Hydrolysed proteins

DOCUMENT M-CA, Section 9

LITERATURE DATA

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CA 9 LITERATURE DATA

Literature Review for Systematic Literature Search for the active substance "Hydrolysed Proteins"

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Background

Plant protection products are 'pesticides' that protect crops or desirable or useful plants. They are primarily used in the agricultural sector but also in forestry, horticulture, amenity areas and in home gardens. EU countries authorise plant protection products on their territory and ensure compliance with EU rules.

Hydrolysed proteins, originated from either plants or animals are used as plant protection products. These are used as attractant to trap the insects. Hydrolysed protein is a protein that has been hydrolysed or broken down into its component amino acids.

Proteins can cause a wide range of functional as well as adverse effects. As enzymes, they catalyse chemical reactions, certain proteins and peptides exhibit hormonal activity, and some act as antigens (i.e., allergens) or carrier molecules. On the other hand, peptide sequences from protein hydrolysates also can cause a wide range of functional as well as adverse effects. Development in the field of functional foods will no doubt address the impact of, for instance, bioactive peptides on human health. For example, milk protein-derived bioactive peptides are inactive within the sequence of the parent protein and can be released by enzymatic proteolysis during gut digestion or food processing. Once they are liberated in the human body, bioactive peptides may act as regulatory compounds with hormone-like activity (USEPA, 2000).

Protein hydrolysis: The method of choice for the hydrolysis of proteins depends on their sources. For example proteins from feathers, bristles, horns, beaks or wool contain the keratin structure and, therefore, are usually hydrolysed by acidic or alkaline treatment, or by bacterial keratinases. In contrast, animal products (e.g., casein, whey, intestine, and meat) and plant ingredients (e.g., soy, wheat, rice, pea, and cottonseed proteins) are often subject to general enzymatic or microbial hydrolysis. The hydrolysis of proteins by cell-free proteases, microorganisms, acids, or bases results in the production of protein hydrolysates (Hou et al., 2017).

In this document literature search was carried out for three types of hydrolysed proteins including animal tissue hydrolysate, beet molasses-urea hydrolysate and collagen protein hydrolysate.

Animal tissue hydrolysate: This is used in agriculture as a bait or food attractant of Diptera in crops of deciduous fruit trees, citrus and olives tress. It can also be used as a foliar spray in mixture with an insecticide, applied in some trees in some branches of trees in orchards and olive groves.

Beet molasses-urea hydrolysate: This is used in fields to control and suppress the population of olive-fly and Mediterranean fruit fly by spot bait sprays in combination with an insecticide.

Collagen protein hydrolysate: This is used as a foliar spray in mixture with an insecticide, applied in some trees in some branches of trees in orchards and olive groves and as a bait for trapping for flies.

To get more insight on the hydrolysed proteins a systematic bibliographic search was carried out. All the literature search was carried out and reported in accordance to EFSA guideline "Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009."

Identification and selection of scientific peer-reviewed open literature

For the literature search, a variety of relevant databases were chosen. A single concept search strategy was used. The search included references published up to January, 2018. The initial search was primarily carried out in the PubMed database. Followed by PubMed based search, the search was extended to other medical and toxicology databases to identify additional literature. The searched databases included, but was not limited to:

- Medline (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)
- CHEMID *plus* (http://chem.sis.nlm.nih.gov/chemidplus/setupenv.html)
- PubChem (https://pubchem.ncbi.nlm.nih.gov/)
- ECHA (https://echa.europa.eu/)
- AGRIS (http://agris.fao.org/agris-search/index.do)
- BPDB (https://sitem.herts.ac.uk/aeru/bpdb/index.htm)

In the above mentioned databases, a **single concept search strategy** was used. The following search terms were used.

- Hydrolysed protein
- Beet molasses Urea hydrolysate
- Collagen protein hydrolysate
- Animal tissue hydrolysate

Criteria for selecting the relevant articles

The main criteria for selecting the relevant articles from the above mentioned databases as per the EFSA guideline 2012 are as follows.

Data requirements on plant protection products based on chemical preparations (Annex III, part A, Directive 91/414/EEC):

- Toxicological studies (and exposure data) (OECD code: IIIA 7)
- Residues in or on treated products, food and feed (metabolism and residues studies) (OECD code: IIIA 8)
- Fate and behaviour in the environment (OECD code: IIIA 9)
- Ecotoxicological studies (OECD code: IIIA 10)
- Other data requirements for which information may have a direct or indirect effect on the overall risk assessment (OECD code: IIIA 1 - IIIA 2 - IIIA 3 - IIIA 4 - IIIA 5) (only data requirements under these points having a direct impact on the risk assessment need to be considered)

Table 1: Search process for Hydrolysed protein

Data requirement(s) captured in the search	Details of the searches					
Active substance only (Hydrolysed protein**) (covers all data requirements)**	**PubMed**	**ECHA**	**AGRIS**	**BPDB**	**PubChem**	**ChemIDplus**
	Justification for choosing the source: PubMed comprises over 22 million citations and abstracts for biomedical literature indexed in NLM's MEDLINE database, as well as from other life science journals and online books. PubMed citations and abstracts include the fields of biomedicine and health, and cover portions of the life sciences, behavioural sciences, chemical sciences, and bioengineering. PubMed also provides access to additional relevant websites and links to other NCBI resources, including its various molecular biology databases.	**Justification for choosing the source:** Resource for Information on the hazards, risks and safe use of chemical substances that registrant (company) manufacture or import	**Justification for choosing the source:** AGRIS is the International System for Agricultural Science and Technology providing access to bibliographic information on agricultural science and technology. It offers more than 8.9 million links to information produced by more than 350 data providers (which include research centres, development programs, international and national organizations) from more than 140 countries.	**Justification for choosing the source:** A comprehensive relational database of data relating to pesticides derived from natural substances.	**Justification for choosing the source:** A database of chemical molecules and their activities against biological assays.	**Justification for choosing the source:** A free, web search system that provides access to the structure and nomenclature authority files used for the identification of chemical substances

	Date of the search: 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	
	Date span of the search: 12th January 2008 – 13th January 2018	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	
	Date of the latest database update included in the search: Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Thursday 14 December 2017	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	
	Search strategies used for this data requirement (Publication dates: 10 years; Limit: Language- English)	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	
	(Hydrolysed[All Fields] AND ("proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])): 655 results	Hydrolysed protein	Hydrolysed protein: 536 Results	Hydrolysed protein	Hydrolysed protein	Hydrolysed protein	
	(Hydrolyzed[All Fields] AND ("proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields])): 3416 results	Hydrolyzed protein	Hydrolyzed protein: 1603 Results	Hydrolyzed protein	Hydrolyzed protein	Hydrolyzed protein	
	("ceratitis capitata"[MeSH Terms] OR ("ceratitis"[All Fields] AND "capitata"[All	-	Hydrolyzed protein AND Bactrocera oleae: 37 Results Rhagoletis cerasi AND Bait: 7 results	-	-	-	

