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Safety evaluation of the food enzyme containing trypsin, chymotrypsin, α -amylase and triacylglycerol lipase from porcine pancreas

EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP),
Claude Lambré, José Manuel Barat Baviera, Claudia Bolognesi, Pier Sandro Cocconcelli,
Riccardo Crebelli, David Michael Gott, Konrad Grob, Evgenia Lampi, Marcel Mengelers,
Alicja Mortensen, Gilles Rivière, Inger-Lise Steffensen, Christina Tlustos, Henk Van Loveren,
Laurence Vernis, Holger Zorn, Boet Glandorf, Ursula Gundert-Remy, Lieve Herman,
Dominique Turck, Magdalena Andryszkiewicz, Natália Kovalkovičová, Joaquim Maia, Yi Liu,
Rainieri Sandra and Andrew Chesson

Abstract

The food enzyme complex, containing trypsin (EC 3.4.21.4), chymotrypsin (EC 3.4.21.1), α -amylase (1,4- α -D-glucan glucohydrolase, EC 3.2.1.1) and triacylglycerol lipase (triacylglycerol acylhydrolase, EC 3.1.1.3), is obtained from porcine pancreas by American Laboratories, Inc., USA. The food enzyme is intended primarily for the hydrolysis of milk proteins to be used in foods for special medical or nutritional dietary management. [REDACTED] is extensively used in the manufacturing process, and residual amounts of the solvent remain in the food enzyme. The applicant estimates a typical range of [REDACTED] in the food enzyme to be 10,000–13,000 mg/kg. Directive 2009/32/EC sets a maximum residue level of 10 mg/kg for foods and food ingredients produced in the EU or imported into the EU. The use of [REDACTED] for the production of a food enzyme falls within the scope of Directive 2009/32/EC. Consequently, the food enzyme does not comply with the existing requirements within the EU governing residual amount of solvent.

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Correspondence: fip@efsa.europa.eu

Panel members: José Manuel Barat Baviera, Claudia Bolognesi, Andrew Chesson, Pier Sandro Cocconcelli, Riccardo Crebelli, David Michael Gott, Konrad Grob, Claude Lambré, Evgenia Lampi, Marcel Mengelers, Alicja Mortensen, Gilles Rivière, Vittorio Silano (until 21 December 2020[†]), Inger-Lise Steffensen, Christina Tlustos, Henk Van Loveren and Laurence Vernis, Holger Zorn.

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[†] Deceased.

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1. Introduction

Article 3 of the Regulation (EC) No 1332/2008¹ 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 1332/2008¹ 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 1331/2008² 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 CEF Panel, 2009) 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 1332/2008¹ on food enzymes.

An application has been introduced by the applicant 'American Laboratories, Inc.' for the authorisation of the food enzyme pancreatin from porcine pancreas.

Following the requirements of Article 12.1 of Regulation (EC) No 234/2011³ implementing Regulation (EC) No 1331/2008², 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.

1.1.2. Terms of Reference

The European Commission requests the European Food Safety Authority to carry out the safety assessment on the following food enzyme: pancreatin from porcine pancreas in accordance with Article 17.3 of Regulation (EC) No 1332/2008¹ on food enzymes.

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, p. 15–24.

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 a food enzyme complex with four declared activities (trypsin, chymotrypsin, α -amylase and triacylglycerol lipase) from porcine pancreas.

2. Data and methodologies

2.1. Data

The applicant has submitted a dossier in support of the application for authorisation of the food enzyme pancreatin.

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, 2009) 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 CEP Panel, 2009) has been followed for the evaluation of the application with the exception of the exposure assessment, which was carried out in accordance with the updated 'Scientific Guidance for the submission of dossiers on food enzymes' (EFSA CEP Panel, 2021).

