Safety evaluation of the food enzyme rennet containing chymosin and pepsin A from calf abomasum

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Abstract

The food enzyme containing chymosin (EC 3.4.23.4) and pepsin A (EC 3.4.23.1) is prepared from the abomasum of calves by RENCO New Zealand. The food enzyme is intended to be used in milk processing for cheese production. As no concerns arise from the animal source of the food enzyme or from its manufacture and based on the history of safe use and consumption, the Panel considered that toxicological data were not required, and the estimation of dietary exposure was unnecessary. On the basis of literature data, the Panel considered that the risk of allergic sensitisation and elicitation reactions by dietary exposure could not be excluded, but the likelihood for this to occur was considered to be low. The Panel concluded that this food enzyme does not give rise to safety concerns under the intended conditions of use.

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Keywords: food enzyme, chymosin, EC 3.4.23.4, pepsin A, EC 3.4.23.1, abomasum, calves, rennet

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Question number: EFSA-Q-2021-00759
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Declarations of interest: The declarations of interest of all scientific experts active in EFSA’s work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Acknowledgments: The Panel wishes to thank Helen Regina, Natalia Kovalkovicova for the support provided to this scientific output.

Note: The full opinion will be published in accordance with Article 12 of Regulation (EC) No 1331/2008 once the decision on confidentiality will be received from the European Commission.

Suggested citation: EFSA CEP Panel (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids), Lambré C, Barat Baviera JM, Bolognesi C, Cocconcelli PS, Crebelli R, Gott DM, Grob K, Lampi E, Mengelers M, Mortensen A, Rivière G, Steffensen I-L, Tlustos C, Van Loveren H, Vernis L, Zorn H, Herman L, Andryszkiewicz M, Liu Y and Chesson A, 2022. Scientific Opinion on the safety evaluation of the food enzyme rennet containing chymosin and pepsin A from calf abomasum. EFSA Journal 2022;20(6):7361, 10 pp. https://doi.org/10.2903/j.efsa.2022.7361

ISSN: 1831-4732

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The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.

† Deceased.
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1. Introduction

Article 3 of the Regulation (EC) No 1332/2008\(^1\) provides definition for ‘food enzyme’ and ‘food enzyme preparation’.

‘Food enzyme’ means a product obtained from plants, animals or micro-organisms or products thereof including a product obtained by a fermentation process using micro-organisms: (i) containing one or more enzymes capable of catalysing a specific biochemical reaction; and (ii) added to food for a technological purpose at any stage of the manufacturing, processing, preparation, treatment, packaging, transport or storage of foods.

‘Food enzyme preparation’ means a formulation consisting of one or more food enzymes in which substances such as food additives and/or other food ingredients are incorporated to facilitate their storage, sale, standardisation, dilution or dissolution.

Before January 2009, food enzymes other than those used as food additives were not regulated or were regulated as processing aids under the legislation of the Member States. On 20 January 2009, Regulation (EC) No 1332/2008 on food enzymes came into force. This Regulation applies to enzymes that are added to food to perform a technological function in the manufacture, processing, preparation, treatment, packaging, transport or storage of such food, including enzymes used as processing aids. Regulation (EC) No 1331/2008\(^2\) established the European Union (EU) procedures for the safety assessment and the authorisation procedure of food additives, food enzymes and food flavourings. The use of a food enzyme shall be authorised only if it is demonstrated that:

- it does not pose a safety concern to the health of the consumer at the level of use proposed;
- there is a reasonable technological need;
- its use does not mislead the consumer.

All food enzymes currently on the European Union market and intended to remain on that market, as well as all new food enzymes, shall be subjected to a safety evaluation by the European Food Safety Authority (EFSA) and approval via an EU Community list. The ‘Guidance on submission of a dossier on food enzymes for safety evaluation’ (EFSA, 2009a) lays down the administrative, technical and toxicological data required.

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

1.1.1. Background as provided by the European Commission

Only food enzymes included in the European Union (EU) Community list may be placed on the market as such and used in foods, in accordance with the specifications and conditions of use provided for in Article 7(2) of Regulation (EC) No 1332/2008\(^1\) on food enzymes.