	Fields]) OR "ceratitis capitata"[All Fields]) OR (("tephritidae"[MeSH Terms] OR "tephritidae"[All Fields] OR "rhagoletis"[All Fields]) AND cerasi[All Fields]) OR (("tephritidae"[MeSH Terms] OR "tephritidae"[All Fields] OR "bactrocera"[All Fields]) AND oleae[All Fields]) AND Bait[All Fields] AND English[lang]: 42 results		Ceratitis capitata AND Hydrolyzed protein: 18 results				
	Total number of summary records retrieved: 4071	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved: 2201**	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 0	
	Total number of summary records retrieved after removing duplicates						**n = 6272**

Table 2: Results of the study selection process, for each data requirement or group of data requirements searched-Hydrolysed protein

Data requirement(s) captured in the search (as indicated in Table 1)	n
Total number of summary records retrieved after all* searches of peer-reviewed literature (excluding duplicates)	6272
Number of summary records excluded from the search results after rapid assessment for relevance	6255
Total number of full-text documents assessed in detail*	17
Number of studies excluded from further consideration after detailed assessment for relevance	0
Number of studies not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	17

*both from bibliographic databases and other sources of peer-reviewed literature

Table 3: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by data requirement(s)-Hydrolysed protein

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements				
Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**
Mexican fruit fly, *Anastrepha ludens* (Loew), West Indian fruit fly, *Anastrepha obliqua* (Macquart), and Mediterranean fruit fly, Ceratitis capitata (Wiedemann)	Moreno et al.	2001	Field Evaluation of a Phototoxic Dye, Phloxine B, Against Three Species of Fruit Flies (Diptera: Tephritidae)	Journal of economic entomology. 2001 Dec;94(6):1419-27
Wild female oriental fruit fly (*Bactrocera dorsalis* (Hendel)), melon fly (*B. cucurbitae* (Coquillett)), and Mediterranean fruit fly (*Ceratitis capitata* (Wiedemann))	Pinero et al.	2010	A comparative assessment of the response of three fruit fly species (Diptera: Tephritidae) to a spinosad-based bait:	Bulletin of entomological research. 2011 Aug;101(4):373-81

			effect of ammonium acetate, female age, and protein hunger	
Mediterranean fruit fly, *Ceratitis capitate* (Wiedemann)	Pinero et al.	2015	Ammonium acetate enhances the attractiveness of a variety of protein-based baits to female Ceratitis capitata (Diptera: Tephritidae).	Journal of economic entomology. 2015 Mar 18;108(2):694-700
Anastrepha fraterculus (Wiedemann) and *Ceratitis capitata* (Wiedemann)	Silva et al.	2013	Neem derivatives are not effective as toxic bait for tephritid fruit flies. Journal of economic entomology	Journal of economic entomology. 2013 Aug 1;106(4):1772-9
European cherry fruit fly, *Rhagoletis cerasi*	Bockmann et al.	2014	Bait spray for control of European cherry fruit fly: an appraisal based on semi-field and field studies	Pest management science. 2014 Mar 1;70(3):502-9.
Bactrocera oleae	Canale et al.	2013	Ingestion toxicity of three Lamiaceae essential oils incorporated in protein baits against the olive fruit fly, Bactrocera oleae (Rossi)(Diptera Tephritidae)	Natural product research. 2013 Nov 1;27(22):2091-9
Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann) (Diptera: Tephritidae) and *Cryptolaemus montrouzieri* (Mulsant), *Neoseiulus californicus* (McGregor), and *Aphidius colemani* (Viereck)	Urbaneja et al.	2009	Chemical alternatives to malathion for controlling Ceratitis capitata (Diptera: Tephritidae), and their side effects on natural enemies in Spanish citrus orchards	Journal of economic Entomology, 102(1), pp.144-151
Bactrocera oleae	Varikou et al.	2016	Improvement of bait sprays for the	Crop Protection. 2016 Mar 1;81:1-8

			control of Bactrocera oleae (Diptera: Tephritidae). Crop Protection	
Bactrocera oleae	Varikou et al.	2015	Residual attractiveness of various bait spray solutions to Bactrocera oleae.	Crop Protection. 2015 Feb 1;68:60-6
Bactrocera oleae	Varikou et al.	2017	Refreshing bait spots in an olive orchard for the control of Bactrocera oleae (Diptera: Tephritidae).	Crop protection. 2017 Feb 1;92:153-9
Bactrocera oleae (Gmelin) (Diptera: Tephritidae)	Varikou et al.	2014	Comparative field studies of Bactrocera oleae baits in olive orchards in Crete.	Crop Protection. 2014 Nov 1;65:238-43
Bactrocera oleae	Ruiz Torres et al.	2007	Efficacy of treatments with tree-bait against olive fruit fly (Bactrocera oleae Gmel.; Diptera: Tephritidae) in province of Jaén (Spain).	Boletín de Sanidad Vegetal. Plagas (España). 2007
Rhagoletis cerasi	Haniotakis	1989	Control of the European cherry fruit fly *Rhagoletis cerasi* with bait sprays	In fruit flies of economic importance 87: proceedings of the CEC/IOBC International Symposium, Rome 7-10, April 1987/edited by R. Cavalloro 1989. Rotterdam: Published for the Commission of the European Communities by AA Balkema, 1989
Bactrocera oleae	Bjelis	2009	Control of olive fruit fly– Bactrocera oleae	Zbornik predavanj in referatov. 2009;9:397-401

			Rossi (Diptera, Tephritidae) by mass trapping and bait sprays methods in dalmatia.	
Bactrocera oleae	Goncalves and Torres	2013	The use of trap captures to forecast infestation by the olive fly, Bactrocera oleae (Rossi)(Diptera: Tephritidae), in traditional olive groves in north-eastern Portugal.	International journal of pest management. 2013 Oct 1;59(4):279-86.
Mexican fruit flies, *Anastrepha ludens*	Herrera et al.	2016	Comparison of hydrolyzed protein baits and various grape juice products as attractants for Anastrepha fruit flies (Diptera: Tephritidae).	Journal of economic entomology. 2015 Sep 22;109(1):161-6
Bactrocera oleae and *Candidatus Erwinia dacicola*	Pavlidi et al.	2017	Transcriptomic responses of the olive fruit fly *Bactrocera oleae* and its symbiont *Candidatus Erwinia dacicola* to olive feeding.	Scientific reports. 2017 Feb 22;7:42633

Table 4: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by author(s)-Hydrolysed protein