3. Assessment⁴

The food enzyme under application contains four declared activities:

| | |
|--------------------|-------------------------------------|
| IUBMB nomenclature | Trypsin |
| Synonyms | α -trypsin, β -trypsin |
| IUBMB No | EC 3.4.21.4 |
| CAS No | 9002-07-7 |
| EINECS No | 232-650-8 |

Trypsin is a serine endopeptidase that catalyses the hydrolysis of peptide bonds on the carboxyl-terminal (C-terminal) side of the amino acids lysine and arginine, releasing polypeptides.

| | |
|--------------------|--|
| IUBMB nomenclature | Chymotrypsin |
| Synonyms | Chymotrypsin A and B, α -chymar ophth |
| IUBMB No | EC 3.4.21.1 |
| CAS No | 9004-07-3 |
| EINECS No | 232-671-2 |

Chymotrypsin, also a serine endopeptidase, catalyses the hydrolysis of peptide bonds on the C-terminal side of the amino acids tryptophan, tyrosine, phenylalanine and leucine (to lower extent), releasing polypeptides.

| | |
|--------------------|--|
| IUBMB nomenclature | α -Amylase |
| Systematic name | 1,4- α -D-glucan glucohydrolase |
| Synonyms | Glycogenase, endoamylase |
| IUBMB No | EC 3.2.1.1 |
| CAS No | 9000-90-2 |
| EINECS No | 232-565-6 |

α -Amylases catalyse the hydrolysis of 1,4- α -glucosidic linkages in starch (amylose and amylopectin), glycogen and related polysaccharides and oligosaccharides, resulting in the generation of soluble dextrans and other oligosaccharides.

⁴ Technical dossier/p. 1, 6–7, 30; Technical dossier/Pancreatin_EFSA Dossier Detailed summary/p. 1.

| | |
|--------------------|-------------------------------|
| IUBMB nomenclature | Triacylglycerol lipase |
| Systematic name | Triacylglycerol acylhydrolase |
| Synonyms | Lipase, triglyceride lipase |
| IUBMB No | EC 3.1.1.3 |
| CAS No | 9001-62-1 |
| EINECS No | 232-619-9 |

Triacylglycerol lipases catalyse, in the presence of water, the hydrolysis of the ester linkages in triacylglycerols, resulting in the generation of glycerol, free fatty acids, diacylglycerols and monoacylglycerols.

The food enzyme, under the heading of Pancreatin, carries the CAS No 8049-47-6 and the EINECS No 232-468-9.

The food enzyme is intended primarily in the hydrolysis of milk proteins to be used in foods for special medical or nutritional dietary management.⁵

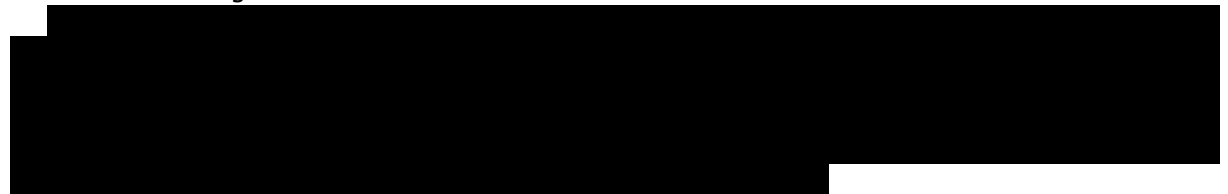
3.1. Source of the food enzyme⁶

The food enzyme is produced from the pancreas of pigs (*Sus scrofa domestica*) in North America and is imported into the EU. Pigs that are used in the manufacturing of the food enzyme are authorised fit for human consumption and have passed ante- and post-mortem veterinary inspection at the time of slaughter.⁵ They are obtained only from facilities routinely inspected by the United States Department of Agriculture – Food Safety Inspection Service (FSIS) or Agri-Food Canada – Canadian Food Inspection Agency (CFIA).⁷ The inspection standards applied are considered equivalent to those used in the EU.

Pigs are not included in the list of the specific risk material defined by Commission Regulation (EU) No 2015/1162⁸. Porcine pancreas is considered as edible offal in the EU as defined in Regulation (EC) No 853/2004⁹.

3.2. Production of the food enzyme¹⁰

The food enzyme is manufactured in accordance with a Quality Assurance scheme and current Good Manufacturing Practice.