Six applications have been introduced by the companies “Decernis, LLC”, “Keller and Heckman LLP”, the Association of Manufacturers and Formulators of Enzyme Products (AMFEP)” and “Novozymes A/S” for the authorisation of food enzymes cyclomaltodextrin glucanotransferase from Geobacillus stearothermophilus, dextranase from Chaetomium gracile, subtilisin from Bacillus licheniformis, mucorpepsin from Rhizomucor miehei, animal rennet consisting of chymosin and pepsin from the abomasum of Bos primigenius (cattle), Bubalus bubalis (buffalo), Capra aegagrus hircus (goat) and Ovis aries (sheep), and lipase from a genetically modified strain of Aspergillus niger (strain NZYM-DB) respectively.

Following the requirements of Article 12.1 of Regulation (EC) No 234/2011\(^3\) implementing Regulation (EC) No 1331/2008\(^2\), the Commission has verified that the application falls within the scope of the food enzyme Regulation and contains all the elements required under Chapter II of that Regulation.

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\(^1\) Regulation (EC) No 1332/2008 of the European Parliament and of the Council of 16 December 2008 on Food Enzymes and Amending Council Directive 83/417/EEC, Council Regulation (EC) No 1493/1999, Directive 2000/13/EC, Council Directive 2001/112/EC and Regulation (EC) No 258/97. OJ L 354, 31.12.2008, p. 7–15.

\(^2\) Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 354, 31.12.2008, p. 1–6.

\(^3\) Commission Regulation (EU) No 234/2011 of 10 March 2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 64, 11.03.2011, p. 15–24.
1.1.2. Terms of Reference

The European Commission requests the European Food Safety Authority to carry out the safety assessments on the food enzymes cyclomaltodextrin glucanotransferase from *Geobacillus stearothermophilus*, dextranase from *Chaetomium gracile*, subtilisin from *Bacillus licheniformis*, mucorpepsin from *Rhizomucor miehei*, animal rennet consisting of chymosin and pepsin from the abomasum of *Bos primigenius* (cattle), *Bubalus bubalis* (buffalo), *Capra aegagrus hircus* (goat) and *Ovis aries* (sheep), and lipase from a genetically modified strain of *Aspergillus niger* (strain NZYM-DB) in accordance with Article 17.3 of Regulation (EC) No 1332/2008 on food enzymes.

1.2. Interpretation of the Terms of Reference

The present scientific opinion addresses the European Commission’s request to carry out the safety assessment of food enzyme glucan animal rennet from *Bos primigenius* (cattle), *Bubalus bubalis* (buffalo), *Capra aegagrus hircus* (goat) and *Ovis aries* (sheep) submitted by AMFEP.

The application was submitted initially as a joint dossier4 and identified as the EFSA-Q-2015-00237. During the risk assessment phase, it was found that the technical dossier is too generic to be evaluated. A solution was found on 16 March 2020 via an ad hoc meeting between EFSA, the European Commission and representatives from the Association of Manufacturers and Formulators of Enzyme Products (AMFEP).5 It was agreed that joint dossiers will be split into individual data packages.

The current opinion addresses one data package originating from the joint dossier EFSA-Q-2015-00237. This data package, identified as EFSA-2021-00759, concerns the food enzyme Animal rennet that is produced with a strain of *Bos taurus* (cattle) and submitted by RENCO New Zealand.

2. Data and methodologies

2.1. Data

The applicant has submitted a dossier in support of the application for authorisation of the food enzyme rennet containing chymosin and pepsin A from the abomasum of suckling calves.

Additional information was requested from the applicant during the assessment process on 23 February 2022 and received on 22 March 2022 (see ‘Documentation provided to EFSA’).

2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA ‘Guidance on transparency in the scientific aspects of risk assessment’ (EFSA, 2009b) and following the relevant guidance documents of EFSA Scientific Committee.

The current ‘Guidance on the submission of a dossier on food enzymes for safety evaluation’ (EFSA CEF Panel, 2009, 2021a) has been followed for the evaluation of the application with the exception of the exposure assessment, which was carried out in accordance to the updated ‘Scientific Guidance for the submission of dossiers on food enzymes’ (EFSA CEP Panel, 2021a).