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements				
Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**
Bactrocera oleae	Bjelis	2009	Control of olive fruit fly–Bactrocera oleae Rossi (Diptera, Tephritidae) by mass	Zbornik predavanj in referatov. 2009;9:397-401

			trapping and bait sprays methods in dalmatia.	
European cherry fruit fly, *Rhagoletis cerasi*	Bockmann et al.	2014	Bait spray for control of European cherry fruit fly: an appraisal based on semi-field and field studies	Pest management science. 2014 Mar 1;70(3):502-9.
Bactrocera oleae	Canale et al.	2013	Ingestion toxicity of three Lamiaceae essential oils incorporated in protein baits against the olive fruit fly, Bactrocera oleae (Rossi)(Diptera Tephritidae)	Natural product research. 2013 Nov 1;27(22):2091-9
Bactrocera oleae	Goncalves and Torres	2013	The use of trap captures to forecast infestation by the olive fly, Bactrocera oleae (Rossi)(Diptera: Tephritidae), in traditional olive groves in north-eastern Portugal.	International journal of pest management. 2013 Oct 1;59(4):279-86.
Rhagoletis cerasi	Haniotakis	1989	Control of the European cherry fruit fly *Rhagoletis cerasi* with bait sprays	InFruit flies of economic importance 87: proceedings of the CEC/IOBC International Symposium, Rome 7-10, April 1987/edited by R. Cavalloro 1989. Rotterdam: Published for the Commission of the European Communities by AA Balkema, 1989
Mexican fruit flies, *Anastrepha ludens*	Herrera et al.	2016	Comparison of hydrolyzed protein baits and various grape juice products as attractants for Anastrepha fruit flies (Diptera: Tephritidae).	Journal of economic entomology. 2015 Sep 22;109(1):161-6
Mexican fruit fly, *Anastrepha ludens* (Loew), West Indian fruit fly, *Anastrepha obliqua* (Macquart),	Moreno et al.	2001	Field Evaluation of a Phototoxic Dye, Phloxine B, Against Three	Journal of economic entomology. 2001 Dec;94(6):1419-27

and Mediterranean fruit ßy, Ceratitis capitata (Wiedemann)			Species of Fruit Flies (Diptera: Tephritidae)	
Bactrocera oleae and *Candidatus Erwinia dacicola*	Pavlidi et al.	2017	Transcriptomic responses of the olive fruit fly *Bactrocera oleae* and its symbiont *Candidatus Erwinia dacicola* to olive feeding.	Scientific reports. 2017 Feb 22;7:42633
Wild female oriental fruit fly (*Bactrocera dorsalis* (Hendel)), melon fly (*B. cucurbitae* (Coquillett)), and Mediterranean fruit fly (*Ceratitis capitata* (Wiedemann))	Pinero et al.	2010	A comparative assessment of the response of three fruit fly species (Diptera: Tephritidae) to a spinosad-based bait: effect of ammonium acetate, female age, and protein hunger	Bulletin of entomological research. 2011 Aug;101(4):373-81
Mediterranean fruit fly, *Ceratitis capitate* (Wiedemann)	Pinero et al.	2015	Ammonium acetate enhances the attractiveness of a variety of protein-based baits to female Ceratitis capitata (Diptera: Tephritidae).	Journal of economic entomology. 2015 Mar 18;108(2):694-700
Bactrocera oleae	Ruiz Torres et al.	2007	Efficacy of treatments with tree-bait against olive fruit fly (Bactrocera oleae Gmel.; Diptera: Tephritidae) in province of Jaén (Spain).	Boletín de Sanidad Vegetal. Plagas (España). 2007
Anastrepha fraterculus (Wiedemann) and *Ceratitis capitata* (Wiedemann)	Silva et al.	2013	Neem derivatives are not effective as toxic bait for tephritid fruit flies. Journal of economic entomology	Journal of economic entomology. 2013 Aug 1;106(4):1772-9
Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann) (Diptera: Tephritidae) and *Cryptolaemus montrouzieri* (Mulsant), *Neoseiulus californicus* (McGregor), and *Aphidius colemani* (Viereck)	Urbaneja et al.	2009	Chemical alternatives to malathion for controlling Ceratitis capitata (Diptera: Tephritidae), and their side effects on natural enemies in Spanish citrus orchards	Journal of economic Entomology, 102(1), pp.144-151
Bactrocera oleae	Varikou et al.	2016	Improvement of bait sprays for the control	Crop Protection. 2016 Mar 1;81:1-8

			of Bactrocera oleae (Diptera: Tephritidae). Crop Protection	
Bactrocera oleae	Varikou et al.	2015	Residual attractiveness of various bait spray solutions to Bactrocera oleae.	Crop Protection. 2015 Feb 1;68:60-6
Bactrocera oleae	Varikou et al.	2017	Refreshing bait spots in an olive orchard for the control of Bactrocera oleae (Diptera: Tephritidae).	Crop protection. 2017 Feb 1;92:153-9
Bactrocera oleae (Gmelin) (Diptera: Tephritidae)	Varikou et al.	2014	Comparative field studies of Bactrocera oleae baits in olive orchards in Crete.	Crop Protection. 2014 Nov 1;65:238-43

Table 5: Search process for Beet molasses Urea hydrolysate

Data requirement(s) captured in the search	**Details of the searches**						
Active substance only (Beet molasses – urea hydrolysate**) (covers all data requirements)**	**PubMed**	**ECHA**	**AGRIS**	**BPDB**	**PubChem**	**ChemIDplus**	**Google (general search)**
	Justification for choosing the source: Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.
	Date of the search: 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 12th January 2018	**Date of the search:** 15th January 2018
	Date span of the search: 12th January 2008 – 13th January 2018	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable
	Date of the latest database update included in the search: Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Thursday 14 December 2017	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable
	Search strategies used for this data requirement (Publication dates: 10 years; Limit: Language- English)	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable

	Beet molasses Urea hydrolysate	Beet molasses Urea hydrolysate	Beet molasses Urea hydrolysate	Beet molasses Urea hydrolysate	Beet molasses Urea hydrolysate	Beet molasses Urea hydrolysate	Beet molasses Urea hydrolysate	
	Total number of summary records retrieved: 0	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 1	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 0	
	Total number of summary records retrieved after removing duplicates							**n = 1**

Table 6: Results of the study selection process, for each data requirement or group of data requirements searched- Beet molasses Urea hydrolysate

Data requirement(s) captured in the search (as indicated in Table 1)	n
Total number of summary records retrieved after all* searches of peer-reviewed literature (excluding duplicates)	1
Number of summary records excluded from the search results after rapid assessment for relevance	0
Total number of full-text documents assessed in detail*	1
Number of studies excluded from further consideration after detailed assessment for relevance	0
Number of studies not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0

*both from bibliographic databases and other sources of peer-reviewed literature

Table 7: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by data requirement(s)-Beet molasses Urea hydrolysate

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements				
Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**
All endpoints details	BPDB	Updated on December 2017	-	BPDB

Table 8: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by author(s)-Beet molasses Urea hydrolysate

Not applicable

Table 9: Search process for Collagen protein hydrolysate

Data requirement(s) captured in the search	**Details of the searches**						
Active substance only (Collagen protein hydrolysate**) (covers all data requirements)**	**PubMed**	**ECHA**	**AGRIS**	**BPDB**	**PubChem**	**ChemIDplus**	**Google (general search)**
	Justification for choosing the source: Same as mentioned in Table 1	**Justification for choosing the source:** Same as mentioned in Table 1	**Justification for choosing the source:** Same as mentioned in Table 1	**Justification for choosing the source:** Same as mentioned in Table 1	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1
	Date of the search: 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018
	Date span of the search: 15th January 2008 – 16th January 2018	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable
	Date of the latest database update included in the search: Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Thursday 14 December 2017	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable
	Search strategies used for this data requirement (Publication dates: 10 years; Limit: Language-English)	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable
	Collagen protein hydrolysate	Collagen protein hydrolysate	Collagen protein hydrolysate	Collagen protein hydrolysate	Collagen protein hydrolysate	Collagen protein hydrolysate	Collagen protein hydrolysate

