Nutrimune and immune defence against pathogens in the gastrointestinal and upper respiratory tracts: evaluation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006


Abstract

Following an application from H.J. Heinz Supply Chain Europe B.V. submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to Nutrimune and immune defence against pathogens in the gastrointestinal (GI) tract and upper respiratory tract (URT). The food Nutrimune (a pasteurised cow’s skim milk fermented with Lactobacillus paracasei CBA L74) which is the subject of the health claim is sufficiently characterised. The Panel considers that immune defence against pathogens in GI tract and URT is a beneficial physiological effect. Two human intervention studies were submitted as being pertinent to the claim, which were evaluated by the Panel in the previous application. One human intervention study from which conclusions could be drawn showed an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT. The post hoc re-analysis of the two human studies combined does not address the methodological limitations of the second study raised in the previous opinion, i.e. that the study was not planned, designed, randomised and analysed as a multicentre study, and that the large disparity of subjects in the three centres was not duly justified. The results from one animal study could support an effect of Nutrimune on defence against pathogens in the GI tract. No evidence was provided for a plausible mechanism by which Nutrimune could exert the claimed effect in vivo in humans. The Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of Nutrimune and immune defence against pathogens in the GI tract and URT.

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Keywords: Nutrimune, defence against pathogens, gastrointestinal tract, upper respiratory tract, infection, children, health claim

Requestor: Competent Authority of the Netherlands following an application by H.J. Heinz Supply Chain Europe B.V.

Question number: EFSA-Q-2018-00727

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Competing interests: A waiver was granted to Jean-Louis Bresson in accordance with Article 21 of the Decision of the Executive Director on Competing Interest Management. Pursuant to Article 21(6) of the afore-mentioned Decision, the concerned expert was allowed to take part in the discussion and in the drafting phase of the scientific output.


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Summary

Following an application from H.J. Heinz Supply Chain Europe B.V., submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to Nutrimune and immune defence against pathogens in the gastrointestinal (GI) tract and upper respiratory tract (URT).

The scope of the application was proposed to fall under a health claim referring to children’s development and health.

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications and the guidance on the scientific requirements for health claims related to the immune system, the GI tract and defence against pathogenic microorganisms.

The food proposed by the applicant as the subject of the health claim is Nutrimune. The Panel considers that Nutrimune (a pasteurised cow’s skim milk fermented with Lactobacillus paracasei CBA L74), which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is ‘supports the immune system in defence against pathogens in the upper respiratory and gastrointestinal tract of young children’. The proposed target population is ‘young children aged 12 – 48 months old’. The Panel considers that immune defence against pathogens in the GI tract and URT is a beneficial physiological effect.

In the present application, the applicant has submitted two human intervention studies as being pertinent to the claim, which were evaluated by the Panel in the previous application (a one-centre study and a multicentre study).

A number of textbooks/consensus opinions used for the diagnosis of upper respiratory tract infection (URTI) and acute gastroenteritis were also provided. The Panel considers that the criteria used for the diagnosis of URTI in the human intervention studies submitted have been further defined by the applicant.

The post hoc statistical re-analysis of the two human intervention studies provided has been submitted. According to the applicant, the combined analysis aimed to: (a) increase the power of the studies by assigning a positive event to the drop-outs, and (b) identify potential heterogeneity between the two studies in order to address the multicentre approach in one of the studies.

The Panel notes that in the multicentre study, centre was found to be a significant confounder for the effect of Nutrimune on the incidence of infections, and that this effect was attributed to two centres. The Panel also notes that tests for heterogeneity involving a small number of studies (or centres) are likely to be underpowered, and therefore, non-significant p values are not necessarily a proof of non-heterogeneity. The Panel considers that the post hoc re-analysis of the two human intervention studies combined does not address the methodological limitations of the multicentre study raised by the Panel in its previous opinion, i.e. that the study was not planned, designed, randomised and analysed as a multicentre study (as acknowledged by the applicant), and that the large disparity of subjects recruited in the three centres was not duly justified.

As in the previous assessment, the Panel considers that the one-centre study shows an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT, whereas no conclusions can be drawn from the multicentre study due to the high risk of bias.

As in the previous assessment, the Panel considers that the results from the animal study may support an effect of Nutrimune on defence against pathogens in the GI tract, albeit the effects shown are small, and found in a model that is very different from infections in humans.