3. Assessment

The food enzyme under application contains two declared activities.

| IUBMB nomenclature     | Chymosin                        |
|------------------------|---------------------------------|
| Synonyms               | Rennin, preprorennin            |
| IUBMB No.              | 3.4.23.4                        |
| CAS No.                | 9001-98-3                       |
| EINECS No.             | 232-645-0                       |

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4 Commission Implementing Regulation (EU) No 562/2012 of 27 June 2012 amending Commission Regulation (EU) No 234/2011 with regard to specific data required for risk assessment of food enzymes Text with EEA relevance OJ L 168, 28.6.2012, p. 21–23.

5 The full detail is available at the [https://www.efsa.europa.eu/en/events/event/ad-hoc-meeting-industry-association-amfep-joint-dossiers-food-enzymes](https://www.efsa.europa.eu/en/events/event/ad-hoc-meeting-industry-association-amfep-joint-dossiers-food-enzymes).

6 Technical dossier/summary/risk assessment data, p. 28.
Chymosin is an aspartic endopeptidase that catalyses the hydrolysis of the 104-Ser-Phe-/Met-Ala-107 bonds of κ-casein, resulting in the destabilisation of casein micelles and causing milk to clot.

| IUBMB nomenclature | Pepsin A       |
|---------------------|----------------|
| Synonyms            | pepsin; lactated pepsin; pepsin fortior; fundus-pepsin |
| IUBMB No.           | 3.4.23.1       |
| CAS No.             | 9001-75-6      |
| EINECS No.          | 232-629-3      |

Pepsin A also an aspartic endopeptidase, breaks down peptide bonds in proteins and peptide molecules with the formation of shorter peptides, and free amino acids. It preferably cleaves peptide bonds between hydrophobic and aromatic amino acids.

The food enzyme is intended to be used in milk processing for cheese production.7

3.1. Source of the food enzyme8

The food enzyme is obtained from the abomasum of suckling calves (Bos taurus) obtained only from Government licensed meat production facilities in New Zealand (NZ) and Australia. Such facilities are directly supervised by the NZ Ministry for Primary Industries or the Australian Department of Agriculture, Fisheries and Food. Only animals fit for human consumption are used.

The abomasum of bovine animals is not regarded as a Specified Risk Material (See Regulation EC 999/2001). No issues of concern arising from the safety of the source material were identified by the Panel.

3.2. Production of the food enzyme

The food enzyme is manufactured in accordance with the current NZ Risk Management Programme which includes the principles of Hazard Analysis of Critical Control Points (HACCP) and meets European Union Food Standards.

The applicant provided information on the identity of the substances used in the extraction and in the subsequent downstream processing.

The Panel considered that sufficient information has been provided on the manufacturing process and the quality assurance system implemented by the applicant to exclude issues of concern.

3.3. Characteristics of the food enzyme

3.3.1. Properties of the food enzyme

Data from literature indicates that the chymosin from the abomasum of calves is a single polypeptide chain of 381 amino acids with a molecular mass of 36.5 kDa (Kumar et al., 2010). The pepsin A from the abomasum of calves is a single polypeptide chain of 386 amino acids with a molecular mass of 35 kDa (Munoz et al., 2004).10 No other enzyme activities were reported by the applicant.11

The determination of combined chymosin and pepsin A activities is based on the official method ISO 11815/IDF157:2007 for bovine rennet. The time needed for visual flocculation of a standard milk substrate with 0.5 g/L of calcium chloride (pH ≈ 6.5) is determined. The clotting time is compared

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7 The applicant provided information on the identity of the substances used in the extraction and in the subsequent downstream processing.
8 Technical dossier/summary/risk assessment data, p. 38.
9 Technical dossier/summary/risk assessment data, p. 45 and ANNEX list/Annex 15.
10 Technical dossier/p. 35.
11 Technical dossier/p. 36.
against that obtained using a reference standard with a known milk-clotting activity. The total milk-clotting activity is expressed in International Milk-Clotting Units (IMCU).\textsuperscript{12}

The relative contents of chymosin and pepsin A present in the rennet were determined by chromatographic analysis, based on the recognized official method ISO 15163/IDF 110:2012 for milk and milk products, indicated for calf rennet and adult bovine rennet.\textsuperscript{13} Chymosin was responsible for approximately 95% of the milk clotting activity.