The applicant provided full information on the production process including the identity of the substances used in the extraction and in the subsequent downstream processing of the food enzyme.¹⁰

3.3. Characteristics of the food enzyme

3.3.1. Properties of the food enzyme

The applicant provided data taken from the literature on the amino acid sequence and calculated molecular mass of the four declared activities:

⁵ Technical dossier/p. 2.

⁶ Technical dossier/p. 2, 12, 16; Technical dossier/Pancreatin_EFSA Dossier Detailed summary/p. 2.

⁷ Technical dossier/p. 2, 12, 16, 28.

⁸ Commission Regulation (EU) No 2015/1162 of 15 July 2015 amending Annex V to Regulation (EC) No 999/2001 of the European Parliament and of the Council laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies. OJ L 188, 16.7.2015, p. 3–5.

⁹ 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 L 139, 30.4.2004, p. 55–205.

¹⁰ Technical dossier/p. 13–17.

- Trypsin – a single polypeptide chain of 231 amino acids with a molecular mass of 23.3 kDa.¹¹
- Chymotrypsin – a single polypeptide chain of 245 amino acids with a molecular mass of 25.6 kDa.¹¹
- α -Amylase – a single polypeptide chain of 475 amino acids with a molecular mass of 55.4 kDa.¹²
- Triacylglycerol lipase – a single polypeptide chain of 449 amino acids with a molecular mass of 55 kDa.

The data provided for chymotrypsin was for the bovine enzyme.

No other enzymatic activities were reported.

The in-house determination of protease activity is based on the hydrolysis of a casein solution and the release of aromatic amino acids (reaction conditions: pH 8, 40°C, 60 min). The reaction is stopped by adding trichloroacetic acid which precipitates any intact casein remaining in the solution. The precipitate is removed by filtration and the aromatic amino acids in the filtrate are determined spectrophotometrically at 280 nm. The protease activity is expressed in USP Protease Units (USPP)/g. One USPP is the amount of pancreatin that liberates an amount of non-precipitated peptides equivalent to 15 nmol of tyrosine per minute under conditions of the assay.¹³

The in-house determination of α -amylase activity is based on the hydrolysis of starch (reaction conditions: pH 6.8, 25°C, 10 min) and is determined by the rate at which the iodine-staining capacity decreases, measured spectrophotometrically at 660 nm. The α -amylase activity is expressed in Amylase USP units (AUSP/g). One AUSP is the amount of pancreatin that hydrolyses 0.16 microequivalents (μ eq) of starch glycosidic linkages per minute under the conditions of the assay.¹⁴

The in-house determination of triacylglycerol lipase activity is based on the hydrolysis of olive oil (reaction conditions: pH 9.0, 37°C, 1 min). The enzymatic activity is determined by titration of the released fatty acids with sodium hydroxide. The triacylglycerol lipase activity is expressed in Lipase USP units (LUSP/g). One LUSP Unit is the amount of pancreatin that liberates 1.0 μ eq of acid per minute under conditions of the assay.¹⁵

3.3.2. Chemical parameters¹⁶

Data on the batch-to-batch variation of the declared activities have been provided for 50 food enzyme batches. For protease, the mean activity and \pm SD was 265,000 \pm 17,250 USPP/g, for α -amylase 302,500 \pm 26,500 AUSP/g and for triacylglycerol lipase 1,405,000 \pm 249,000 LUSP/g.^{17,18}

The data provided by the applicant were insufficient to calculate the total organic solids (TOS) content of the food enzyme.

3.3.3. Purity¹⁹

No data on the lead or total heavy metal content of the food enzyme were provided.

The food enzyme preparation complies with the microbiological criteria for *Escherichia coli* and *Salmonella* as laid down in the general specifications for enzymes used in food processing (FAO/WHO, 2006).²⁰ Average total aerobic microbial counts for three batches was 237 CFU/g.