As in the previous assessment, the Panel considers that no evidence has been provided for a plausible mechanism by which Nutrimune could exert the claimed effect in vivo in humans.

In weighing the evidence, the Panel took into account that one human intervention study from which conclusions could be drawn showed an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT, and that the results from one animal study could support an effect of Nutrimune on defence against pathogens in the GI tract. The Panel also took into account that the results of this study have not been replicated, and that no evidence was provided for a plausible mechanism by which Nutrimune could exert the claimed effect in vivo in humans.

On the basis of the data provided, the Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of Nutrimune and immune defence against pathogens in the GI tract and URT.
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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006 harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children’s development and health in a Community list of permitted claims.

According to this Regulation, an application shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

1.2. Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: Nutrimune and immune defence against pathogens in the gastrointestinal and upper respiratory tracts.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of Nutrimune, a positive assessment of its safety, nor a decision on whether Nutrimune is, or is not, classified as a foodstuff. 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 wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

2. Data and methodologies

2.1. Data

Information provided by the applicant

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is ‘Nutrimune, a heat-treated fermented milk product. It is fermented with Lactobacillus paracasei CBA L74’.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect relates to: ‘supports the immune defence against pathogens in the upper respiratory- and gastrointestinal tract’.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

The applicant claims that ‘claimed effects elicited by Nutrimune are mediated by a number of non-immune and immune defence mechanisms. Nutrimune acts: through direct interaction with human enterocytes regulating the innate immune response and modulating cell growth and differentiation, intestinal permeability and mucus thickness, all well-known non-immune defence mechanisms against infections. Indirectly through the gut microbiota, shaping and increasing the abundance of healthy gut bacteria able to produce the short chain fatty acid butyrate, which in turn is responsible for a further modulation of immune and non-immune defence mechanisms against infectious disease’.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: ‘Nutrimune supports the immune system in defence against pathogens in the upper respiratory and gastrointestinal tract of young children’.

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Specific conditions of use as proposed by the applicant

According to the applicant, the target population for the intended health claim is ‘young children aged 12 – 48 months old’. The applicant stated that ‘in the human trials doses of 7 gram of Nutrimune, in spray-dried form, have been consumed daily for a period of 3 months by the target group. This quantity of Nutrimune can be obtained through consumption of a range of products to which Nutrimune can be added to. It is anticipated to apply Nutrimune in a range of products, in line with existing legal/regulatory requirements and dietary consumption patterns for the target group’.

Data provided by the applicant

Health claim application on Nutrimune and immune defence against pathogens in the gastrointestinal (GI) tract and upper respiratory tract (URT) pursuant to Article 14 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims.2

As outlined in the General guidance for stakeholders on health claim applications,3 it is the responsibility of the applicant to provide the totality of the available evidence.

2.2. Methodologies

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016a).

The scientific requirements for health claims related to the immune system, the GI tract and defence against pathogenic microorganisms are outlined in a specific EFSA guidance (EFSA NDA Panel, 2016b).

The application contains data claimed as confidential: International Depository Access Number, the primers sequence, the melting temperature, the amplification thermal cycle and the manufacturing process.

The application contains data claimed as proprietary: International Depository Access Number, primers sequence, the melting temperature and the amplification thermal cycle.

3. Assessment

3.1. Characterisation of the food/constituent

The food proposed by the applicant as the subject of the health claim is Nutrimune.

Nutrimune is cow’s skim milk fermented with *Lactobacillus paracasei* CBA L74. Fermentation is followed by pasteurisation to kill viable bacteria. The final product is available as a spray-dried milk powder containing at least $7 \times 10^{10}$ colony forming units (CFU) of non-viable *L. paracasei* CBA L74 per 100 g of the product. It is anticipated that Nutrimune will be used as an ingredient in liquid, semi-liquid and dry form in a variety of food products.

*L. paracasei* CBA L74 has been deposited in the internationally recognised Belgian collection BCCM/LMG.

The species was identified using repetitive extragenic palindromic polymerase chain reaction (rep–PCR) and a specific PCR. A single primer fingerprinting technique was used to identify the strain. 16S rRNA and 23S rRNA gene sequence analysis were performed confirming the identification of the bacterial strain.

Detailed specifications of the manufacturing process, nutritional composition of the final product, and information on stability (all claimed as confidential), were provided by the applicant.