The rennet milk clotting activity has a pH optimum around pH 6.5 and a temperature optimum between 40°C and 42°C (pH 6.5). This activity decreased above 42°C, showing no residual activity above 55°C.\textsuperscript{14}

### 3.3.2. Chemical parameters

Data on the chemical parameters of the food enzyme were provided for three batches (Table 1).\textsuperscript{15} The mean total organic solids (TOS) is 0.6% and the mean milk clotting activity/mg TOS ratio is 42.8 IMCU/mg TOS. The high ash content is a result of the NaCl solution used to elute the food enzyme from the ion exchange resin.

| Parameters                        | Unit              | Batches          |
|-----------------------------------|-------------------|------------------|
| Milk clotting activity            | IMCU/g batch(\textsuperscript{a}) | 258 261 263      |
| Protein                           | %                 | 0.3 0.2 0.2      |
| Ash                               | %                 | 15.4 15.8 15.4   |
| Water                             | %                 | 83.8 83.6 84.1   |
| Total organic solids (TOS)(\textsuperscript{b}) | %   | 0.8 0.6 0.5    |
| Milk clotting activity/mg TOS     | IMCU/mg TOS       | 32.3 43.5 52.6   |

(a): IMCU: International Milk-Clotting Units (see Section 3.3.1).
(b): TOS calculated as 100% – % water – % ash.

### 3.3.3. Purity\textsuperscript{16}

The lead content in the three batches was below 5 mg/kg which complies with the specification for lead as laid down in the general specifications for enzymes used in food processing (FAO/WHO, 2006).\textsuperscript{17,18}

The food enzyme complies with the microbiological criteria (for total coliforms, Escherichia coli and Salmonella) as laid down in the general specifications for enzymes used in food processing (FAO/WHO, 2006). In three batches of the food enzyme, Listeria spp. was absent in 25 g, Staphylococcus aureus was absent in 2 mL of the food enzyme and yeasts and filamentous fungi were below the limit of quantification (LoQ) (1 CFU/mg).\textsuperscript{19} No analytical data was provided confirming the absence of Campylobacter jejuni, Campylobacter coli and Shiga toxin-producing E. coli in the end product. However, the Panel considered that the manufacturing process\textsuperscript{20} the use of in the final formulation is sufficient to exclude microbiological risks.

The Panel considered that the information provided on the purity of the food enzyme is sufficient.

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\textsuperscript{12} Technical dossier/p. 35–36/ANNEX list/Annex 07a.

\textsuperscript{13} Technical dossier/p. 31–32/ANNEX list/Annex 08a.

\textsuperscript{14} Technical dossier/p. 36–37.

\textsuperscript{15} Technical dossier/p. 31/ANNEX list/Annexes: 01–03, 04, 05, 06.

\textsuperscript{16} Technical dossier/summary/risk assessment data, p. 9.

\textsuperscript{17} Technical dossier/p. 33–35 and ANNEX list/Annexes: 09–11a, 17.

\textsuperscript{18} Technical dossier/Additional information, 22.03.2022/Appendix 1/LoD: Pb = 0.0010 mg/kg.

\textsuperscript{19} Technical dossier/p. 33–35 and ANNEX list/Annexes: 09–11a.

\textsuperscript{20} Technical dossier/p. 42–46 and Additional information, 22.03.2022.

\textsuperscript{21} Technical dossier/p. 42–46.

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3.4. Toxicological data

According to the Commission Implementing Regulation (EU) No 562/2012, an application for the safety evaluation of a food enzyme does not need to include toxicological data if the food enzyme is obtained from edible parts of animals intended or reasonably expected to be ingested by humans.

According to the EFSA 'Guidance on the submission of a dossier on food enzymes for safety evaluation', the justification for not supplying toxicological data may include a documented history on the safety of the source of the food enzyme, the composition and the properties of the food enzyme, as well as its use in foods, demonstrating no adverse effects on human health when consumed in a comparable way (EFSA CEF Panel, 2009).

The Panel considers that these requirements are fulfilled, because:

i) rennet obtained from the abomasum of suckling calves has been safely used in the production of cheese and related products for many centuries.
ii) the abomasum from suckling calves is consumed throughout the EU and elsewhere in the world as a meat product.
iii) the manufacturing process of the food enzyme is not considered to introduce substances that could raise safety concerns.
iv) the compositional and purity data provided on the food enzyme are considered sufficient.