	Total number of summary records retrieved: 116	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 48	**Total number of summary records retrieved:** 1	**Total number of summary records retrieved:** 1	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 1	
	Total number of summary records retrieved after removing duplicates							**n = 167**

Table 10: Results of the study selection process, for each data requirement or group of data requirements searched- Collagen protein hydrolysate

Data requirement(s) captured in the search (as indicated in Table 1)	n
Total number of summary records retrieved after all* searches of peer-reviewed literature (excluding duplicates)	167
Number of summary records excluded from the search results after rapid assessment for relevance	163
Total number of full-text documents assessed in detail*	4
Number of studies excluded from further consideration after detailed assessment for relevance	1
Number of studies not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	3

*both from bibliographic databases and other sources of peer-reviewed literature

Table 11: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by data requirement(s)- Collagen protein hydrolysate

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements				
Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**
Absorption	Watanabe-Kamiyama et al.	2010	Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats.	PubMed Journal of agricultural and food chemistry. 2009 Dec 3;58(2):835-41
Contact urticaria	Niinimaki et al.	1998	Contact urticaria from protein hydrolysates in hair conditioners	Google: Allergy. 1998 Nov 1;53(11):1078-82
All endpoints details	NA	Updated on December 2017	-	BPDB

NA: Not applicable

Table 12: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by author(s)- Collagen protein hydrolysate

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements

Data requirement (indicated by the corresponding OECD data point number)	Author(s)	Year	Title	Source
All endpoints details	NA	Updated on December 2017	-	BPDB
Contact urticaria	Niinimaki et al.	1998	Contact urticaria from protein hydrolysates in hair conditioners	Google: Allergy. 1998 Nov 1;53(11):1078-82
Absorption	Watanabe-Kamiyama et al.	2010	Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats.	PubMed Journal of agricultural and food chemistry. 2009 Dec 3;58(2):835-41

Table 13: Search process for Animal tissue hydrolysate

Data requirement(s) captured in the search	Details of the searches						
Active substance only (Animal tissue hydrolysate**) (covers all data requirements)**	**PubMed**	**ECHA**	**AGRIS**	**BPDB**	**PubChem**	**ChemIDplus**	**Google (general search)**
	Justification for choosing the source: Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.	**Justification for choosing the source:** Same as mentioned in Table 1.
	Date of the search: 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018	**Date of the search:** 15th January 2018
	Date span of the search: 15th January 2008 – 16th January 2018	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable	**Date span of the search:** Not applicable
	Date of the latest database update included in the search: Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Thursday 14 December 2017	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable	**Date of the latest database update included in the search:** Not applicable
	Search strategies used for this data requirement (Publication dates: 10 years; Limit: Language- English)	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable	**Search strategies used for this data requirement** Not applicable
	Animal tissue hydrolysate	Animal tissue hydrolysate	Animal tissue hydrolysate	Animal tissue hydrolysate	Animal tissue hydrolysate	Animal tissue hydrolysate	Animal tissue hydrolysate
	Total number of summary records retrieved: 154	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 26	**Total number of summary records retrieved:** 1	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 4 (only relevant articles are reflected here)

	Total number of summary records retrieved after removing duplicates			**n = 185**

Table 14: Results of the study selection process, for each data requirement or group of data requirements searched

Data requirement(s) captured in the search (as indicated in Table 1)	n
Total number of summary records retrieved after all* searches of peer-reviewed literature (excluding duplicates)	185
Number of summary records excluded from the search results after rapid assessment for relevance	180
Total number of full-text documents assessed in detail*	5
Number of studies excluded from further consideration after detailed assessment for relevance	0
Number of studies not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	5

*both from bibliographic databases and other sources of peer-reviewed literature

Table 15: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by data requirement(s)

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements				
Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**
Trapping of *Ceratitis capitata* (Weidmen)	Pezhman H	2016	Comparison of various protein hydrolysates for mass trapping of *Ceratitis capitata* (Weidmen) (Dip.: Tephritidae) in a pomegranate orchard in Shiraz region.	Google: Plant Pest Research. 2016;6(1)
Single dose toxicity study	Maeno et al.	2005	Studies of the Toxicological Potential of Tripeptides (L-Valyl-L-prolyl-L-proline and L-Isoleucyl-L-prolyl-L-proline): III. Single- and/or Repeated-Dose Toxicity of	Google: International Journal of Toxicology, 24(Suppl. 4):13–23, 2005

			Tripeptides-Containing Lactobacillus helveticus–Fermented Milk Powder and Casein Hydrolysate in Rats	
13-week toxicity study	Mizuno et al.	2005	Studies of the toxicological potential of tripeptides (L-Valyl-L-prolyl-L-proline and L-lsoleucyl-L-prolyl-L-proline): V. A 13-week toxicity study of tripeptides-containing casein hydrolysate in male and female rats	Google: International journal of toxicology, 24(4_suppl), pp.41-59.
Photosensitizing properties	Cavani et al.	2006	Photosensitizing properties of protein hydrolysate-based fertilizers	Google: Journal of agricultural and food chemistry. 2006 Nov 29;54(24):9160-7
All endpoints details	NA	Updated on December 2017	-	BPDB

NA: Not applicable

Table 16: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by author(s)

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements				
Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**
Photosensitizing properties	Cavani et al.	2006	Photosensitizing properties of protein hydrolysate-based fertilizers	Google: Journal of agricultural and food chemistry. 2006 Nov 29;54(24):9160-7
Single dose toxicity study	Maeno et al.	2005	Studies of the Toxicological	Google:

			Potential of Tripeptides (L-Valyl-L-prolyl-L-proline and L-Isoleucyl-L-prolyl-L-proline): III. Single- and/or Repeated-Dose Toxicity of Tripeptides-Containing Lactobacillus helveticus–Fermented Milk Powder and Casein Hydrolysate in Rats	International Journal of Toxicology, 24(Suppl. 4):13–23, 2005
13-week toxicity study	Mizuno et al.	2005	Studies of the toxicological potential of tripeptides (L-Valyl-L-prolyl-L-proline and L-lsoleucyl-L-prolyl-L-proline): V. A 13-week toxicity study of tripeptides-containing casein hydrolysate in male and female rats	Google: International journal of toxicology, 24(4_suppl), pp.41-59.
Trapping of *Ceratitis capitata* (Weidmen)	Pezhman H	2016	Comparison of various protein hydrolysates for mass trapping of *Ceratitis capitata* (Weidmen) (Dip.: Tephritidae) in a pomegranate orchard in Shiraz region.	Google: Plant Pest Research. 2016;6(1)
All endpoints details	NA	Updated on December 2017	-	BPDB

APPENDICES

APPENDIX A – List of end points for the active substance and the representative formulation

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name)	**Animal tissue Hydrolysate (under the general term Hydrolysed Protein)**	**Beet molasses-Urea Hydrolysate (under the general term Hydrolysed Protein)**	**Collagen Protein Hydrolysate (under the general term Hydrolysed Protein)**
Function (*e.g.* fungicide)	Insect attractant	Insect attractant	Insect attractant
Rapporteur Member State	Greece	Greece	Greece

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	Not applicable.	Not applicable.	Not applicable.
Chemical name (CA)	Not applicable.	Not applicable.	Not applicable.
CIPAC No	901	901	901
CAS No	Not applicable.	Not applicable.	Not applicable.
EC No (EINECS or ELINCS)	Not applicable.	Not applicable.	Not applicable.
FAO Specification (including year of publication)	None.	None.	None.
Minimum purity of the active substance as manufactured	≥ 35.0 % w/w	Hydrolysed protein (Crude protein eq.) min 50% w/w; Urea 17% w/w	Aminoacids and peptides mixture: 32-42% and Molass: 10 - 14%
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	None.	None.	None.
Molecular formula	Not applicable.	Not applicable.	Not applicable.

