneration or is related to vision in people with healthy eyes. Therefore, macular pigment density is not a suitable outcome measure to substantiate a claim on the maintenance of normal vision.

The extrapolation of results obtained from individuals with diagnosed vision impairments (e.g. people with cataracts, age-related macular degeneration, diabetic retinopathy, inherited retinal degeneration, retinal vascular occlusive disease) to the target population (e.g. general population) requires evidence that the mechanism by which the food constituent exerts an effect on vision is similar in disease and health. Where appropriate, the confounding role of medication should be considered. A rationale for the extent to which results obtained in individuals with vision impairments can be extrapolated to the target population for the claim should be provided and considered on a case-by-case basis.

### 4.4. Claims on sleep

The Panel considers that the maintenance of normal sleep is a beneficial physiological effect, whereas improvement of a specific aspect of sleep might be a beneficial physiological effect. Specific aspects of sleep include sleep onset latency (time taken to fall asleep), sleep duration, sleep efficiency (ratio of total sleep time to total time in bed), and sleep quality (defined as perceived quality of sleep).

Normal sleep can be measured by validated subjective or objective methods. Established methods for the assessment of sleep include validated questionnaires (e.g. global symptom questionnaire or index), sleep diaries, polysomnography and actigraphy.

The extrapolation of results obtained from patients with diagnosed sleep disorders to the target population (e.g. general population) requires evidence that the mechanism by which the food constituent exerts an effect on sleep is similar in disease and health. Where appropriate, the confounding role of medication should be considered. A rationale for the extent to which results obtained in individuals with sleep disorders can be extrapolated to the target population for the claim should be provided and considered on a case-by-case basis.

## CONCLUSIONS

The draft guidance document focused on two key issues regarding the substantiation of health claims related to neurological and psychological functions:

- claimed effects which are considered to be beneficial physiological effects;
- studies/outcome measures which are considered to be appropriate for the substantiation of health claims.

The document has been drawn from scientific opinions of the NDA Panel on health claims related to neurological and psychological functions. Thus, it represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas.

## GLOSSARY AND ABBREVIATIONS

| | |
|---|---|
| ADHD | Attention deficit hyperactivity disorders |
| CANTAB | Cambridge automated neurological test battery |
| DASS | Depression, anxiety, and stress scales |
| EEG | Electroencephalogram |
| ERP | Event Related Potential |
| IgA | Immunoglobulin A |
| MAPSS | Mood, alertness and physical sensations scales |
| MAACL | Multiple affect adjective checklist |
| PSS | Perceived stress scale |
| PANAS | Positive and negative affect schedule |
| POMS | Profile of mood state |
| STAI | State trait anxiety inventory |
| TEA | Test of everyday attention |
| VAMS | Visual analogue mood scales |
| VEP | Visual evoked potential |