

1 **SCIENTIFIC OPINION**

2 **DRAFT**

3 **Guidance on the scientific requirements for health claims related to gut and**
4 **immune function¹**

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

6 European Food Safety Authority (EFSA), Parma, Italy

7 **SUMMARY**

8 The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products Nutrition and
9 Allergies to draft guidance on scientific requirements for health claims related to gut and immune
10 function. This guidance has been drawn from EFSA's scientific opinions on health claims related to
11 the gastrointestinal tract and immune system. Thus, it represents the views of the NDA Panel based on
12 the experience gained to date with the evaluation of health claims in these areas. It is not intended that
13 the document will include an exhaustive list of beneficial effects and studies/outcome measures that
14 are acceptable. Rather it presents examples drawn from evaluations already carried out to illustrate the
15 approach of the Panel as well as some examples which are currently under consideration within
16 ongoing evaluations.

17 **KEY WORDS**

18 Health claims, scientific requirements, gut and immune
19
20

¹ On request from EFSA, Question No EFSA-Q-2010-01139, adopted on DD Month YYYY.

² Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

Suggested citation: EFSA on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on on the scientific requirements for health claims related to gut and immune function. EFSA Journal 2010;volume(issue):NNNN. [10 pp.] doi:10.2903/j.efsa.20YY.NNNN.

Available online: www.efsa.europa.eu/efsajournal.htm

21	TABLE OF CONTENTS	
22	Summary	1
23	Table of contents	2
24	Background as provided by EFSA	3
25	Terms of reference as provided by EFSA	3
26	Assessment	4
27	1. Introduction	4
28	2. General considerations	4
29	2.1. Beneficial physiological effect.....	4
30	2.2. Studies/outcome measures appropriate for substantiation of claims	5
31	3. Gastro-intestinal tract	6
32	3.1. Claims on bowel function	6
33	3.2. Claims on gastrointestinal discomfort.....	6
34	3.3. Claims on gastrointestinal microbiota.....	6
35	3.4. Claims on digestion/absorption of nutrients	8
36	4. Immune System	8
37	4.1. Claims on the function of the immune system.....	8
38	4.2. Claims on reduction of inflammation	9
39	4.3. Claims on reducing a risk factor for infections or allergy	9
40	Conclusions	10
41		

42 **BACKGROUND AS PROVIDED BY EFSA**

43 Regulation (EC) No 1924/2006³ harmonises the provisions that relate to nutrition and health claims
44 and establishes rules governing the Community authorisation of health claims made on foods.
45 According to the Regulation, health claims should be only authorised for use in the Community after a
46 scientific assessment of the highest possible standard to be carried out by EFSA.

47 EFSA and its NDA Panel has been engaging in consultation with stakeholders and has published
48 guidance on scientific substantiation of health claims since 2007⁴. Most recently, a briefing document
49 on scientific evaluation of health claims was published for consultation in April 2010, followed by a
50 technical meeting with experts from the food industry, Member States and the European Commission
51 in Parma, in June 2010⁵.

52 Based on experiences gained with the evaluation of health claims and to further assist applicants in
53 preparing and submitting their applications for the authorisation of health claims, the NDA Panel is
54 asked to develop a guidance document on the scientific requirements for the substantiation of specific
55 types of health claims.

56 **TERMS OF REFERENCE AS PROVIDED BY EFSA**

57 The NDA Panel is requested by EFSA to develop a guidance document on the scientific requirements
58 for health claims related to gut and immune function. Specific issues to be addressed in this guidance
59 include:

- 60
- which claimed effects are beneficial physiological effects?
 - which studies/outcome measures are appropriate for the substantiation of function claims and
62 disease risk reduction claims?

63 The NDA Panel is initially requested to draft a guidance to be released for public consultation and to
64 be discussed at a technical meeting with scientific experts in the fields of health claims related to gut
65 and immune functions.

66 Before its adoption by the NDA Panel the draft guidance needs to be revised taking into account the
67 comments received during the public consultation and at the technical meeting.

