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Safety evaluation of the food enzyme rennet containing chymosin and pepsin A from the abomasum of suckling goats, lambs and calves

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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 suckling goats, lambs and calves by Laboratoires Abia. 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 and the estimation of dietary exposure were not required. On the basis of literature data, the Panel considered that, under the intended conditions of use, the risk of allergic reactions by dietary exposure could not be excluded, but the likelihood for this to occur was considered low. Based on the data provided, the Panel concluded that this food enzyme does not give rise to safety concerns under the intended conditions of use.

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

Requestor: European Commission

Question number: EFSA-Q-2022-00180

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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 microorganisms or products thereof including a product obtained by a fermentation process using microorganisms: (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 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), 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.

[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, pp. 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, pp. 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, pp. 15–24.

1.1.2. Terms of Reference

The European Commission requests the European Food Safety Authority to carry out the safety assessments of 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 the food enzyme animal rennet consisting of chymosin and pepsin A from the abomasum of *Bos primigenius* (cattle), *Bubalus bubalis* (buffalo), *Capra aegagrus hircus* (goat) and *Ovis aries* (sheep).

The application was submitted initially as a joint dossier[4] and identified as the EFSA-Q-2015-00237. During the risk assessment phase, it was found that the technical dossier was 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-Q-2022-00180, concerns the food enzyme rennet containing chymosin and pepsin A from suckling goats, lambs and calves and submitted by Laboratoires ABIA.

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 goats, lambs and calves.

Additional information was requested from the applicant during the assessment process on 06 May 2022 and received on 29 July 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 existing guidance documents of EFSA Scientific Committee.

The current 'Scientific Guidance for the submission of dossiers on Food Enzymes' (EFSA CEP Panel, 2021) has been followed for the evaluation of the application.

3. Assessment

The food enzyme under application contains two declared activities: chymosin and pepsin A.

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

[4] A Joint Dossier is permitted by the Regulation (EU) 562/2012. To be completed with the full citation.

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

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, hydrolyses peptide bonds in proteins and peptide molecules with the formation of shorter peptides and free amino acids. It preferentially cleaves peptide bonds between hydrophobic, preferably aromatic, amino acids.

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

3.1. Source of the food enzyme[6]

The food enzyme is obtained from the abomasa of suckling goats (*Capra aegagrus hircus*), lambs (*Ovis aries*) or calves (*Bos taurus*) from certified French suppliers, surveyed and approved by the competent authorities. The food enzyme is exclusively obtained from healthy animals slaughtered under the supervision of official health authorities, following the requirements of the relevant EU hygiene regulations, the Food Hygiene Regulation (EC) No 852/2004[7] and Regulation (EC) No 853/2004[8].

In EU, according to Regulation (EC) 1774/2002[9], the stomach (abomasum) of goats, lambs and calves is considered fit for human consumption, as an edible offal as defined in Regulation (EC) No 853/2004[8]. 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 according to the Food Hygiene Regulation (EC) No 852/2004[7], with food safety procedures based on Hazard Analysis and Critical Control Points, and in accordance with current Good Manufacturing Practice.[10]

The food enzyme is extracted from the abomasa of suckling goats, lambs and calves. After the animals are slaughtered, the abomasa are trimmed to remove other tissues and then frozen before processing. The frozen abomasa are sliced and macerated in salted water at low pH. At the end of the extraction process, the resulting slurry is drained by gravity and then pressed to maximise recovery of the liquid fraction. Salt is added to the recovered liquid fraction, which is acidified to activate the two declared enzymatic activities. The extract is then clarified by flocculation and filtration to remove any remaining insoluble material. The clarified solution may be standardised by concentration (ultra-filtration), followed by a final microbiological filtration.[11] The applicant provided information on the identity of the substances used in the extraction and in the subsequent downstream processing.[12]

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.

[6] Technical dossier/Additional information July 2022/Annexes 01.1, 01.2, 02, 03, 04, 05, 06 & 07.
[7] Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs. OJ L 139, 30.4.2004, pp. 54.
[8] Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin. OJ L226, p. 22, 25/06/2004.
[9] Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption.
[10] Technical dossier/Annex 23.
[11] Technical dossier/Dossier p. 37.
[12] Technical dossier/Dossier p. 37–41.

3.3. Characteristics of the food enzyme

3.3.1. Properties of the food enzyme

Data from the literature indicate that the chymosin from the abomasa of suckling goats, lambs and calves is a single polypeptide chain of 381 amino acids with a molecular mass of about 36 kDa (Kumar et al., 2010). The pepsin A from the abomasum of suckling goats, lambs and calves is a single polypeptide chain of 386 amino acids with a molecular mass of 35 kDa of the mature protein (Munoz et al., 2004).[13] No other enzymatic activities were reported by the applicant.

The relative contents of chymosin and pepsin A present in the rennet were determined by chromatographic analysis, based on the methods IDF 110A/1987 and IDF 110B/1997.[14]

The rennet milk-clotting activity has a pH optimum around pH [redacted] and a temperature optimum between 45 and 46°C. This activity decreased above [redacted]°C, showing very low residual activity above [redacted]°C.[15]

3.3.2. Chemical parameters

Data on the chemical parameters of the food enzyme were provided for nine batches used for commercialisation, three from the abomasa of calves (Table 1), three from the abomasa of goats (Table 2) and three from the abomasa of lambs (Table 3). The means of the total organic solids (TOS) are 2.5%, 1.2% and 1.5%, respectively.