██████████ is extensively used in the manufacture of the food enzyme.²¹ Since any heat treatment to aid the removal of the solvent is precluded by the nature of the food enzyme, residual amounts of the solvent remain. The applicant estimates a typical range of ██████████ in the food enzyme to be 10,000–13,000 mg/kg.²² The use of ██████████ for the production of food enzymes falls within the scope of Directive 2009/32/EC²³. This Directive sets a maximum residue level of ██████████ of

¹¹ Technical dossier/p. 7, 21, 30.

¹² Technical dossier/p. 6, 21.

¹³ Technical dossier/p. 9–10; Technical dossier/Annex 34-0012.

¹⁴ Technical dossier/p. 9–10; Technical dossier/Annex 34-0013.

¹⁵ Technical dossier/p. 9–10; Technical dossier/Annex 34-0014.

¹⁶ Technical dossier/p. 8, 36–38; Technical dossier/Annex 34-0003.

¹⁷ Technical dossier/p. 8, 36–38.

¹⁸ Technical dossier/Annex 34-0012; Annex 34-0013; Annex 34-0014.

¹⁹ Technical dossier/p. 8–9; Technical dossier/Annex 32-0001; Annex 32-0002; Annex 32-0003.

²⁰ Technical dossier/p. 39; Technical dossier/Annex 32-0001; Annex 32-0002.

²¹ Technical dossier/p. 24.

²² Technical dossier/p. 24; Technical dossier/Annex 34-0136B.

²³ Directive 2009/32/EC of the European Parliament and of the Council of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients. OJ L 141, 6.6.2009, p. 3–11.

10 mg/kg in foods and food ingredients in the EU (Annex I, part II) or imported into the EU (Article 8). The amount of [REDACTED] detected in the food enzyme greatly exceeded the permitted residual level. Consequently, this food enzyme does not comply with the existing rules within the EU governing residual solvents for all food uses.

3.4. Toxicological data

The applicant justifies the absence of toxicological studies because of the widespread consumption of pork and pork offal, including the pancreas; the listing of pancreatin (a preparation with the same declared enzyme activities) in the United States and European Pharmacopoeia and the results of an acute toxicity study in rats made with pancreatin (> 10,000 mg/kg body weight (bw)).²⁴

The Panel acknowledges that human data on the safety of pancreatic enzymes are available from their therapeutic use. Pancreatic enzymes of porcine origin have been used for decades in drugs used to treat patients with pancreatic insufficiency, including infants, with the diagnosis of cystic fibrosis (Brady et al., 1991; Graff et al., 2010; Whitcomb et al., 2010; Gubergrits et al., 2011; Littlewood et al., 2011; Sander-Struckmeier et al., 2013; Kashirskaya et al., 2015). The most serious reported adverse effect of pharmaceutical porcine pancreatic enzymes is fibrosing colonopathy. This rare phenomenon is associated with therapeutic doses and prolonged use of the drug (Smyth, 1996).

Post-marketing data most commonly reported undesired effects of drugs produced from porcine pancreas are gastrointestinal disorders that are generally of mild or moderate severity. Pruritus, urticaria and rash, blurred vision, myalgia, muscle spasms and asymptomatic elevations of pancreatic enzymes have been reported but the incidences are rare. No specific adverse effects have been identified in infants.

The Panel identified that the most concerning side effect documented by the consumption of the pancreatic enzymes when used as drugs is hypersensitivity to the product. However, the intact enzymes in this evaluation may be inactivated by heat treatment depending on the food manufacturing process to which they are applied.²⁵ In such cases the Panel considered that the likelihood of adverse effects of the intact enzyme to occur is low.

3.4.1. Allergenicity²⁶

The applicant argues that porcine proteins are not considered a major allergen, according to Regulation 1169/2011²⁷ on Food Information to Consumers, as it is not included in the Annex II of that regulation. The Panel accepts that pig is not a source included in the list of substances or products causing allergies or intolerances. However, in studies performed on enzymes of porcine origin employed as pharmaceutical preparations, adverse allergic incidences have been reported (see Section 3.4).