Molecular mass	Not applicable.	Not applicable.	Not applicable.
Structural formula	Not applicable.	Not applicable.	Not applicable.

Physical and chemical properties (Annex IIA, point 2): Open (data gaps)

	Animal tissue Hydrolysate (under the general term Hydrolysed Protein)	**Beet molasses-Urea Hydrolysate (under the general term Hydrolysed Protein)**	**Collagen Protein Hydrolysate (under the general term Hydrolysed Protein)**
Melting point (state purity)	Near 0ºC		below 4ºC
Boiling point (state purity)	102ºC		
Temperature of decomposition (state purity)			
Appearance (state purity)	Dark brown liquid at 20ºC (≥ 35.0% w/w)	Deep reddish brown; liquid Hydrolysed protein (Crude protein eq.) min 50% w/w; Urea 17% w/w	Brown coloured liquid; Aminoacids and peptides mixture: 32-42% and Molass: 10 - 14%
Vapour pressure (state temperature, state purity)			
Henry’s law constant			
Solubility in water (state temperature, state purity and pH)	Very soluble in water pH 4.5 – 5.5 at 20ºC	Insoluble in water: max 0,7%; pH normal value : 6.75 pH range 6.2-8.0(7.3)*	Complete soluble in water; pH relative to 10% w/w solution: 3.5-4.5
Solubility in organic solvents (state temperature, state purity)	Soluble in polar organic solvents Partially soluble in non-polar organic solvents		
Surface tension (state concentration and temperature, state purity)			
Partition co-efficient (state temperature, pH and purity)			
Dissociation constant (state purity)			

UV/VIS absorption (max.) incl. (state purity, pH)			
Flammability (state purity)	Non-flammable	Non-flammable	Can cause explosion if exposed to sparks and flames
Density	1.10 g/mL at 20ºC	1.35 g/mL	1.22-1.28 g/mL

*: pH value 7.3 may appear after 1 year of storage. The maximum pH value 8.0 may appear after two years of storage with no other effect on specifications and no significant effect on application as when diluted in application rates gives lower pH.

Activity against pests

Baiting is a method which is used to reduce adult fruit fly numbers. Bait sprays consist of a liquid food (protein) attractant and an insecticide. Baits are generally sprayed on to the foliage and trunks of trees and plants. Both the male and female adult flies are attracted to the baits while foraging over the leaves for food and are poisoned after feeding on the spray droplets.

Efficacy of different bait sprays (hydrolysed proteins) were investigated against various fruit flies. The bait is prepared by hydrolysed protein obtained from various sources. The details of these baits are provided in below table.

Efficacy of different bait sprays

Type of bait	Pest	Efficacy	Reference
Biocebo (animal tissue hydrolysate)	*Chrysopa sp* and Vespid wasps	The maximum captured moths were observed in traps baited with Biocebo (6.07 numbers) compared to other formulations	Pezhman et al., 2016
Xanthene dye phloxine B (D&C Red #28) bait	Mexican fruit fly, *Anastrepha ludens* (Loew), West Indian fruit fly, *Anastrepha obliqua* (Macquart), and Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann)	Toxic activity of phloxine B against these fruit flies is as good as that of malathion-bait sprays. Also, the type of protein used with phloxine B can dramatically influence its efficacy	Moreno et al., 2001
Seven commercially available protein baits 1) Nu-Lure Insect Bait (44% corn gluten meal, hydrolysed); 2) Buminal (38.67% hydrolyzed protein); 3) Bugs 4 Bugs AY50 Yeast Autolysate (50% yeast autolysate); 4) DacGel Fruit Fly Bait Powder (yeast protein autolysate and natural soluble mucilage); 5) MazofermE802 (44% protein condensed fermented corn extract; 6) Solulys 095E (44% Protein Corn Steep; 7) Provesta STT-F Yeast Extract (44% yeast extract)	Mediterranean fruit fly, *Ceratitis capitate* (Wiedemann)	The addition of ammonium acetate to commercially available proteinaceous baits and to beer waste can greatly improve their attractiveness to *C. capitata*, potentially increasing the bait's effectiveness for fruit fly monitoring and suppression.	Pinero et al., 2010
Spinosad based GF-120 NF Naturalyte Fruit Fly Bait© formulated to	Wild female oriental fruit fly (*Bactrocera dorsalis* (Hendel)), melon fly (*B. cucurbitae*	The effects of varying amounts of ammonium acetate present in GF-120 can be modulated by the physiological stage of the female flies and that the response of	Pinero et al, 2015

contain either 0, 1 or 2% ammonium acetate	(Coquillett)), and Mediterranean fruit fly (*Ceratitis capitata* (Wiedemann))	female B. cucurbitae to GF-120 was consistently greater than that of *B. dorsalis* over the various ages and levels of protein starvation regimes evaluated.	
Neem (*Azadirachta indica* A. Juss) products in baits	*Anastrepha fraterculus* (Wiedemann) and *Ceratitis capitata* (Wiedemann)	The estimated LCs_{50} values for *A. fraterculus* and *C. capitata* were 7522 ppm (18.40 ppm of azadirachtin) and 1368 ppm (3.35 ppm of azadirachtin), respectively, using an aqueous extract of neem seeds in bait after 10 d of experimentation. No significant differences in the mortality of *A. fraterculus* and *C. capitata* adults exposed to baits made from different extracts and neem oil were observed after 3 h or 2 or 6 day.	Silva et al., 2013
Bait sprays containing two families of plant-derived insecticides: azadirachtins (NeemAzal-T and NeemAzal-T/S) and pyrethrins (Spruzit Neu)	European cherry fruit fly, *Rhagoletis cerasi*	Bait sprays containing neem are a promising alternative for the management of *R. cerasi*, especially where the risk of immigration of fertilised females is low, as in isolated orchards or as part of area-wide treatments.	Bockmann et al., 2014
Lamiaceae essential oils (EOs) - Hyptis suaveolens, Rosmarinus officinalis and Lavandula angustifolia - incorporated in protein baits	*Bactrocera oleae*	All the tested EOs showed dose-dependent toxicity on *B. oleae*, with mortality rates ranging from 12% (EO concentration: 0.01% w:v) to 100% (EO concentration: 1.75% w:v)	Canale et al., 2013
Baited insecticides	Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann) (Diptera: Tephritidae) and *Cryptolaemus montrouzieri* (Mulsant), *Neoseiulus californicus* (McGregor), and *Aphidius colemani* (Viereck)	A high Mediterranean fruit fly mortality was obtained for all baited insecticides (phosmet and spinosad) except lambdacyhalothrin, which caused the lowest mortality and showed a novel disabling effect on surviving Mediterranean fruit fly adults. Spinosad proved to be the most selective bait treatment for *C. montrouzieri* and *N. californicus*, whereas for *A. colemani* the most selective bait was phosmet and lambda-cyhalothrin.	Urbaneja et al., 2009
The trophical attractant (hydrolysed protein at 75% w/w) mixed with alpha-cypermethrin, thiacloprid, thiacloprid + deltamethrin or dimethoate,	*Bactrocera oleae*	All of the bait spraying solutions of the tested products were effective against *B. oleae* at all of the doses tested and resulted in significantly lower olive fly populations compared with the standard recommended dose, which was indicated by the fly catches in the nets of McPhail traps within the experimental plots.	Varikou et al 2016

