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Safety evaluation of the food enzyme phospholipase A2 from porcine pancreas

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Abstract

The food enzyme phospholipase A2 (phosphatidylcholine 2-acylhydrolase, EC 3.1.1.4) is obtained from porcine pancreas by Sanyo Fine Co., Ltd. It is intended to be used in three food manufacturing processes: egg processing, flavouring production and yeast processing. In the absence of sufficient data provided by the applicant to characterise the source of food enzyme, its production and chemical characterisation, coupled with insufficient information about food manufacturing processes to which the food enzyme is applied, the Panel was unable to assess the safety of the food enzyme.

Keywords: food enzyme, phospholipase A2, phosphatidylcholine 2-acylhydrolase, EC 3.1.1.4, porcine pancreas

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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[1] 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 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 1332/2008[1] on food enzymes.

Five applications have been introduced by the companies 'Amano Enzyme Inc.' for the authorisation of the food enzymes cyclomaltodextrin glucanotransferase from *Geobacillus stearothermophilus* (strain AE-KCGT), cyclomaltodextrin glucanotransferase from *Paenibacillus macerans* (strain AE-CGT) and thermolysin from *Geobacillus stearothermophilus* (strain AE-TP), 'Sanyo Fine Co., Ltd.' for the authorisation of the food enzyme phospholipase A2 from porcine pancreas, and 'Nagase (Europa) GmbH' for the authorisation of the food enzyme beta-amylase from soybean (*Glycine max*).

Following the requirements of Article 12.1 of Commission Regulation (EU) No 234/2011[3] implementing Regulation (EC) No 1331/2008[2], the Commission has verified that the five applications fall 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, 11.3.2011, pp. 15–24.

1.1.2. Terms of Reference

The European Commission (EC) requests the European Food Safety Authority (EFSA) to carry out the safety assessments on the food enzymes cyclomaltodextrin glucanotransferase from *Geobacillus stearothermophilus* (strain AE-KCGT), cyclomaltodextrin glucanotransferase from *Paenibacillus macerans* (strain AE-CGT), thermolysin from *Geobacillus stearothermophilus* (strain AE-TP), phospholipase A2 from porcine pancreas, and beta-amylase from soybean (*Glycine max*) in accordance with Article 17.3 of Regulation (EC) No 1332/2008[1] 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 phospholipase A2 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 phospholipase A2 from porcine pancreas.

EFSA identified the need for additional data on the source organism of the food enzyme, production and characteristics of the food enzyme, allergenicity and exposure assessment. Additional information was requested from the applicant during the assessment process on 24 March 2021. Based on the understanding that the additional data request did not reach the applicant, EFSA resent the request to the applicant on 19 August 2021 with the deadline extended to 19 November 2021. A reminder to provide the additional data was sent on 25 November 2022, to which the applicant did not reply. On 9 December 2022, EFSA informed the applicant of the decision to finalise this assessment on the basis of the data provided in the original application.

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 the EFSA Scientific Committee.

The 'Guidance on the submission of a dossier on food enzymes for safety evaluation' (EFSA CEF 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. Assessment[4]

IUBMB nomenclature	phospholipase A2
Systematic name	phosphatidylcholine 2-acylhydrolase
Synonyms	lecithinase A, phosphatidase, phosphatidolipase
IUBMB No	3.1.1.4
CAS No	9001-84-7
EINECS No	232-637-7

Phospholipases A2 catalyse the hydrolysis of the acyl ester bond at the sn-2 position of the glycerol moiety of fats, resulting in the formation of 2-acyl-2-lysophospholipids and free fatty acids.[5] The enzyme under assessment is intended to be used in three food processes: egg processing, flavouring production and yeast processing.

[4] Technical dossier/p. 4, 19–20, 41.
[5] Technical dossier/p. 12, 24, 28–29.

3.1. Source of the food enzyme[6]

The food enzyme is obtained from the pancreas of porcine (*Sus scrofa domesticus*). According to the applicant, the enzyme was extracted from pigs slaughtered and approved for human consumption in Japan[7], handled in accordance with specific procedures to avoid contamination and preserve good hygiene standards.[7] However, the applicant did not provide confirmation that the Japanese legislation related to the slaughter and handling of animal carcass for human consumption is essentially equivalent to EU legislation (the Food Hygiene Regulation (EC) No 853/2004)[8] and whether all carcasses are subject to veterinary inspection. This fails to meet the requirements of the EFSA 'Guidance on the submission of a dossier on food enzymes for safety evaluation' (EFSA CEF Panel, 2009).