Occupational respiratory allergies to enzyme dust of pig pancreatic enzymes also have been described in workers after industrial exposure and in medical laboratory technicians (Colten et al., 1975; Kempf et al., 1999; van Kampen et al., 2016). These proteins from porcine pancreas are not reported to be food allergens. The Panel noted that an allergic reaction upon oral ingestion of this food enzyme pancreatin, produced by porcine pancreas, in individuals respiratory sensitised to food enzyme cannot be ruled out, but the likelihood of such a reaction to occur is considered to be low.

Hydrolysis of milk is performed in order to reduce the allergenicity of milk proteins. Proteases used in milk hydrolysis are manufactured in an equivalent manner to those used in pharmaceutical preparations. Foods in which the enzyme has been applied have been on the market with only rare reports of adverse allergic reactions in infants (EFSA FAF Panel, 2020). The specificity of these adverse reactions has not been established. Although the immune system of infants is not fully developed, occasional cases of anaphylactic reactions to food have been reported (Mehl et al., 2005).

[REDACTED] used as a processing aid (solvent) during enzyme manufacture, is known to be a mild irritant for the eyes and mucous membranes, and should be considered as a potential allergen in

²⁴ Technical dossier/p. 26.

²⁵ Technical dossier/p. 2, 18.

²⁶ Technical dossier/p. 27–28.

²⁷ Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. OJ L 304, 22.11.2011, p. 18–63.

patients with eczema who have contact with this substance [REDACTED] reported allergic contact dermatitis from [REDACTED] in a commercial disinfectant swab and [REDACTED] described delayed hypersensitivity to [REDACTED]. Allergy after oral exposure to [REDACTED] has not been reported.

3.5. Dietary exposure

3.5.1. Intended use of the food enzyme

The food enzyme is primarily intended for the hydrolysis of milk proteins to be used in foods for special medical or nutritional dietary management.²⁸ The recommended use level of the food enzyme is [REDACTED].²⁹ However, in the absence of adequate data on the composition of the food enzyme (see Section 3.3.2), the Panel is unable to express a proper use level in mg TOS/kg protein.

No use levels were proposed for processes involving starch or fats.

The potential target food categories for amino acids and peptides produced with the food enzyme include foods intended for particular nutritional uses, foods for infants and young children, infant formulae, follow-on formulae, other foods for young children, dietary foods for infants and young children for special medical purposes as defined by Directive 1999/21/EC³⁰ and special formulae for infants, and dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5).²⁹

3.5.2. Dietary exposure estimation

The limited data provided on the use level for protein hydrolysis precludes an estimate of dietary exposure.

4. Conclusion

The use of [REDACTED] for the production of the food enzymes falls within the scope of Directive 2009/32/EC²³ which sets a maximum residue level of 10 mg/kg in foods and food ingredients. The estimate made of the actual residue levels of [REDACTED] far exceeds this limit. Consequently, the food enzyme does not comply with the existing requirements in the EU governing residual amount of solvent.

5. Documentation as provided to EFSA

Technical dossier Pancreatin. 10 March 2015. Submitted by American Laboratories, Inc.

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²⁸ Technical dossier/p. 20–22.

²⁹ Technical dossier/p. 22.

³⁰ Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. *OJ L* 91, 7.4.1999, p. 29–36.

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Abbreviations

| | |
|----------------|--|
| AUSP | Amylase USP unit |
| bw | body weight |
| CAS | Chemical Abstracts Service |
| CEF | EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids |
| CEP | EFSA Panel on Food Contact Materials, Enzymes and Processing Aids |
| CFIA | Canadian Food Inspection Agency |
| CFU | colony forming units |
| EFSA FAF Panel | EFSA Panel on Food Additives and Flavourings |
| EINECS | European Inventory of Existing Commercial Chemical Substances |
| FAO | Food and Agricultural Organization of the United Nations |
| FSIS | Food Safety Inspection Service |

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| IUBMB | International Union of Biochemistry and Molecular Biology |
| JECFA | Joint FAO/WHO Expert Committee on Food Additives |
| LUSP | Lipase USP unit |
| μ eq | microequivalents |
| SD | standard deviation |
| USPP | USP Protease Units |
| USP Units | United States Pharmacopoeia Units |
| TOS | total organic solids |
| WHO | World Health Organization |