Two formulations of hydrolysed proteins at 55% and 75% w/w mixed with various insecticides (alpha-cypermethrin, lambda-cyhalothrin and dimethoate) and a spinosad solution, applied either in McPhail traps or sprayed in olive foliage (except lambda-cyhalothrin),	*Bactrocera oleae*	Among all bait spraying solutions tested against *B. oleae*, the highest catches were recorded with both protein solutions of alpha-cypermethrin; its capture rate ranged from 7.6 to 10.5 olive fruit flies/trap/solution age (seven measurements were made when the trap solution was changed at 3, 7, 10, 14, 17, 20 and 24 days after its preparation). A three-day-old solution of any protein mixed with alpha-cypermethrin was significantly more attractive to olive fruit flies (at least three times) compared with the solutions at other ages, as indicated by the capture of flies in the McPhail traps. No differences were observed among solution ages for dimethoate solutions or spinosad solutions (less than 6 olive fruit flies/trap/week). When olive foliage was sprayed with the solutions under field conditions, they attracted approximately 0.3–1.5 adults per day for a 10-day period. The highest number of flies was recorded on both proteins combined with or without alpha-cypermethrin solution, as indicated by the catches on sticky transparent panels. Finally, changes in the pH values of the aforementioned solutions over time were associated with increased fly catches.	Varikou et al., 2015
A bait spraying solution (alpha-cypermethrin plus hydrolysed protein at 75% w/w)	*Bactrocera oleae*	Significantly reduced olive fruit fly captures in treated plots compared to the captures recorded in plots with the classical bait spray. The percentages of live infestation of *B. oleae* were very low (<2%) and did not differ significantly between the two tested practices.	Varikou et al., 2017
Two formulations of hydrolysed proteins equal to 55% and 75% w/w) at 0.5, 1, 2, 4 and 8% concentrations	*Bactrocera oleae* (Gmelin) (Diptera: Tephritidae)	Lower concentrations than the 2% concentration recommended for both tested proteins (highest captures of 31.4 olive fruit flies/trap/week were recorded at 1% for protein equal to 55% and 28.5 at 0.5% for protein equal to 75%) were also attractive to olive fruit flies, whereas 8% was the least attractive concentration for both attractants (18.7 and 9.9 olive fruit fly/trap/week respectively).	Varikou et al., 2014
Protein (food bait) and pheromone in olive tree, around of other tree without applications. In this method, olive tree treatments are only 20-25% of total. Insecticide applied was dimethoate, spinosad and imidacloprid.	*Bactrocera oleae*	Treatment against olive fruit fly with tree-bail was applied in 2004 and 2005. In all years, pest was controlled under limits accepted in oil extraction factories. This method with tree-bait is a good alternative for aerials bait treatments.	Ruiz Torres et al., 2007
Bait spray	*Rhagoletis ceratis*	Bait sprays were timed on the basis of fly numbers caught on yellow sticky panels with ammonium bicarbonate dispensers were very effective in suppressing population and economical as well. Experimental results suggest one bait spray accurately timed will be enough to maintain pest population density to subeconomic levels for a number of years	Haniotakis, 1989

Bait Spray/mass trapping	*Bactrocera oleae*	Control of olive fruit fly was evaluated by mass trapping and bait sprays methods in dalmatia. Evaluation shows no difference between average number of olive fruit flies captured on control traps during experiment on bait spray and mass trapping method. Evaluation of effectiveness showed higher effectiveness of mass trapping method in comparation with seven bait spray treatments. Evaluation of effectiveness results confirmed high effectiveness of both improved methods.	Bjelis, 2009
Yellow sticky traps baited with pheromone, and McPhail traps baited with diammonium phosphate	*Bactrocera oleae*	The variation in infestation is explained by captures of adults in both traps. Thus, even if infestation has changed significantly between years as well as groves and olive tree varieties, captures obtained by both types of trap can be valuable indicators of fruit infestation in Terra Quente, and probably in other regions that have a continental Mediterranean climate.	Goncalves and Torres, 2013
CeraTrap, an enzymatic hydrolyzed protein,	Mexican fruit flies, *Anastrepha ludens*	Attraction to grape lures was compared with CeraTrap and the standard protein Captor +borax trap. In general, CeraTrap was more attractive than different commercial grape products in several experiments.	Herrera et al., 2016

Methods of Analysis

No data available for all the three hydrolysates

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of absorption

Collagen Protein Hydrolysate

Absorption: Collagen, a major extracellular matrix macromolecule, is widely used for biomedical purposes. The absorption mechanism of low molecular weight collagen hydrolysate (LMW-CH) was investigated in rats. When administered to Wistar rats with either [^{14}C] proline (Pro group) or glycyl-[^{14}C] prolyl-hydroxyproline (CTp group), LMW-CH rapidly increased plasma radioactivity. LMW-CH was absorbed into the blood of Wistar rats in the peptide form. Glycyl-prolylhydroxyproline tripeptide remained in the plasma and accumulated in the kidney. In both groups, radioactivity was retained at a high level in the skin until 14 days after administration (Watanabe-Kamiyama et al., 2010).

No data available for beet molasses urea hydrolysate and animal tissue hydrolysate.

Distribution: No data available

Potential for accumulation: No data available

Rate and extent of excretion: No data available

Metabolism in animals: No data available

Toxicologically relevant compounds (animals and plants): No data available

Toxicologically relevant compounds (environment): No data available

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	Data available for animal tissue hydrolysate*
Rabbit LD_{50} dermal	No data available
Rat LC_{50} inhalation	No data available
Skin irritation	No data available
Eye irritation	No data available
Skin sensitisation	Data available for animal tissue hydrolysate*

*- details of studies are provided below

Acute oral study:

Animal tissue hydrolysate

LD_{50} > 2000 mg/kg rat

On the basis of the experimental results, interpreted according to Italian Ministerial Decree dated April 28, 1997, the product is classified “NON TOXIC”. On the basis of the results, interpreted according to OECD No 420 dated 17th December 2001, the product is included in the category 5 of the GHS classification (Greece, 2011; DAR, Vol 1, 2008).