3.2. Production of the food enzyme[9]

According to the applicant, the food enzyme is manufactured in accordance with current Japanese Good Manufacturing Practice.[10] However, no evidence was provided to support this statement. In addition, no information on the food safety management system was provided.

The food enzyme is extracted from minced porcine pancreas which have been stored frozen. The pH of the minced pancreas is adjusted with NaOH and the slurry is filtered. The solids are then suspended in water, acidified to pH 4 and, after a period of extraction, tissue material is removed by filtration, leaving the aqueous solution containing the food enzyme. The filtrate is concentrated by ultrafiltration in which the enzyme protein is retained while most of the low molecular mass material passes the filtration membrane and is discarded.[11] The concentrated enzyme solution is then heated to 65°C for 30 min before formulation as a liquid or solid product.

The Panel considered that insufficient information has been provided on the materials used in the manufacturing process and, consequently, an assessment of their toxicity could not be made.

3.3. Characteristics of the food enzyme

3.3.1. Properties of the food enzyme

The phospholipase A2 is a single polypeptide chain of 124 amino acids.[12] The calculated molecular mass of the mature protein, derived from the amino acid sequence, was not provided by the applicant. The food enzyme was analysed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis.[13] A consistent protein pattern was observed across all batches. The gels showed a major protein band corresponding to an apparent molecular mass of about 15 kDa.[14] No other enzyme activities were reported.[15]

The in-house determination of phospholipase A2 activity[16] is based on the hydrolysis of soybean lecithin (reaction conditions: 40°C, pH 8.0, 5 min), measuring the release of fatty acids by titration with potassium hydroxide. The definition of units of activity was not provided by the applicant.

The food enzyme has a temperature optimum around 60°C (pH 8.0)[7] and a pH optimum around 9 (40°C).[17] The applicant did not provide data on thermostability.

[6] Technical dossier/p. 7, 26.
[7] Technical dossier/p. 26.
[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 L 139, 30.4.2004, p. 55–205.
[9] Technical dossier/p. 7–8, 13, 27–28; Technical dossier/Annex 4.
[10] Technical dossier/p. 7; Technical dossier/Annex 3.
[11] Technical dossier/p. 7–8, 26–28; Technical dossier/Annex 4.
[12] Technical dossier/p. 24.
[13] Technical dossier/p. 21.
[14] Technical dossier/p. 23–24.
[15] Technical dossier/p. 7, 22–25.
[16] Technical dossier/Annex 1.
[17] Technical dossier/p. 7, 25.

3.3.2. Chemical parameters[18]

Data on the chemical parameters of the food enzyme were provided for three batches used for commercialisation (Table 1). The mean total organic solids (TOS) was 3.4% and the mean enzyme activity/TOS ratio was 346 U/mg TOS.

Table 1: Composition of the food enzyme

Parameters	Unit	Batches		
		1	2	3
Phospholipase A2 activity	U/mL batch[(a)]	11,200	12,500	11,100
Protein	%	3.4	3.2	3.1
Ash	%	0.1	0.1	0.1
Water	%	96.3	96.7	96.6
Total organic solids (TOS)[(b)]	%	3.6	3.2	3.3
Activity/TOS	U/mg TOS	311	391	336

(a): U: Unit (see Section 3.3.1).
(b): TOS calculated as 100% – % water – % ash.

The applicant did not provide the certificates of analysis for the chemical parameters shown in Table 1.

3.3.3. Purity[19]

The lead content[20] in the three commercial 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).

The food enzyme complies with the microbiological criteria for total coliforms, *Escherichia coli* and *Salmonella*),[21] as laid down in the general specifications for enzymes used in food processing (FAO/WHO, 2006).