68

³ European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

⁴ <http://www.efsa.europa.eu/en/nda/ndaclaims.htm>

⁵ <http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf>

69 ASSESSMENT

70 1. Introduction

71 To assist applicants in preparing and submitting their applications for the authorisation of health
72 claims, EFSA has had ongoing consultation with stakeholders and has published guidance on
73 scientific substantiation of health claims since 2007⁶. Most recently, a briefing document on scientific
74 evaluation of health claims was published for consultation in April 2010, followed by a technical
75 meeting with experts from the food industry, Member States and the European Commission in Parma,
76 in June 2010⁷. This outlines EFSA's approach to evaluation of health claims in general. In response to
77 requests from industry EFSA has indicated that it will engage in further consultation with stakeholders
78 and develop additional guidance on specific types of claims.

79 The objective of the present public consultation is to discuss with scientific experts in the field the
80 scientific requirements for the substantiation of health claims related to the gastrointestinal tract and
81 immune system. This consultation document will be revised to take into account the comments
82 received in order to provide additional guidance to applicants for the substantiation of health claims in
83 these areas.

84 The consultation document focuses on two key issues related to substantiation of health claims on the
85 gastrointestinal tract and immune system:

- 86 • which claimed effects are considered beneficial physiological effects?
- 87 • which studies/outcome measures are considered appropriate for the substantiation of health
88 claims?

89 Issues related to substantiation that are common to health claims in general (e.g. characterization of the
90 food/constituent) are addressed in the briefing document.

91 This document has been drawn from EFSA's scientific opinions on health claims related to the
92 gastrointestinal tract and immune system. Thus, it represents the views of the NDA Panel based on the
93 experience gained to date with the evaluation of health claims in these areas. The document should be
94 read in conjunction with the briefing document for stakeholders on the evaluation of Article 13.1, 13.5
95 and 14 health claims, 2010 (see footnote 7).

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

100 2. General considerations

101 2.1. Beneficial physiological effect

102 According to the Regulation, the use of health claims shall only be permitted if the food/constituent,
103 for which the claim is made, has been shown to have a beneficial physiological effect. In assessing
104 each claim, the NDA Panel makes a scientific judgement on whether the claimed effect is considered
105 to be a beneficial physiological effect in the context of the specific claim as described in the
106 information provided and taking into account the population group for whom the claim is intended.
107 For function claims, a beneficial effect may relate to maintenance or improvement of a function.

⁶ <http://www.efsa.europa.eu/en/nda/ndaclaims.htm>

⁷ <http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf>

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

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

117 The extent to which the reduction of a risk factor is beneficial in the context of a reduction of disease
118 risk claim needs to be considered on a case-by-case basis.

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

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

131 **2.2. Studies/outcome measures appropriate for substantiation of claims**

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

- 136 • whether the studies have been carried out with the food/constituent for which the claim is
137 made. This requirement means that there should be sufficient definition of the food/constituent
138 for which the claim is made and of the food/constituent that has been investigated in the
139 studies that have been provided for substantiation of the claim. The evaluation also considers
140 how the conditions under which the human studies were performed relate to the conditions of
141 use (e.g. quantity and pattern of consumption of the food/constituent) proposed for the claim.
- 142 • whether the design and quality of the studies allow scientific conclusions to be drawn for the
143 substantiation of the claim. The evaluation takes into account the hierarchy of evidence as
144 described in the EFSA guidance (ref), e.g. intervention studies generally provide stronger
145 evidence than observational studies. Intervention studies should be appropriately conducted so
146 as to minimise bias. In observational studies adequate control of confounders is important.
147 Each health claim is assessed separately and there is no pre-established formula as to how
148 many or what type of studies are needed to substantiate a claim. In this regard, the
149 reproducibility of the effect of the food/constituent as indicated by consistency between
150 studies is an important consideration.
- 151 • whether the studies have been carried out in a study group representative of the population
152 group for which the claim is intended such that the results obtained in the studied population

153 can be extrapolated to the target population. For studies in groups (e.g. subjects with a disease)
154 other than the target group (e.g. general population) for a claim, the NDA Panel considers on a
155 case-by-case basis, the extent to which it is established that extrapolation from the study group
156 to the target group is biologically justifiable.