The Panel considers that the food Nutrimune (a pasteurised cow’s skim milk fermented with *Lactobacillus paracasei* CBA L74), which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is ‘supports the immune defence against pathogens in the upper respiratory- and gastrointestinal tract’. The proposed target population is ‘young children aged 12–48 months old’.

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As explained in the Guidance on the scientific requirements for health claims related to the immune system, the GI tract and defence against pathogenic microorganisms (EFSA NDA Panel, 2016b), the scientific evidence for the substantiation of health claims related to defence against pathogens in the upper respiratory tract (URT) can be obtained from human intervention studies showing an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms) of the upper respiratory tract (e.g. rhinitis, pharyngitis, sinusitis, otitis media, common cold). Upper respiratory tract infections (URTI) clinically diagnosed by the primary care or hospital physician following well defined criteria can be used as an appropriate outcome variable for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes (e.g. allergic diseases) of the signs and symptoms used for diagnosis of the URTI have been applied (i.e. differential diagnosis). Microbiological data could also be used to ascertain the infectious aetiology of clinically diagnosed episodes.

For health claims related to defence against pathogens in the GI tract, clinical outcomes related to GI infections, for example incidence, severity and/or duration of diarrhoeal episodes could be used. The infectious aetiology of diarrhoeal episodes, however, should be ascertained. In this context, GI infection clinically diagnosed by the primary care or hospital physician following well-defined criteria can be used as an appropriate outcome variable for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes of diarrhoea have been applied. Microbiological data could also be used to ascertain the infectious aetiology of diarrhoeal episodes.

Other outcome variables, such as changes in relevant immunological markers, may provide supportive evidence on the mechanism (e.g. through the activation of the immune system) by which the food/constituent could exert the claimed effect, but alone are not appropriate for the substantiation of claims related to immune defence against pathogens.

The Panel considers that immune defence against pathogens in the GI tract and URT is a beneficial physiological effect.

3.3. Scientific substantiation of the claimed effect

In 2016, the Panel assessed a claim on ‘Nutrimune’ and ‘immune defence against pathogens in the gastrointestinal and upper respiratory tracts’ pursuant to Article 14 of Regulation (EC) No 1924/2006 (EFSA NDA Panel, 2017).

At that time, the applicant provided two human intervention studies (Nocerino, 2013; unpublished study report; Corsello et al., 2015, unpublished study report) as being pertinent to the claim. The applicant also provided one animal efficacy study (Zagato et al., 2014), as well as in vitro studies (Sarno et al., 2013, abstract; Paparo et al., 2014, abstract) in support of the mechanisms by which Nutrimune could exert the claimed effect.

The Panel considered that the study by Corsello et al., 2015 (unpublished study report) was at high risk of bias and that no conclusions could be drawn for the scientific substantiation of the claim.

In weighing the evidence, the Panel took into account that one human intervention study from which conclusions could be drawn showed an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT (Nocerino, 2013, unpublished study report), and that the results from one animal study could support an effect of Nutrimune on defence against pathogens in the GI tract (Zagato et al., 2014). The Panel also took into account the inconsistencies in the reporting of the process and criteria used for the diagnosis of URTI in the human intervention study, that the results of this study have not been replicated, and that no evidence was provided for a plausible mechanism by which Nutrimune could exert the claimed effect in vivo in humans.

The Panel concluded that the evidence provided was insufficient to establish a cause and effect relationship between the consumption of Nutrimune and immune defence against pathogens in the GI tract and URT.

For the present application, the applicant has provided:

1) Three publications (Berni Canani et al., 2016; Corsello et al., 2017; Nocerino et al., 2017) reporting on the two human intervention studies which were provided in the previous application as unpublished study reports (Nocerino, 2013; Corsello et al., 2015). For convenience, these studies will be quoted as Nocerino et al., 2017 and Corsello et al., 2017 in this opinion.

2) A statistical re-analysis (Calame, 2018, unpublished) of the two human intervention studies.
3) Text books/consensus opinions used for the diagnosis of URTI and acute GI infections (Guarino et al., 2008; Marchisio et al., 2010; Chiappini et al., 2012; Hersh et al., 2013; Lieberthal et al., 2013).

4) One animal efficacy study provided in the previous application (Zagato et al., 2014).

5) Three publications reporting on mechanistic studies (Sarno et al., 2014; Berni Canani et al., 2017; Paparo et al., 2018), two of which (Sarno et al., 2014; Paparo et al., 2018) were submitted in the previous application as abstracts only and could not be considered by the Panel for a full scientific assessment.

