

Health is the ability to adapt

How to substantiate health claims for gut health and immunity

Health and functional claims made on foods, frequently focus on the digestive tract and already, there is a large market for gut-functional food products worldwide.

However, we need to take into account the guidelines as drawn up by the European Food Safety Authority (EFSA). These guidelines make the substantiation of a health claim in the area of gut health and immunity quite a challenge.

In this white paper we will discuss the definition of a health claim, the most important EFSA guidelines and our solution to substantiating health claims: challenge studies.

Health and health claims

Before giving you more information about the EFSA guidelines, let's focus first on the following two questions:

1. What is a health claim?
2. What is health?

What is a health claim?

The European Regulation on Nutrition and Health Claims (EC) No. 1924/2006 provides legislation allowing health claims to be made on foods in a uniform manner throughout the member states in the European Union (EU).

According to this regulation, a health claim is “any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health”.

This regulation differentiates between three health claims:

- Reduction of disease risk claim (Article 14 claim)
- Health claims referring to children's development and health (Article 14 claim)
- Health claims other than those referring to the reduction of disease risk and to children's development and health (Article 13 claim)

Among EFSA's guidelines is that the "specific study group(s) in which the evidence is obtained is representative of the target population for which the claim is intended." Therefore, efficacy of functional ingredients that are aimed for the general healthy population should be tested in healthy subjects. However, great variation exists in what is considered normal healthy gut and immune function. Thus, whilst it is possible to measure many aspects of digestion and immunity, it is more difficult to interpret the benefits to individuals within what is considered to be a normal range.

For complete information on health claims, consult the following official documents:

- [Regulation on Nutrition and Health Claims made on foods](#) of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods.
- [Guidance on the implementation of Regulation \(EC\) N° 1924/2006 on nutrition and health claims made on foods](#) approved by the Standing Committee on the Food Chain and Animal Health on 14 December 2007.
- Read the [complete scientific requirements for health claims related to gut and immune function \(EFSA Journal, 2011\)](#)

What is health?

Health has always been regarded as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO, 1948).

However, in an article in the [Lancet](#) (2009) it states that health is not a "state of complete physical, mental, and social well-being". Nor is it "merely the absence of disease or infirmity". The article says the WHO definitions of health will not do in an era marked by new understandings of disease at molecular, individual, and societal levels.

In the [Lancet](#), health is defined as "the body's ability to adapt to changing circumstances and to show sufficient resilience under conditions of social, physical and emotional disturbance (challenge) to which we are exposed from time to time".

Challenge studies

So now we know that health is the body's ability to adapt to changing circumstances and to show sufficient resilience.

But how to study this ability? By conducting challenge studies.

Challenge studies assess the effect of foods and ingredients in healthy people by introducing a controlled stressor, such as the consumption of a high-fat diet, endurance sport or an experimental infection.

Challenge studies can indicate whether people are in optimal health or tend to divert from health. Furthermore, through challenge studies, you can live up to the EFSA guideline of using "specific study groups in which the evidence obtained is representative of the target population for which the claim is intended".

Appropriate outcomes

In the [EFSA Journal \(2011;9:1984\)](#) EFSA states that:

For functional claims related to defence against pathogens in the gastro-intestinal tract, appropriate outcome measures are:

- gastro-intestinal infections (e.g. number of episodes and severity or duration of infection).
- the reduction of the presence of specific pathogens, their toxins or other virulence factors, as measured in suitable samples (e.g. stools).

For a claim related to immune defense against pathogens, similar outcome measures together with concomitant changes in relevant immunological parameters can be used.

There are two ways to study the health benefits of functional food ingredients on defence against pathogens:

Natural infections

Natural enteric infections include people who are travelling to a country of high risk for traveler's diarrhea (Eur J Clin Nutr 2010;64:146). Primary outcomes that can be studied are the number of bowel movements and average consistency of the stools as well as occurrence of abdominal discomfort, flatulence, bloating or vomiting.

Other populations at risk for infections, are children in developing countries. Acute diarrhea and acute respiratory tract infections (ARTIs) continue to lead the infectious cause of morbidity and mortality among children in developing countries. The primary outcomes include the number and duration of diarrheal episodes, and the number and duration of ARTI episodes. For example, in a 6-months double blind, placebo-controlled

study of 494 apparently healthy children aged 1- 6 years, incidence of all diarrhea episodes (≥ 2 loose/liquid stools in 24 hrs) was significantly reduced by 32% in the *L. reuteri* group as compared to the placebo (Pediatrics 2012;129:e1155).