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

160 3. Gastro-intestinal tract

161 3.1. Claims on bowel function

162 Normal bowel habits vary considerably from person to person with regard to frequency of bowel
163 movements and bulk and consistency of stool. Constipation is associated with longer transit time, less
164 frequent bowel movements, reduced faecal bulk and harder stools and may contribute to diverticular
165 disease. Changes in bowel function within the normal range might be considered beneficial
166 physiological effects.

167 Appropriate outcome measures of the claimed effect in human studies include transit time, frequency
168 of bowel movements, stool bulk. These outcomes may be measured by generally accepted methods.

169 3.2. Claims on gastrointestinal discomfort

170 Episodes of abdominal pain or discomfort (e.g. distension/bloating, abdominal pain/cramp,
171 borborygmi (rumbling) etc.) in the absence of organic disease or biochemical abnormalities are
172 commonly associated with food or drug intake or alterations of bowel habit and vary between
173 individuals in frequency and severity.

174 Reducing gastrointestinal discomfort is considered a beneficial physiological effect.

175 Appropriate outcome measures of the claimed effect in human studies include validated subjective
176 global symptom severity questionnaire(s).

177 Irritable Bowel Syndrome (IBS) is a functional bowel disorder characterized by chronic or recurrent
178 abdominal pain or discomfort mostly associated with changes in defecation or bowel habit and in the
179 absence of a detectable organic cause. Episodes of abdominal pain or discomfort occur both in healthy
180 people and in individuals suffering from IBS, the difference being the higher frequency and greater
181 severity of the symptoms in IBS. IBS patients are generally considered an appropriate study group to
182 support claims on gastrointestinal discomfort intended for the general population.

183 3.3. Claims on gastrointestinal microbiota

184 The composition of the microbiota in the intestine may be altered by food constituents. Based on
185 current scientific knowledge, it is not possible to define the exact numbers of the different bacterial
186 groups that would constitute a normal microbiota. The evidence available to the panel does not
187 establish that increasing the number of specific microorganisms or any groups of microorganisms,
188 including lactobacilli and/or bifidobacteria, is in itself a beneficial physiological effect.

189 The abnormal presence of pathogenic or toxicogenic microorganisms in the intestine may lead in
190 certain circumstances to gastrointestinal infection. The Panel considers that reducing the numbers of
191 specific pathogenic microorganisms in these ecosystems is a beneficial physiological effect.

192 The presence of pathogens and/or toxinogenic microorganisms in the gastrointestinal tract is also
193 considered by the Panel as a risk factor for infections and reducing the numbers of specific pathogenic
194 microorganisms or their toxins in these ecosystems is considered a beneficial physiological effect in
195 the context of reducing a risk factor for infection.

196 Appropriate outcome measures of the claimed effect in human studies include reduction of numbers of
197 pathogenic microorganisms or their toxins in stools or other suitable samples. The composition of
198 microbiota in the gastrointestinal tract show great variability. Therefore, a microbiologically relevant
199 reduction of pathogens, which is sustained over time in the same study group, should be demonstrated.
200 Generally, a decrease by less than 1 log value is not considered meaningful.

201 There is a distinction in evaluation of effects on pathogenic or toxicogenic microorganisms for
202 function claims and for disease reduction claims.

203 For disease risk reduction claims studies that show only a reduction in incidence or duration of
204 infection(s) would not constitute evidence for a reduction of the risk factor (e.g. numbers of
205 pathogens). However, clinical outcomes (e.g. number of episodes of infection, severity of symptoms,
206 or duration of infection such as indicated by diarrhoea diagnosed as infection-related using specific
207 criteria), demonstrated in human intervention studies could be supportive of the claimed effect related
208 to pathogens.