**Human intervention studies**

The applicant has submitted two human intervention studies as being pertinent to the claim, which were evaluated by the Panel in the previous application. The Panel concluded that Nocerino et al. (2017) showed an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT. The Panel noted, however, inconsistencies in the reporting of the process and in the criteria used for the diagnosis of URTI. In relation to the second study (Corsello et al., 2017), the Panel noted that the vast majority of the participants were recruited in one centre (i.e. 105 in Naples, 17 in Milan, and 24 in Palermo), that the statistical analysis provided is not appropriate for the study data (i.e. the same weight is given to all centres, regardless of their sample size), and that if the study was not planned, designed, randomised and analysed as a multicentre study (as acknowledged by the applicant), the aleatory recruitment of subjects in three different centres is not duly justified. The Panel also noted that this study shared the same inconsistencies in the reporting of the process and criteria used for the diagnosis of URTI as identified for the study by Nocerino et al. (2017). The Panel considered that this study was at high risk of bias and that no conclusions could be drawn for the scientific substantiation of the claim.

In the present application, a number of textbooks/consensus opinions used for the diagnosis of URTI and acute gastroenteritis were provided (Guarino et al., 2008; Marchisio et al., 2010; Chiappini et al., 2012; Hersh et al., 2013; Lieberthal et al., 2013). The Panel considers that the criteria used for the diagnosis of URTI in the studies by Nocerino et al. (2017) and Corsello et al. (2017) have been further defined by the applicant.

The post hoc statistical re-analysis (Calame, 2018, unpublished) consists of a combined analysis with data from one study (Nocerino et al., 2017) and data from each centre (n = 3) participating in the second study (Corsello et al., 2017). According to the applicant, the combined analysis aimed to: (a) increase the power of the studies by assigning a positive event to the drop-outs, and (b) identify potential heterogeneity between the two studies in order to address the multicentre approach in the study by Corsello et al. (2017).

In order to establish how the results from the two studies differ, heterogeneity was tested as follows:

a) By meta-analysis on both studies using aggregated data and applying the random effects model for GI infections, URTI and overall number of infections, for the intention to treat (ITT) and per protocol (PP) populations. Heterogeneity between the two studies was assessed using Chi-squared and I-squared. The same approach was followed when the analysis was restricted to the Naples centre in both studies.

b) By a General Equations Estimation model used in a paired stepwise dummy fashion to assess the effect of Nutrimune on the outcome while considering possible confounders, including centre. This analysis was conducted in the PP population.

c) By a cumulative meta-analysis to assess the centre effect on the outcome and determine the heterogeneity in the outcome between the various centres (ITT population). A stepwise analysis per centre was followed starting with the centre with the lowest number of participants. Heterogeneity was assessed using the Egger test.

The results of these analyses lead the applicant to the following conclusions:

a) No significant heterogeneity was found between the results of two studies in any of the meta-analysis performed.

b) Centre was found to be a significant confounder related to the low power in the Milan and Palermo centres in the study by Corsello et al. (2017).

c) No significant heterogeneity was found among centres in the cumulative meta-analysis.
The Panel notes that centre was found to be a significant confounder for the effect of Nutrimune on the incidence of infections, and that this effect was attributed to the Milan and Palermo centres in the study by Corsello et al. (2017). The Panel also notes that tests for heterogeneity involving a small number of studies (or centres) are likely to be underpowered, and therefore non-significant p values are not necessarily a proof of non-heterogeneity.

The Panel considers that the post hoc re-analysis of the two human intervention studies combined does not address the methodological limitations of the study by Corsello et al. (2017) raised by the Panel in its previous opinion, i.e. that the study was not planned, designed, randomised and analysed as a multicentre study (as acknowledged by the applicant), and that the large disparity of subjects recruited in the three centres was not duly justified.

As in the previous assessment (EFSA NDA Panel, 2017), the Panel considers that the study by Nocerino et al. (2017) shows an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT, whereas no conclusions can be drawn from the study by Corsello et al. (2017) due to the high risk of bias.

Animal efficacy studies

The applicant provided one animal study for the scientific substantiation of the claim (the same as in the previous application) (Zagato et al., 2014). Twenty mice were fed with Nutrimune or non-fermented milk (control) for 10 days and then were challenged intragastrically with a lethal dose of Salmonella typhimurium FB62 (106 CFU in 200 µL carbonate buffer). Mice receiving Nutrimune survived slightly longer (statistically significantly) than mice in the control group.