Table 1: Composition of the food enzyme rennet from the abomasum of suckling calves

Parameters	Unit	Batches		
		1	2	3
Chymosin	mg/L[(a)]	573	571	585
Pepsin A	mg/L[(a)]	352	366	346
Protein	%	2.0	1.9	1.2
Ash	%	16.8	16.8	16.7
Water	%	80.8	80.7	80.7
Total organic solids (TOS)[(b)]	%	2.4	2.5	2.6

(a): Determined by chromatographic analysis, based on the method IDF 110A/1987 and IDF 110B/1997 (see Section 3.3.1).
(b): TOS calculated as 100%–% water–% ash.

Table 2: Composition of the food enzyme rennet from the abomasum of suckling goats

Parameters	Unit	Batches		
		1	2	3
Chymosin	mg/L[(a)]	239	227	231
Pepsin A	mg/L[(a)]	36	35	36
Protein	%	0.5	0.5	0.4
Ash	%	16.9	17.1	17.4
Water	%	82.0	81.7	81.3
Total organic solids (TOS)[(b)]	%	1.1	1.2	1.3

(a): Determined by chromatographic analysis, based on the method IDF 110A/1987 and IDF 110B/1997 (see Section 3.3.1).
(b): TOS calculated as 100%–% water–% ash.

[13] Technical dossier/Additional information July 2022/Annexes 10, 33 & 34.
[14] Technical dossier/Annexes 10 & 11.
[15] Technical dossier/dossier p. 31–32.

Table 3: Composition of the food enzyme rennet from the abomasum of suckling lambs

Parameters	Unit	Batches		
		1	2	3
Chymosin	mg/L[(a)]	249	248	242
Pepsin A	mg/L[(a)]	61	63	75
Protein	%	0.9	1.1	0.7
Ash	%	17.3	17.2	17.4
Water	%	81.4	81.2	81.0
Total organic solids (TOS)[(b)]	%	1.3	1.6	1.6

(a): Determined by chromatographic analysis, based on the method IDF 110A/1987 and IDF 110B/1997 (see Section 3.3.1).
(b): TOS calculated as 100%–% water–% ash.

3.3.3. Purity

The lead content[16] in the nine commercial batches was below 0.04 mg/kg, which complies with the specification for lead (≤ 5 mg/kg) as laid down in the general specifications for enzymes used in food processing (FAO/WHO, 2006).[17] In addition, the levels of arsenic and cadmium[16] were below the limits of quantification (LOQs) of the employed methods.[18] The panel noted that, in two of the commercial batches (one from lambs and one from goats), the levels of mercury were 0.014 mg/kg and 0.016 mg/kg, respectively.[19] Given the proposed use level of the food enzyme, these concentrations raised no concern.

The microbiological analyses of nine commercial batches were reported. The food enzyme from all three animal sources complied 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). Additional microbiological parameters (sulfite-reducing anaerobes, *Streptococcus*, *Staphylococcus*, *Listeria monocytogenes*, fungi, yeasts) were also reported and raised no concern.[20] *Campylobacter* spp. were not detected in 10 g of food enzyme from six commercial batches.[21]

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

3.4. Toxicological data

According to the Commission Implementing Regulation (EU) No 562/2012[22], 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, 2009a).

The Panel considers that these requirements are fulfilled, because:

i) Rennet obtained from the abomasum of suckling goats, lambs and calves has been safely used in the production of cheese and related products for many centuries;
ii) The abomasum from suckling goats, lambs and 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.

[16] Technical dossier/Annex 1–9.
[17] LOQ: Pb = 0.04 mg/kg.
[18] LOQs: As = 0.03 mg/kg, Hg = 0.005 mg/kg; Cd = 0.01 mg/kg.
[19] Technical dossier/Annex 4 and 9.
[20] Technical dossier/Annex 12–20.
[21] Technical dossier/Additional information July 2022/Annexes 21–26.
[22] 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. OJ L 168, 28.6.2012, pp. 21–23.

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 was waived.

3.4.1. Allergenicity

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

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

Occupational respiratory allergies and skin sensitisation to dust of chymosin and pepsin 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.

The Panel noted that milk proteins are present in the rennet paste. However, as the paste is used in cheese making, this will not pose an additional risk to cheese consumption.

The Panel considered that the likelihood of food allergic reactions to this food enzyme obtained from the abomasum of suckling goats, lambs and calves is low and, therefore, does not give rise to safety concerns under the intended conditions of use.

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 1 and 16 mg TOS/kg milk.[23]

Animal rennet is added to milk to separate milk into solid curd and liquid whey (coagulation). Both chymosin and pepsin contribute to the milk-clotting activity.[24] 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 (approximately 10%). 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 was expected that the food enzyme may remain active in cheese, depending on the cheese-making process.

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 remain the major source of human exposure to the food enzyme. Cheese and by-products of cheese making have been consumed by humans in Europe and many other parts of the world for millennia. In addition, the abomasum from ruminants is consumed in some European countries, although this constitutes only a minor fraction of the overall exposure to the food enzyme in the EU.

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

3.6. Margin of exposure

Since the Panel considered that a toxicological assessment was unnecessary and the estimation of a dietary exposure not required, the margin of exposure was not calculated.

[23] Technical dossier/p. 47.
[24] Technical dossier/Fig. 3.2–5.

4. Conclusion

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

5. Documentation as provided to EFSA

Dossier "Animal rennet and 'Presure' from young Bos primigenius (cattle), young Capra aegagrus hircus (goat) and young Ovis cries (sheep)". March 2022. Submitted by Laboratoires Abia.

Additional information. July 2022. Submitted by Laboratoires Abia.

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Abbreviations

CAS	Chemical Abstracts Service
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 Organisation of the United Nations
IDF	International Dairy Federation
IUBMB	International Union of Biochemistry and Molecular Biology
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kDa	kiloDalton
LOQ	limit of quantification
TOS	total organic solids
WHO	World Health Organisation