209 The following is a non-exhaustive list of groups of microorganisms that are considered “pathogenic or
210 toxicogenic” and do not need further characterisation of their pathogenicity:

211 A) food-borne microorganisms, e.g.: *Salmonella*, *Campylobacter*, *Listeria*, some *Escherichia coli*
212 strains (including e.g. ETEC, EHEC, EPEC, EIEC strains), *Yersinia*, *Shigella*; Toxin producing
213 bacteria such as *Staphylococcus aureus*, *Clostridium botulinum*, *Bacillus cereus* (living organism is
214 not needed for disease, only toxin), *Vibrio vulnificus/parahaemolyticus*, rotavirus, noroviruses,
215 verotoxigenic *E. coli*, *Enterobacter sakazakii*, toxigenic *C. perfringens* (type A and B), food-borne
216 parasites (*Echinococcus*, *Toxoplasma*, *Giardia*);

217 B) Gastrointestinal pathogens that are transmitted between humans or originate from environment: e.g.
218 *Helicobacter pylori*, *Clostridium difficile*, *Clostridium tetani* (note: disease via wound infections
219 although can be part of the GI microbiota).

220 The following is a non-exhaustive list of groups of microorganisms that are considered potentially
221 “pathogenic or toxicogenic” at genus or species level, but that require further characterisation to
222 establish their pathogenicity (i.e. the pathogenicity depends on individual properties/specific
223 characteristics):

224 *Candida*, *Clostridium perfringens* (when producing enterotoxin), other clostridia, *Escherichia coli*
225 (certain serotypes). Sufficient characterisation is required in the studies to confirm their pathogenicity.

226 For claims related to maintaining normal defence against pathogens in the gastrointestinal tract,
227 appropriate outcome measures could include reduction of numbers of pathogenic microorganisms or
228 their toxins in suitable samples as well as clinical outcomes (e.g. number and duration of episodes of
229 infection, severity of symptoms, duration of infection, e.g. as measured by infection-related diarrhoea),
230 demonstrated in human intervention studies. (A similar approach would be appropriate for claims
231 related to maintaining normal defence against pathogens at other sites, e.g. urinary tract, upper
232 respiratory tract). While effects on intestinal permeability, production of short chain fatty acids, pH,
233 can be assessed in human studies, such outcomes are in themselves insufficient for the substantiation
234 of the claim. However, they may be considered supportive evidence of the claim in as much as they
235 are proposed as mechanism of action leading to the effect.

236 **3.4. Claims on digestion/absorption of nutrients**

237 Improved digestion or absorption of nutrients might be considered as beneficial physiological effects.
238 Examples of effects considered beneficial to date include improved lactose digestion and improved
239 iron absorption.

240 In Europe, around 4-60 % of the population groups has lactose maldigestion due to a reduced enzyme
241 capacity to digest lactose. Individuals with clinical symptoms of after lactose intake often display
242 nausea, cramping, bloating, diarrhoea and flatulence. Improvement in lactose digestion may alleviate
243 lactose intolerance symptoms and is considered a beneficial physiological effect. The format of such
244 claims may relate to the effect of a food/constituent (e.g. lactose hydrolysing bacteria or enzymes) on
245 lactose digestion when consumed with lactose containing foods.

246 To assess lactose digestion, studies in susceptible populations, defined either by clinical symptoms or
247 by lactase genotyping, with appropriate assessment of symptoms, and/or measurement of breath
248 hydrogen and methane are required.

249 Iron deficiency is one of the most common micronutrient deficiencies in the EU and can result in
250 anemia. Non-haem iron is generally not well absorbed in the human intestine and can be a limiting
251 factor for the maintenance of adequate iron status. Improving iron absorption is considered a
252 beneficial physiological effect. The format of such claims may relate to the effect of a food/constituent
253 (e.g. ascorbic acid) on iron absorption when consumed with iron containing foods.

254 Iron absorption can be measured in humans by generally accepted methods.

255 It should be noted that the claimed effect (improved nutrient absorption) is only considered beneficial
256 where absorption is a limiting factor for the maintenance of adequate status of the nutrient.

257 **4. Immune System**

258 **4.1. Claims on the function of the immune system**

259 An effectively functioning immune system is crucial for maintaining physiological integrity and thus
260 health. The immune system provides defence against infections caused by pathogenic microorganisms.
261 Allergic manifestations, such as asthma, urticaria, and eczema, are caused by undesired immune
262 responses to environmental allergens.

263 The Panel considers that maintaining a normal immune function is a beneficial physiological effect.
264 Given the multiple roles of the immune system, the specific aspect of immune function that is the
265 subject of the claim should be indicated, e.g. related to defence against pathogens or response to
266 allergens. In this regard, it is considered that claims related to 'natural defences' need to be defined
267 more clearly regarding the specific aspect of immune function that is the subject of the claim.