No evidence of the absence of hepatitis E virus, *Salmonella* spp., *Campylobacter* and *E. coli* was provided, and the counts of Enterobacteriaceae, filamentous fungi and yeast was not determined. This fails to meet the requirements of EFSA 'Guidance on the submission of a dossier on food enzymes for safety evaluation' (EFSA CEF Panel, 2009).

In addition, the applicant did not provide detailed description of the analytical methods, limits of detection/quantification or the certificates of analysis for any parameter regarding food enzyme purity.

The Panel considered that the information provided on the purity of the food enzyme was insufficient.

3.4. Toxicological data[22]

Porcine pancreas is an edible offal as defined in Regulation (EC) No 853/2004[23] and is described as a meat by-product (Marti et al., 2011; Nollet and Toldrá, 2011). However, it has not been reported to be commonly consumed in the European Union, and data on the consumption by infants or others in the general population have not been identified by the Panel.

Therefore, the Panel considered that, for this enzyme, a toxicological evaluation is necessary.

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

[18] Technical dossier/p. 21; Technical dossier/Annex 6, Annex 7, Annex 8.
[19] Technical dossier/p. 7, 23, 41; Technical dossier/Annex 2, Annex 3, Annex 9.
[20] Technical dossier/p. 7; 23, 41; Technical dossier/Annex 3, Annex 9.
[21] Technical dossier/p. 7, 23, 41; Technical dossier/Annex 3, Annex 10, Annex 11.
[22] Technical dossier/p. 10, 13, 36–37.
[23] 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.

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 showed that the 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 considered the most concerning documented side effect when used as drugs is hypersensitivity.

The applicant did not provide evidence that the enzyme may be inactivated by heat treatment, depending on the food manufacturing process to which it is applied. In such cases, the Panel considered that the likelihood of adverse effects of the intact enzyme to occur cannot be excluded.

3.4.1. Allergenicity[24]

No assessment of allergenicity was provided by the applicant.

No information is available on oral and respiratory sensitisation or elicitation reactions of this phospholipase A2. In addition, no allergic reactions upon dietary exposure to any phospholipase A2 have been reported in the literature.

Phospholipase A2 is considered the major allergen of honeybee venom (Okano et al., 1999; Perez-Riverol et al., 2019), but Guérin et al. (2002) found that the oral intake of phospholipase A2 is not of concern even for individuals sensitive to bee venom.

The Panel noted that pigs and products thereof are not a source included in the list of substances or products causing allergies or intolerances (EU Reg. 1169/2011).[25] 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 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). However, the proteins from porcine pancreas have not been reported to be food allergens. Several studies have shown that adults with occupational asthma to a food enzyme (as described for α-amylase from *A. oryzae*) may be able to ingest the corresponding allergen without acquiring clinical symptoms of food allergy (Cullinan et al., 1997; Poulsen, 2004; Armentia et al., 2009).

The Panel noted that an allergic reaction upon oral ingestion of this food enzyme phospholipase A2 from porcine pancreas cannot be excluded, but the likelihood is low.

3.5. Dietary exposure

3.5.1. Intended use of the food enzyme

The food enzyme is intended to be used in three food processes at the recommended use levels summarised in Table 2.

Table 2: Intended uses and recommended use levels of the food enzyme as provided by the applicant(a)

Food manufacturing process	Raw material (RM)	Recommended dosage of the food enzyme (mg TOS/kg RM)
Egg processing	Whole egg	13–67
Flavouring production	Egg yolk	40–800
Yeast processing	Yeast	< 800

TOS: total organic solids.
(a): Technical dossier/p. 33/Table 3.

[24] Technical dossier/p. 10, 37–38.
[25] 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 Text with EEA relevance. OJ L 304, 22.11.2011, p. 18–63.

In egg processing, the food enzyme is intended to be added to the whole egg, to egg white or to egg yolk.[26] It improves foaming properties of egg white and emulsifying properties of egg yolk. The food enzyme–TOS remains in the processed egg products.

A flow chart was provided to indicate that the phospholipase A2 may be used in the production of flavouring substances and/or preparations.[27] However, the information is not sufficiently detailed to be useful for the evaluation of the food enzyme under assessment.

In yeast processing, the food enzyme is intended to be added to yeast biomass during autolysis or to the yeast extract and cell wall.[28] It enables the formation of savoury ingredients. The food enzyme–TOS remains in the processed yeast products.