Single dose toxicity study of casein hydrolysate was conducted at the dose level of 2000 mg/kg. Gross observations, body weight, and food consumption parameters or postmortem (necropsy) did not exhibit any evidence of either systemic or local toxicity (Maeno et al., 2005).

Sensitisation: Protein hydrolysates of hair cosmetics can cause contact urticaria, especially in patients with atopic dermatitis (Niinimaki et al., 1998).

The photosensitising properties of protein hydrolysate-based fertilizers (PHFs; animal origin) were investigated in water solutions (0.8 g of total organic carbon/L) within the wavelength range of 300-450 nm, using furfuryl alcohol (FA) as a probe to test the involvement of singlet oxygen and Irgarol 1051 as an example of organic pollutant. PHFs photosensitise the transformation of FA (10^{-4} M), and the kinetics of FA disappearance follows an apparent first-order rate law. The photosensitising properties of PHFs might be due to pigments naturally present in tissues from which they are extracted or to compounds generated during the production processes (Cavani, 2006).

Short term toxicity (Annex IIA, point 5.3)

Only one 91-days repeated dose toxicity study was identified with casein hydrolysate (animal tissue hydrolysate)

Target / critical effect: No

Relevant oral NOAEL: 1000 mg/kg/day*

Relevant dermal NOAEL: Not data available

Relevant inhalation NOAEL: Not data available

No relevant short term toxicity data was identified with other two hydrolysate (beet molasses urea hydrolysate and collagen protein hydrolysate)

***Repeat dose toxicity study for casein hydrolysate (animal tissue hydrolysate):** Groups of 12 male and 12 female Charles River rats were administered once daily doses of 0, 40, 200, or 1000 mg of powdered casein hydrolysate. Powdered casein hydrolysate (CH) known to contain 0.6% VPP (L-valyl-L-prolyl-Lproline) plus IPP (L-isoleucyl-L-prolyl-L-proline). All rats survived until the scheduled termination of the study and no treatment-related clinical signs were observed. Food consumption was unaffected by administration of CH. All animals gained weight and there were no statistical differences between groups with respect to weight gains. There were no meaningful changes in haematological or coagulation parameters. Mid- and high-dose males (but not females) had slightly (<2%) increased mean serum chloride concentrations, but because the difference was so small and it was observed in only one sex, the authors considered its association with CH administration to be doubtful. Urinalysis revealed the occasional presence of crystals, leukocytes, and epithelial cells in animals from all experimental groups. Similarly, ophthalmic changes (lenticular clouding) were observed in both control and dosed animals. Mean relative (to body weight) kidney weight was decreased by 8% in low-dose males and mean relative uterus weight was elevated 46% in low-dose females. Absolute organ weights were not affected. Only naturally occurring microscopic changes were observed in all groups and none could be attributed to CH administration. It was concluded that, under the conditions of these experiments, the maximally tolerated dose (MTD) and **the no-observable effect level (NOEL)** for powdered CH administered once daily for 13 weeks was **greater than 1000 mg/kg/day** or greater than 6 mg of VPP plus IPP/kg BW/day.

There was no evidence of target organ toxicity associated with administration of the tripeptides. This corresponds to a margin of safety (MOS) of 60 based upon current thinking regarding incorporation in food (Mizuno et al., 2005).

Genotoxicity (Annex IIA, point 5.4): No data available

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect Relevant NOAEL Carcinogenicity	No data available

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity Reproduction target / critical effect Relevant parental NOAEL Relevant reproductive NOAEL Relevant offspring NOAEL	No data available

Developmental toxicity **Developmental target / critical effect** Relevant maternal NOAEL Relevant developmental NOAEL Relevant developmental neurotoxicity NOAEL	No data available

Neurotoxicity (Annex IIA, point 5.7) Acute neurotoxicity	No data available

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies	No data available
Studies on metabolites	No data available
Studies on impurities	No data available

Medical data (Annex IIA, point 5.9)

No data available

Summary (Annex IIA, point 5.10)

No data available

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI	No data available	-	
AOEL	No data available	-	
ARfD	No data available	-	

Dermal absorption (Annex IIIA, point 7.3)

No data available

Exposure scenarios (Annex IIIA, point 7.2)

Operator	No data available
Workers	No data available
Bystanders	No data available

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

Animal tissue Hydrolysate (under the general term Hydrolysed Protein)	Beet molasses-Urea Hydrolysate (under the general term Hydrolysed Protein)	Collagen Protein Hydrolysate (under the general term Hydrolysed Protein)
Not classified*	Not classified*	Not classified*

*: Due to lack of proved toxicity of hydrolysed proteins, they are not classifiable for any labelling.

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

No data available
No data available
-

Plant groups covered	No data available
Rotational crops	-
Metabolism in rotational crops similar to metabolism in primary crops?	-
	-
Processed commodities	-

Residue pattern in processed commodities similar to residue pattern in raw commodities? Plant residue definition for monitoring

Plant residue definition for risk assessment

Conversion factor (monitoring to risk assessment)

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	No data available
Time needed to reach a plateau concentration in milk and eggs	-
Animal residue definition for monitoring	-
Animal residue definition for risk assessment	-
Conversion factor (monitoring to risk assessment)	-
Metabolism in rat and ruminant similar (yes/no)	-
Fat soluble residue: (yes/no)	-

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

-

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

-

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

No data available

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	-	-	-

Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	-	-	-
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices: Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-	-	-
Eggs	-	-	-

Summary of residues data according to the representative uses on raw agricultural commodities and feeding stuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

No supervised studies were conducted since hydrolysed protein is exempted from the requirement of residues data.

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	No data available
TMDI (% ADI) according to WHO European diet	-
TMDI (% ADI) according to EFSA PRIMo Model rev.2A	-
TMDI (% ADI) according to national (to be specified) diets	-
IEDI (WHO European Diet) (% ADI)	-
NEDI (specify diet) (% ADI)	-
Factors included in IEDI and NEDI	-
ARfD	No data available
IESTI (% ARfD) according to EFSA PRIMo Model rev.2A	-
NESTI (% ARfD) according to national (to be specified) large portion consumption data	-
Factors included in IESTI and NESTI	-

Hydrolysed proteins as a plant protection product is likely to be of low toxicity and a quantitative consumer risk assessment is not needed unless the required technical specification raises a toxicological concern.

A data gap may be required to reconsider the consumer risk assessment through dietary intake and drinking water pending the outcome of the outstanding data on the specification and on the groundwater exposure assessment.

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)
No study provided. Not required according to the representative uses

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

	No data

Degradation fate of hydrolysed protein

Animal tissue hydrolysate

Hydrolyzed proteins are natural compounds from the hydrolysis of living organism' tissues that can have vegetable or animal origin. Proteins are the most abundant organic molecule in cells. They constitute the 50% of the dry weight of cells, or even more. They can be found in every single cell, since they are fundamental in all aspects of the cell structure and function.

The hydrolysed proteins are biodegradable, so their persistence in the environment is very short, without any tendency for bioaccumulation (Greece, 2011; DAR, Vol 1, 2008).