The Panel considered that sufficient information has been provided on the animal source, its history of safe use and consumption, and the manufacturing process. Therefore, the need for toxicological data is waived.

3.4.1. Allergenicity

The potential allergenicity of the food enzyme containing chymosin and pepsin A derived from the abomasum of calves assessed by comparing its amino acid sequence with those of known allergens is not considered relevant in this case.

Occupational respiratory allergies and skin sensitisation to dust of chymosin and pepsin A have been described in workers upon industrial exposure and in medical laboratory technicians (Cartier et al., 1984; Jensen et al., 2006; van Kampen et al., 2013; Gómez Torrijos et al., 2018; Khan and Selamoglu, 2020). However, several studies have shown that adults with occupational asthma to an enzyme can commonly ingest the corresponding respiratory allergens without acquiring clinical symptoms of food allergy (Cullinan et al., 1997; Brisman, 2002; Poulsen, 2004; Armentia et al., 2009). There are no reports in the literature on adverse reactions upon ingestion of these enzymes in individuals sensitised through the respiratory route.

No information is available on oral sensitisation or elicitation reactions to chymosin, and pepsin A obtained from the abomasum of calves under evaluation.

The Panel considered that, under the intended conditions of use, the risk of allergic sensitisation and elicitation reactions upon dietary exposure to this food enzyme cannot be excluded, but the likelihood of such reactions occurring was considered to be low.

3.5. Dietary exposure

3.5.1. Intended use of the food enzyme

The food enzyme (rennet paste) is intended to be used in milk processing for cheese production at the recommended use level between 0.5 to 1 mg TOS/kg milk, and at the maximum of 2 mg TOS/kg milk.

Animal rennet is added to milk to separate milk into solid curd and liquid whey (coagulation). Both chymosin and pepsin A contribute to the milk-clotting activity. The majority of the food enzyme TOS partitions into the whey and is mostly removed during the draining of the whey. Only a small portion...
of the food enzyme TOS remains in the curd (~ 6–12%). The remaining rennet contributes to the ripening of cheese due to its general proteolytic activity. Based on data provided on thermostability (see Section 3.3.1), it is expected that the remaining food enzyme is inactivated during cheese making.

3.5.2. Dietary exposure estimation

The technology of extracting enzymes from animal abomasum and the technology of using animal rennet for cheese making have remained the same over thousands of years and remains the major source of human exposure to the food enzyme. Cheese and by-products of cheese making have been consumed by human in Europe and many other parts of the world for millennia. In addition, abomasum from ruminants is consumed in some European countries, although this constitutes a minor fraction of the overall exposure to the food enzyme in the EU.

In the view of the Panel, dietary exposure estimation was not required.

3.6. Margin of exposure

Since toxicological assessment and dietary exposure estimation were considered unnecessary by the Panel, the margin of exposure was not calculated.

4. Conclusion

Based on the data provided, the origin of the food enzyme, its history of safe use, and the manufacturing process, the Panel concluded that the food enzyme rennet containing chymosin and pepsin A obtained from the abomasum of calves does not give rise to safety concerns under the intended conditions of use.

5. Documentation as provided to EFSA

Technical dossier “Animal rennet from Bos taurus (cattle)”. 6 December 2021. Submitted by Renco New Zealand.

Additional information. 22 March 2022. Submitted by Renco New Zealand.

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28 Technical dossier/p. 35.
Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| CAS          | Chemical Abstracts Service |
| CFU          | colony forming unit |
| EFSA CEF Panel | EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids |
| EFSA CEP Panel | EFSA Panel on Food Contact Materials, Enzymes and Processing Aids |
| EINECS       | European Inventory of Existing Commercial Chemical Substances |
| FAO          | Food and Agricultural Organization of the United Nations |
| IDF          | International Dairy Federation |
| IMCU         | International Milk-Clotting Units |
| ISO          | International Organization for Standardization |
| IUBMB        | International Union of Biochemistry and Molecular Biology |
| JECFA        | Joint FAO/WHO Expert Committee on Food Additives |
| kDa          | kiloDalton |
| LoQ          | limit of quantification |
| LoD          | limit of detection |
| TOS          | total organic solids |
| WHO          | World Health Organization |