268 Outcome measures of the claimed effect in human studies include incidence of infection (e.g. in upper
269 respiratory tract, gastrointestinal tract, urinary tract, etc.) and reduction of numbers of pathogens for
270 claims related to defence against pathogens, and incidence of allergic manifestations for claims related
271 to response to allergens. However, since the incidence of infection may not necessarily represent an
272 effect on the immune system, for claims involving the immune system, appropriate evidence of a
273 concomitant change in immunological parameters needs to be provided (see section 3.3).

274 Similarly, allergic symptoms are not always easy to distinguish from non-allergic phenomena, and self
275 reported allergies are usually unreliable and insufficient for diagnosis of allergy. Studies on allergic
276 diseases need to include physician diagnosed allergies, and the immunologic nature of these allergies

277 needs to be corroborated with appropriate measures. Clinical as well as laboratory measures are
278 preferentially shown in the same intervention studies.

279 Vaccination confers immunity to certain infectious diseases. Even if a strict correlation between
280 vaccination titres and protection against infection is not always evident, cut off values of vaccination
281 titres indicating protection have been established for many vaccines. It is generally accepted that
282 higher vaccination responses (as measured by increased numbers of individuals attaining protective
283 levels as well as by increments in titres in groups of individuals) are beneficial. For that reason
284 vaccines are usually produced with adjuvants, so that the majority of recipients of vaccines attain
285 sufficient titres to be protected. Stimulation of protective antibody titres could be used to substantiate a
286 health claim on the function of the immune system related to defence against pathogens.

287 Many other markers of the function of the immune system have been proposed as outcomes for
288 substantiation of claims on immune function. These include numbers of various lymphoid
289 subpopulations in the circulation, proliferative responses of lymphocytes, phagocytic activity of
290 phagocytes, lytic activity of natural killer cells and cytolytic T cells, production of cellular mediators,
291 immunoglobulin levels, delayed-type hypersensitivity responses, etc. They may be considered as
292 supportive evidence, in as much as they are proposed as mechanism of the effect.

293 **4.2. Claims on reduction of inflammation**

294 Claims referring to the reduction of inflammation have been proposed. Inflammation is a non-specific
295 physiological response to tissue damage that is mediated by the immune system. Adequate
296 inflammatory responses are of primary importance for the defence against injury of any origin.
297 Changes in markers of inflammation such as various interleukins do not indicate a beneficial
298 physiological effect per se.

299 Chronic inflammation is associated with a number of diseases, and under certain circumstances
300 reducing levels of markers of inflammation might indicate a beneficial physiological effect.

301 Whether or not reduction of inflammatory markers is considered beneficial would depend on the
302 context in which the claim is made (i.e., the health benefit of reducing inflammatory responses and the
303 appropriateness of the markers used for the assessment of the effect would have to be considered on a
304 case-by-case basis).

305 **4.3. Claims on reducing a risk factor for infections or allergy**

306 It is noted that for claims related to reduction of a risk factor for infections or allergy the risk factor
307 may or may not be related to the function of the immune system.

308 Appropriate outcome measures of the risk factor should be assessed in human studies. While human
309 intervention studies that show only a reduction in the incidence or duration of the infectious or allergic
310 diseases could not substitute for evidence of a reduction in a risk factor for the disease, such studies
311 could be supportive for the claim.

312 For claims related to infections the presence of pathogens is considered by the Panel as a risk factor
313 and reducing the numbers of specific pathogenic microorganisms is considered a beneficial
314 physiological effect (see section 4.3). Appropriate outcome measures in human studies include
315 numbers of pathogenic microorganisms in suitable samples.

316 The extent to which the reduction of the risk factor is beneficial in the context of a reduction of disease
317 risk claim needs to be considered on a case-by-case basis. Human intervention studies with clinical
318 outcomes (e.g. number of episodes of infection, duration of infection, incidence of allergic

319 manifestations) could be used to support the validity of the risk factor for a specific dietary
320 intervention.

321 **CONCLUSIONS**

322 To follow