Due to the nature of the hydrolysed proteins and its characteristics regarding its fate and behaviour in the environment. It could be considered very considered very unlikely the existence of relevant residues of hydrolysed proteins in the soil delivered from the application of formulated products containing hydrolysed proteins (Greece, 2011; DAR, Vol 1, 2008).

Beet molasses-Urea hydrolysate

It is totally biodegradable and hydrolysate has minimum risk for the environment (Greece, 2011; DAR, Vol 1, 2008).

Collagen protein hydrolysate

The product is completely degradable but if present in copious quantities can pollute ground and surface waters. The product is constituted by natural substances and consequently is completely biodegradable and have no negative effect on the environment (Greece, 2011; DAR, Vol 1, 2008).

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days	No data available
Non-extractable residues after 100 days	No data available
Metabolites requiring further consideration - name and/or code, % of applied (range and maximum)	No data available

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation	
Mineralization after 100 days	No data available
Non-extractable residues after 100 days	No data available
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	No data available
Soil photolysis	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	No data available

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies

Hydrolysed Protein	Aerobic conditions: No data available

Field studies

Hydrolysed Protein	Aerobic conditions: No data available

pH dependence (yes / no) (if yes type of dependence)	No data available
Soil accumulation and plateau concentration	No data available

Laboratory studies

Hydrolysed Protein	Anaerobic conditions: No data available

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Hydrolysed Protein: No data available

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching	No data available
Aged residues leaching	No data available
Lysimeter/ field leaching studies	No data available

PEC (soil) (Annex IIIA, point 9.1.3)

Hydrolysed Protein	No data available
Method of calculation Application data	-

Route and rate of degradation in water (Annex IIA, point 7.2.1)

	No data available
	No data available

Hydrolytic degradation of the active substance and metabolites > 10 %	No data available
Photolytic degradation of active substance and metabolites above 10 %	No data available

Quantum yield of direct phototransformation in water at ∑ > 290 nm

Readily biodegradable (yes/no)

Degradation in water / sediment

Hydrolysed Protein	No data available

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Hydrolysed Protein Parameters used in FOCUSsw step 1 and 2	No data available
Parameters used in FOCUSsw step 3 (if performed)	-
Application rate	-

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	No data available
Application rate	-

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air	No data available
Quantum yield of direct phototransformation	No data available
Photochemical oxidative degradation in air	No data available
Volatilisation	No data available
Metabolites	-

PEC (air)

Method of calculation No data available

PEC(a)

Maximum concentration	-

Residues requiring further assessment

Environmental occurring residues requiring further assessment by other disciplines (toxicology and ecotoxicology) and or requiring consideration for groundwater exposure	Soil: animal tissue hydrolysate, beet molasses urea hydrolysate, collagen protein hydrolysate Groundwater: animal tissue hydrolysate, beet molasses urea hydrolysate, collagen protein hydrolysate Surface water/sediment: animal tissue hydrolysate, beet molasses urea hydrolysate, collagen protein hydrolysate Air: animal tissue hydrolysate, beet molasses urea hydrolysate, collagen protein hydrolysate

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	-
Surface water (indicate location and type of study)	-
Ground water (indicate location and type of study)	-
Air (indicate location and type of study)	-

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

A data gap needs to be filled before a conclusion may be drawn.

Effects on Non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1; Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals	No data available
Acute toxicity to birds	No data available
Dietary toxicity to birds	No data available
Reproductive toxicity to birds	No data available
Reproductive/long term toxicity to mammals	No data available

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Exposure period	**Crop, use pattern**	**Category (*e.g.*, insectivorous bird)**	**Toxicity endpoint**	**ETE [mg ai/kg bw/day]**	**TER**	**TER risk trigger (from Annex VI)**
Acute						
Short-term						
Long-term						

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Treatment	**Species**	**Study Type**	**LC_{50} /EC_{50}** [mg ai/L]	**LC_0 /NOEC** [mg ai/L]
No data available				

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Organism	**Test substance**	**Toxicity Endpoint**	**PEC (µg/L)**	**TER**	**TER risk trigger value (from 91/414/EEC)**

Bioconcentration

Bioconcentration factor (BCF)	No data available
Annex VI Trigger for the bioconcentration factor	-
Clearance time (CT_{50}) (CT_{90})	-
Level of residues (%) in organisms after the 14 day depuration phase	-

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity	No data available
Acute contact toxicity	No data available

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Test substance	Exposure route	Endpoint	Maximum single application rate	Hazard quotient	Annex VI trigger
Field or semi-field tests					

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Test	Test species	Summary of design	Endpoints
No data available			

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity	No data available
Chronic and reproductive toxicity	No data available

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Test substance	Use pattern	Test type	Endpoint	PECs (µg/kg)	TER	Annex VI trigger

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization	No data available
Carbon mineralization	No data available

Effects on non-target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Preliminary screening data

No data available

Laboratory dose response tests

Most sensitive species	Test substance	ER_{50} (g/ha)[2] vegetative vigour	ER_{50} (g/ha)[2] emergence	Exposure[1] (g/ha)[2]	TER	Trigger
No data available						

Additional studies (e.g. semi-field or field studies)

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	end point
Activated sludge	No data available
Pseudomonas sp	No data available

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	-
water	-
sediment	-
groundwater	-

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

Active substance

RMS/peer review proposal
No data available

Preparation

RMS/peer review proposal
No data available

In conclusion, hydrolysed proteins *per se* are likely to be of low toxicological concern and no risks to human health could be expected from the use as a plant protection product. However due to the fact that a specification to include the main components in the active substance is still outstanding, a final conclusion cannot be drawn whether the technical specification is of toxicological concern and whether data waivers can be accepted and reference values are needed; therefore, a data gap and issues that cannot be finalised were identified (EFSA, 2012).

Abbreviation

°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
ADE	actual dermal exposure
ADI	acceptable daily intake
AGRIS	International System for Agricultural Science and Technology
AOEL	acceptable operator exposure level
ARfD	acute reference dose
BCF	bioconcentration factor
BPDB	Bio pesticide database
bw	body weight
CAS	Chemical Abstracts Service
CH	Collagen hydrolysate
CIPAC	Collaborative International Pesticides Analytical Council Limited
d	day
ECHA	European Chemical Agency
EINECS	European Inventory of Existing Commercial Chemical Substances
ER_{50}	emergence rate/effective rate, median
EU	European Union
FA	furfuryl alcohol
FAO	Food and Agriculture Organisation of the United Nations
g	gram
IPP	L-isoleucyl-L-prolyl-L-proline
IUPAC	International Union of Pure and Applied Chemistry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
MRL	maximum residue limit or level
MSDS	material safety data sheet
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
PEC	predicted environmental concentration
pH	pH-value
PHFs	Protein hydrolysate-based fertilizers
SC	suspension concentrate
SD	standard deviation
TER	toxicity exposure ratio
TK	technical concentrate
TMDI	theoretical maximum daily intake
TWA	time weighted average
UV	ultraviolet
VPP	L-valyl-L-prolyl-Lproline
WHO	World Health Organisation

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