Read more about this NIZO publication: [Probiotic prevents diarrhea in children](#)

Controlled challenge studies

Controlled challenge studies have a number of advantages over natural infections including:

- control of the type timing and dose of the pathogen inoculation;
- the predictability of the time of symptom onset;
- close monitoring of clinical parameters;
- lower noise to signal ratio

Pathogens that have been used in controlled challenge studies in humans include bacteria, viruses, or parasites including *Vibrio cholerae*, *Salmonella typhi*, enterotoxigenic *Escherichia coli*, Influenza A, Rhinovirus and *Streptococcus pneumoniae*.

An interesting option to study the health benefits of functional food ingredients is to use a challenge study with a live but attenuated oral Enterotoxigenic *E. coli* (ETEC) strain, able to survive gastrointestinal transit and still able to induce mild (although short-lived) infection symptoms. ETEC are the most commonly isolated bacterial enteropathogen in children below 5 years of age in developing countries, and also are the most common cause of travellers' diarrhoea. In an ETEC-challenge study, the primary outcomes are pathogen counts, and infectious diarrhea induced by ETEC (Gastroenterol 2003; 125:469). For example, in this proof-of-principle study, calcium from milk improved human resistance to ETEC infection as it inhibits infectious diarrhea (**Figure 1**).

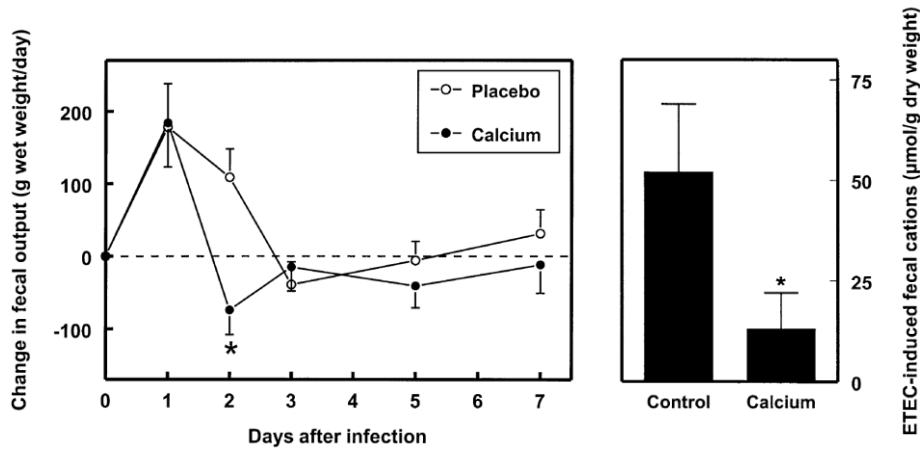


Figure 1 Effect of dietary calcium on the ETEC-induced increase in total fecal output with time in humans (left) and on the ETEC-induced increase in the relative water content of feces in rats (right) (Gastroenterol 2003; 125:469).

Another promising challenge study to determine health benefits of functional food ingredients is a human rhinovirus (HRV) challenge model in healthy volunteers (Antiviral Therapy 2009; 14:33). The experimental model for colds caused by rhinoviruses is a well-established, carefully controlled model for the study of the pathogenesis and treatment of the common cold. The common cold is a benign and self-limited illness most commonly caused by the rhinoviruses. Primary outcomes include rhinovirus load and rhinovirus counts in nasal washes, and upper respiratory symptom scores (sneezing, headache, malaise, chilliness, nasal discharge, nasal obstruction, sore throat etc).

Quotes: this is what they say about challenge studies

In the [PASSCLAIM document](#) on Gut health and immunity, it was stated: “we recommend assessing the functional capacity of the immune system by measuring specific cell functions ex vivo, measuring in vivo responses to challenge, e. g. change in antibody levels in peripheral blood or response to antigens and determining the incidence and severity of infection in target populations during naturally occurring episodes or in response to attenuated pathogens.”

Moreover, according to Henk van Loveren, University of Maastricht, “these studies are promising in substantiating health claims in the area of gut health and immunity”.

Conclusion

The European Regulation on Nutrition and Health Claims provides regulation allowing health claims to be made on foods the European Union. Among the EU's guidelines is that the "specific study group(s) in which the evidence is obtained is representative of the target population for which the claim is intended." Therefore, efficacy of functional ingredients that are aimed for the general healthy population should be tested in healthy subjects. Without relevant validated biomarkers, it is difficult to determine health benefits to individuals within what is considered to be a normal range. Challenging healthy subjects with stressors, such as an experimental infection, is an attractive approach to measure health benefits in otherwise healthy subjects.

Contact

- For general information on challenge studies, contact [Sandra ten Bruggencate](#)
- See our leaflets on [Gut Health and Immune Defense at NIZO](#) and [Biomarkers for Gut Health and immunity](#)
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