No data on the thermostability was provided by the applicant, hence, the Panel could not make any conclusion on the survival of the enzyme activity.

The information provided in the technical dossier lacked important details about certain food manufacturing processes to which the food enzyme may be applied. In particular, 'flavouring production' is likely to overlap with the 'egg processing' and 'yeast processing'. The evidence for the removal of the food enzyme–TOS in certain flavouring substances was also missing.

3.5.2. Dietary exposure estimation

The limited technical information precluded an estimate of the dietary exposure.

4. Conclusions

In the absence of data sufficient to characterise the source of food enzyme, its production and characterisation, coupled with an insufficient information about food manufacturing processes to which the food enzyme is applied, the Panel was unable to complete its assessment of the safety of the food enzyme phospholipase A2 from porcine pancreas.

5. Documentation as provided to EFSA

Technical dossier Application for authorization of phospholipase A2 from porcine pancreas in accordance with Regulation (EC) No 1331/2008. 5 March 2015. Submitted by Sanyo Fine Co., Ltd.

References

Armentia A, Díaz-Perales A, Castrodeza J, Dueñas-Laita A, Palacin A and Fernández S, 2009. Why can patients with baker's asthma tolerate wheat flour ingestion? Is wheat pollen allergy relevant? Allergologia et Immunopathologia, 37, 203–204. https://doi.org/10.1016/j.aller.2009.05.001

Brady MS, Rickard K, Yu PL and Eigen H, 1991. Effectiveness and safety of small vs. large doses of enteric coated pancreatic enzymes in reducing steatorrhea in children with cystic fibrosis: a prospective randomized study. Pediatric Pulmonology, 10, 79–85. https://doi.org/10.1002/ppul.1950100208

Colten HR, Polakoff PL, Weinstein SF and Strieder D, 1975. Immediate hypersensitivity to hog trypsin resulting from industrial exposure. The New England Journal of Medicine, 292, 1050–1053. https://doi.org/10.1056/NEJM197505152922003

Cullinan P, Cook A, Jones M, Cannon J, Fitzgerald B and Newman Taylor AJ, 1997. Clinical responses to ingested fungal α-amylase and hemicellulase in persons sensitized to *Aspergillus fumigatus*? Allergy, 52(1997), 346–349.

EFSA (European Food Safety Authority), 2009. Guidance of EFSA prepared by the Scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: general principles. EFSA Journal 2009;7(5):1051, 22 pp. https://doi.org/10.2093/j.efsa.2009.1051

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2009. Guidance of the Scientific Panel of Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) on the Submission of a Dossier on Food Enzymes for Safety Evaluation by the Scientific Panel of Food Contact Materials, Enzymes, Flavourings and Processing Aids. EFSA Journal 2009;7(8):1305, 26 pp. https://doi.org/10.2903/j.efsa.2009.1305

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, Glandorf B, Herman L, Aguilera J, Andryszkiewicz M, Gomes A, Kovalkovicova N, Liu Y, Rainieri S and Chesson A, 2021. Scientific Guidance for the submission of dossiers on Food Enzymes. EFSA Journal 2021;19(10):6851, 37 pp. https://doi.org/10.2903/j.efsa.2021.6851

[26] Technical dossier/p. 29–30.
[27] Technical dossier/p. 30–31.
[28] Technical dossier/p. 31–32.

FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization), 2006. General specifications and considerations for enzyme preparations used in food processing in Compendium of food additive specifications. 67th meeting. FAO JECFA Monographs, 3, 63–67. Available online:. https://www.fao.org/3/a0675e/a0675e.pdf

Graff GR, Maguiness K, McNamara J, Morton R, Boyd D, Beckmann K and Bennett D, 2010. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with endocrine pancreatic insufficiency and cystic fibrosis: a multicentre, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clinical Therapeutics, 32, 89–103. https://doi.org/10.1016/j.clinthera.2010.01.012

Gubergrits N, Malecka-Panas E, Lehman GA, Vasileva G, Shen Y, Sander-Struckmeier S, Caras S and Whitcomb DC, 2011. A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. Alimentary Pharmacology and Therapeutics, 33, 1152–1161. https://doi.org/10.1111/j.1365-2036.2011.04631.x