As in the previous assessment (EFSA NDA Panel, 2017), the Panel considers that the results from this animal study may support an effect of Nutrimune on defence against pathogens in the GI tract, albeit the effects shown are small, and found in a model that is very different from infections in humans.

Mechanism of action proposed

The applicant claims that 'it has been demonstrated that Nutrimune modulates several non-immune and immune defence mechanisms against pathogens'.

The application contains mechanistic studies provided already in the previous application and a number of new studies. Most of them are presented as abstracts (Cuomo et al., 2013; Sarno et al., 2013; Barone et al., 2014; Paparo et al., 2014, 2016). The limited information provided in these abstracts does not allow the Panel to perform a full scientific evaluation.

Three new studies were submitted as full publications.

Paparo et al. (2018) incubated Caco-2 cells with Nutrimune at different concentrations for 48 h. Nutrimune stimulated cell growth and differentiation, tight junction proteins, mucin 2 expression, and mucus layer thickness in a dose-dependent fashion. Stimulation of beta-defensin-2 (hBD-2) and cathelicidin synthesis, associated with a modulation of toll-like receptor (TLR) pathway, was also observed. In the ex vivo study by Berni et al. (2017), the number of gut microbiota known as butyrate-producers, such as Oscillospira and Faecalibacterium, were increased by Nutrimune. CBA L74 supernatant significantly prevented the entrance of gliadin peptides and reduced reactive oxygen species (ROS) production in human Caco-2 cells (Sarno et al., 2014). The Panel notes that no evidence has been provided to establish a causal relationship between changes in the variables reported in these studies and changes in the outcome variables for the claimed effect assessed in this application (incidence, severity, duration of GI tract and URT infections in vivo in humans).

As in the previous assessment (EFSA NDA Panel, 2017), the Panel considers that no evidence has been provided for a plausible mechanism by which Nutrimune could exert the claimed effect in vivo in humans.

Weighing of the evidence

In weighing the evidence, the Panel took into account that one human intervention study from which conclusions could be drawn showed an effect of Nutrimune on immune defence against pathogens in the GI tract and the URT, and that the results from one animal study could support an effect of Nutrimune on defence against pathogens in the GI tract. The Panel also took into account that the results of the human study have not been replicated, and that no evidence was provided for a plausible mechanism by which Nutrimune could exert the claimed effect in vivo in humans.

The Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of Nutrimune and immune defence against pathogens in the gastrointestinal and upper respiratory tracts.
4. Conclusions

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

- The food/constituent, Nutrimune, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is ‘supports the immune defence against pathogens in the upper respiratory and gastrointestinal tract’. The target population proposed by the applicant is ‘young children aged 12–48 months old’. Immune defence against pathogens in the gastrointestinal and upper respiratory tracts is a beneficial physiological effect.
- The evidence provided is insufficient to establish a cause and effect relationship between the consumption of Nutrimune and immune defence against pathogens in the gastrointestinal and upper respiratory tracts.

Steps taken by EFSA


1) This application was received by EFSA on 21/09/2018.
2) The scope of the application was proposed to fall under a health claim related to reduction of disease risk claims and claims referring to children’s development.
4) On 28/11/2018, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The scientific evaluation was suspended on 13/12/2018 and was restarted on 9/01/2019, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
5) On 16/01/2019, the applicant’s hearing took place to give the opportunity to the applicant to comment/clarify the issues identified by the Working Group on Claims.
6) During its meeting on 14/03/2019, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to Nutrimune and immune defence against pathogens in the gastrointestinal and upper respiratory tracts.

References


**Abbreviations**

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CFU</td>
<td>colony forming units</td>
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<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>hBD-2</td>
<td>human beta-defensin-2</td>
</tr>
<tr>
<td>ITT</td>
<td>intention to treat</td>
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<tr>
<td>NDA</td>
<td>EFSA Panel on Nutrition, Novel Foods and Food Allergens</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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Nutrimune and immune defence against pathogens in the gastrointestinal and upper respiratory tracts

PP per protocol
REP repetitive extragenic palindromic
RNA ribonucleic acid
ROS reactive oxygen species
TLR toll-like receptor
URT upper respiratory tract
URTI upper respiratory tract infection