ARTICLE 4 REQUEST

Regulation (EU) 2015/2283

Recipient Member State: Ireland: Food Safety Authority of Ireland (FSAI)

Name of the Food: Casein hydrolysate containing elevated levels of the tri-peptides; L-valyl-L-prolyl-L-proline (VPP) and L-isoleucyl-L-prolyl-L-proline (IPP)

Description of the Food

The food in question is a spray-dried powdered fraction of casein hydrolysate containing two tri-peptides, L-valyl-L-prolyl-L-proline (VPP) and L-isoleucyl-L-prolyl-L-proline (IPP). The assertion in the original application dossier was that this casein hydrolysate fraction contains relatively higher amounts of the tripeptides VPP and IPP (6.7 - 9.9 mg/g) compared to the unfractionated casein hydrolysate, although no evidence of a direct compositional comparison with unfractionated casein was provided. However, subsequent clarification provided by the applicant establishes that this casein hydrolysate fraction does contain higher levels of the two tripeptides IPP and VPP (6.7+ mg/g of product) in comparison to another casein hydrolysate which they report as having levels of IPP and VPP at below the quantification limit (<0.06 mg/g of product). Therefore, the fractionated casein hydrolysate in question contains more than 100 times the level of these two tri-peptides compared to an unfractionated comparator casein hydrolysate.

Nutritional content of the casein hydrolysate fraction

Constituent	Content
Free amino acid	43.2%
Peptide	39.1%
IPP+VPP	0.67% (overall) & 1% (peptide)
Fat	0.1%
Carbohydrate	7.8%
Ash	3.9%
Water	5.9%

The food ingredient is to be used in the following foods (including beverages) and supplements supplying at least 3.4 mg of the tripeptides per serving:

- Fermented milk beverages, yoghurts and milk-based drinks: 3.4 mg VPP+IPP in 200 ml,
- Fruit juices and nectars, vegetable juices and nectars: 3.4 mg VPP+IPP in 200 ml.
- Miso soup (dehydrated): 3.4 mg VPP+IPP in 6.4 g.
- Water-based drinks: 3.4 mg VPP+IPP in 500 ml.
- Food supplements: 3.4 mg – 4.8 mg VPP+IPP in 1 g.

The source of the ingredient is milk from pasture-fed New Zealand cows and the hydrolysis is an in vitro enzymatic hydrolysis with a protease isolated from the fungus *Aspergillus*

oryzae. Depending on the parameters applied, the enzymatic hydrolysis of casein can result in predominantly free amino acids, or a mixture of free amino acids and various sized peptides.

Novel or Not Novel

The FSAI is of the opinion that the food in question (casein hydrolysate fraction) **is novel** for all food uses.

Reasons why it is Novel

Casein hydrolysate has an established history of food use within the EU and is primarily a source of milk-derived amino acids provided through varying sized peptides depending on the extent and type of hydrolysis. The applicant claims that the casein hydrolysate fraction is not novel as the lacto-tripeptides VPP + IPP are already consumed within the EU to similar levels proposed for this product. The FSAI accepts that these two tri-peptides are present in dairy products consumed in the EU to significant levels through fermented dairy products and in foods and supplements containing added casein hydrolysate. Data provided indicates that the tri-peptides can be found at concentrations up to 443 mg/kg in certain cheeses. The applicant estimates that citizens from at least three EU Member States can consume up to 3-4 mg per day of the tri-peptides from cheese alone. However, it has not been demonstrated that casein hydrolysate with elevated levels of these tri-peptides has been on the EU market prior to 1997.

The production process is not novel, with an enzyme from *Aspergillus oryzae* being used to hydrolyse pH-adjusted pasteurised sodium caseinate. The soluble fraction of the hydrolysate is concentrated by evaporation and spray-dried to its ultimate powder form.

The tri-peptides in this application have been assessed by EFSA (EFSA, 2012) with respect to a health claim application under Regulation (EC) No 1924/2006 regarding the maintenance of blood pressure. EFSA concluded that the studies provided as evidence did not support a cause and effect relationship between the consumption of these tripeptides and a maintenance of blood pressure function. With the EFSA conclusion it could be argued that the tripeptides IPP and VPP as part of this casein hydrolysate fraction are simply an amino acid source and in essence no different from any other casein hydrolysate on the market, which in turn would mean that this casein hydrolysate fraction could be considered not novel.

However, a significant body of scientific literature suggests that consumption of the two tri-peptides may have an effect on blood pressure, with a number of meta-analyses (Cicero *et al*, 2011, Aurelie *et al*, 2018) concluding that these tripeptides may have a small but significant effect on blood pressure. Taking this scientific evidence into consideration, it can be argued that the elevated levels of the two tri-peptides in the fractionated casein hydrolysate could have physiological and nutritional roles rather than just the nutritional role that the lower levels play in the unfractionated casein hydrolysate comparator. It would therefore be reasonable to argue that the casein hydrolysate fraction containing the relatively high levels (100 times that of the comparator) of these two tri-peptides could be considered novel.

In weighing up the possible "Novel" versus "Not novel" scenarios above, it must be remembered that *Article1.2.* of the novel food Regulation (EU) 2015/2283 states that "The

purpose of this Regulation is to ensure the effective functioning of the internal market while providing a high level of protection of human health and consumers' interests".

In conclusion, this casein hydrolysate fraction with relatively high levels of IPP and VPP is considered novel for the following reasons:

1. The food in question is a fraction of casein hydrolysate which has been selectively processed to enrich the levels of two tri-peptides that are present at levels more than 100 times greater than those in the unfractionated casein hydrolysate comparator.
2. If those two tripeptides, even at elevated levels, were simply a source of amino acids similar to the many other peptides present in casein hydrolysate, then it would be difficult to conclude that this casein hydrolysate fraction was novel.
3. Casein hydrolysate with normal low levels of the tri-peptides is primarily a source of protein, peptides and individual amino acids with a history of consumption in the EU. However, this casein hydrolysate fraction potentially with a separate physiological function due to the level of the tri-peptides, does not appear to have a history of consumption on the EU market and is therefore novel.

Appropriate Novel Food Category

The applicant proposes that in the event the food ingredient is considered novel, the appropriate novel food category would be ***Article 3(2)(a)(v)*** "*food consisting of, isolated from or produced from animals or their parts, except for animals obtained by traditional breeding practices which have been used for food production within the Union before 15 May 1997 and the food from those animals has a history of safe food use within the Union*".

The FSAI concurs with this proposed novel food category.

References:

Blood pressure lowering effect of lactotripeptides assumed as functional foods: a meta-analysis of current available clinical trials
A F G Cicero, B Gerocarni, L Laghi & C Borghi
Journal of Human Hypertension volume 25, (2011), pages 425–436

Scientific Opinion on the substantiation of health claims related to isoleucine-proline-proline (IPP) and valine-proline-proline (VPP) and maintenance of normal blood pressure (ID 661, 1831, 1832, 2891, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006
EFSA (2012) http://www.efsa.europa.eu/en/efsajournal/pub/2715

Evaluation of the Blood Pressure Lowering-Effect of the Lactotripeptides Valine-Proline-Proline and Isoleucine-Proline-Proline in Non-Hypertensive Japanese Subjects through a Meta-Analysis of Randomized-Controlled Studies
Aurelie Chanson-Rolle, François Aubin, Veronique Braesco, Ryuji Takeda, Yasuhiro Saito
Food and Nutrition Sciences, (2018), 9, 1221-1253