Guérin V, Dubarryr M, Robic D, Brachet F, Rautureau M, André C, Bourbouze R and Tomé D, 2002. Microsphere entrapped bee-venom phospholipase A2 retains specific IgE binding capacity: a possible use for oral specific immunotherapy. Journal of Microencapsulation, 19, 761–765. https://doi.org/10.1080/02652040210162612

Kashirskaya NY, Kapranov NI, Sander-Struckmeier S and Kovalev V, 2015. Safety and efficacy of Creon® micro in children with exocrine pancreatic insufficiency due to cystic fibrosis. Journal of Cystic Fibrosis, 14, 275–281. https://doi.org/10.1016/j.jcf.2014.07.006

Kempf W, Oman H and Wüthrich B, 1999. Allergy to proteases in medical laboratory technicians: a new occupational disease? Journal of Allergy and Clinical Immunology, 104, 700–701. https://doi.org/10.1016/s0091-6749(99)70345-3

Littlewood JM, Connett GJ, Sander-Struckmeier S, Henniges F and Creon 40,000 Study Group, 2011. A 2-year post-authorization safety study of high-strength pancreatic enzyme replacement therapy (pancreatin 40,000) in cystic fibrosis. Expert Opinion on Drug Safety, 10, 197–203. https://doi.org/10.1517/14740338.2011.552499

Marti DL, Johnson RJ and Mathews KH Jr, 2011. Where's the (not) meat? By products from beef and pork production/LDP-M-209-01 (November 2011). A Report from the Economic Research Service/USDA. Available online:. https://www.thecattlesite.com/articles/3044/wheres-the-not-meat-byproducts-from-beef-and-pork/

Nollet LML and Toldrá F, 2011. Handbook of Analysis of Edible Animal By-Products. CRC Press. 471 p. Print ISBN: 978-1-4398-0360-8. eBook ISBN: 978-1-4398-0361-5.

Okano M, Nishizaki K, Satoskar AR, Yoshino T, Masuda Y and Harn DA Jr, 1999. Involvement of carbohydrate on phospholipase A2, a bee-venom allergen, in *in vivo* antigen-specific IgE synthesis in mice. Allergy, 54, 811–818. https://doi.org/10.1034/j.1398-9995.1999.00096.x

Perez-Riverol A, Lasa AM, Dos Santos-Pinto JRA and Palma MS, 2019. Insect venom phospholipases A1 and A2: roles in the envenoming process and allergy. Insect Biochemistry and Molecular Biology, 105, 10–24. https://doi.org/10.1016/j.ibmb.2018.12.011

Poulsen LK, 2004. Allergy assessment of foods or ingredients derived from biotechnology, gene-modified organisms, or novel foods. Molecular Nutrition and Food Research, 48, 413–423. https://doi.org/10.1002/mnfr.200400029

Sander-Struckmeier S, Beckmann K, Janssen-van Solingen G and Pollack P, 2013. Retrospective analysis to investigate the effect of concomitant use of gastric acid-suppressing drugs on the efficacy and safety of pancrelipase/pancreatin (CREON®) in patients with pancreatic exocrine insufficiency. Pancreas, 42, 983–989. https://doi.org/10.1097/MPA.0b013e31828784ef

Smyth RL, 1996. Fibrosing colonopathy and cystic fibrosis. Archives of Disease in Childhood, 74, 464–468. https://doi.org/10.1136/adc.74.5.464

van Kampen V, Brüning T and Merget R, 2016. Occupational allergies to trypsin and chymotrypsin. Pneumologie, 70, 442–445. https://doi.org/10.1055/s-0042-106509

Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, Sander-Struckmeier S and Caras S, 2010. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. American Journal of Gastroenterology, 105, 2276–2286. https://doi.org/10.1038/ajg.2010.201

Abbreviations

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
EINECS	European Inventory of Existing Commercial Chemical Substances
FAO	Food and Agricultural Organization of the United Nations
IUBMB	International Union of Biochemistry and Molecular Biology
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kDa	kiloDalton
RM	raw material

TOS	total organic solids
U	Unit
WHO	World Health Organization