Hydrolysed proteins

DOCUMENT M-CA, Section 6

RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Version history[1]

Date	Data points containing amendments or additions and brief description	Document identifier and version number

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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CA 6 RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED (BIO)

In the initial application dossier, BIOIBERICA requested the exemption of hydrolysed proteins from animal origin of the requirement of residue data based upon the consideration that the biotic degradation of the hydrolysed proteins results in more simple metabolites like peptides and amino acids. These compounds have no insecticide activity, they are only superficial and they disappear easily with a quick wash or by the rainfall action. Peptides and amino acids are present in living cells, and consequently, they are not considered real waste, since they can be used again by the same living cells in the protein synthesis.

The metabolites that come from the degradation of the formulated product are identical to those that exist in cells in a natural way. Therefore, any analysis of residues would not be capable of determining them. These arguments were found acceptable and no residue data was deemed necessary, as stated in the Draft Assessment Report made by Greece.

The presented rationale was accepted by EFSA and no residue data was considered necessary. No plant metabolism or residues studies were performed during the process of inclusion in Annex I and no definition of residues were established for either monitoring and control, or risk assessment purposes.

No trials were presented either in support of the requested uses, taking into consideration:

- Hydrolysed proteins mainly originate from the hydrolysis of natural proteins, and mostly consist of amino acids and small peptides, undistinguishable from those present naturally in the crop, whether originating in the actual plant or having an exogenous origin in other organisms.
- They are used as attractant substance and have no insecticide capacity per se
- Hydrolysed Proteins derive from hydrolytic cleavage of natural proteins, and are mainly composed by amino acids and small peptides. Because of that, there is no way to distinguish between the hydrolysed proteins coming from the active substance and those formed by field degradation of proteins from living organisms.
- Hydrolysed Proteins are used as an attractant substance. It doesn't have any pesticide effect by itself, thus, it has to be mixed with properly authorized insecticides.

In addition, in the Peer Review (EFSA Journal 2012; 10 (2): 2545) it was noted that hydrolysed proteins are of low toxicity (following pages).

The following pages are a summary of the main aspects assessed in the residues section during the process for inclusion in Annex I of hydrolysed proteins, and the EU-wide agricultural practices evaluated and authorised and the results of the residues testing supported by those practices.

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

Plant groups covered	No study provided. Not required according to the representative uses(1).
Rotational crops	No study provided. Not required according to the representative uses(1).
Metabolism in rotational crops similar to metabolism in primary crops?	Not relevant.
Processed commodities	No study provided. Not required according to the representative uses(1).
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not relevant.
Plant residue definition for monitoring	Not required(1).
Plant residue definition for risk assessment	Not required(1).
Conversion factor (monitoring to risk assessment)	Not applicable

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

Animals covered	No study provided. Not required according to the representative uses(1).
Time needed to reach a plateau concentration in milk and eggs	Not relevant
Animal residue definition for monitoring	Not required(1).
Animal residue definition for risk assessment	Not required(1).
Conversion factor (monitoring to risk assessment)	Not relevant
Metabolism in rat and ruminant similar (yes/no)	Not relevant
Fat soluble residue: (yes/no)	Not relevant

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

Not relevant(1)

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

Not relevant(1)

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

No study provided. Not required according to the representative uses(1).

	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)	Not Required	Not Required	Not Required

Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Not Required	Not Required	Not Required
	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 feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

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

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
No study provided. Not required according to the representative uses[1].						

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use
(c) Highest residue

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

ADI	No data available[1]
TMDI (% ADI) according to WHO European diet	Not required[1]
TMDI (% ADI) according to EFSA PRIMo Model rev.2A	Not required[1]
TMDI (% ADI) according to national (to be specified) diets	Not required[1]
IEDI (WHO European Diet) (% ADI)	Not required[1]
NEDI (specify diet) (% ADI)	Not required[1]
Factors included in IEDI and NEDI	None
ARfD	No data available[1]
IESTI (% ARfD) according to EFSA PRIMo Model rev.2A	Not required[1]
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not required[1]
Factors included in IESTI and NESTI	None

[1]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 (see section 1). 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)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
No study provided. Not required according to the representative uses[1].				

CA 6.1 Storage stability of Residues

CA 6.2 Metabolism, Distribution and Expression of Residues

CA 6.2.1 Metabolism, distribution and expression of residues in plants

CA 6.2.2 Poultry

CA 6.2.3 Lactating ruminants

CA 6.2.4 Pigs

CA 6.2.5 Fish

CA 6.3 Magnitude of Residues Trials in Plants

CA 6.3.1 Crop 1

CA 6.3.2 Crop 2

CA 6.3.3 Crop 3

Add additional data points as required

CA 6.4 Feeding Studies

CA 6.4.1 Poultry

CA 6.4.2 Ruminants

CA 6.4.3 Pigs

CA 6.4.4 Fish

CA 6.5 Effects of Processing

CA 6.5.1 Nature of the residue

CA 6.5.2 Distribution of the residue in inedible peel and pulp

CA 6.5.3 Magnitude of residues in processed commodities

CA 6.6 Residues in Rotational Crops

Hydrolysed proteins are quickly degraded and it is soluble in water. Therefore, once the substance has been degraded, it is not probable that it has an effect on next crops, in case waste could be quantified.

CA 6.6.1 Metabolism in rotational crops

CA 6.6.2 Magnitude of residues in rotational crops

CA 6.7 Proposed Residue Definitions and Maximum Residue Levels

CA 6.7.1 Proposed residue definitions

CA 6.7.2 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed

As stated in the Draft Assessment Report submitted by Greece to EFSA and still valid, there is no MRL's stablished for hydrolysed proteins at the community or member State level. The argumentation was based on these two points:

a) A residue definition of hydrolysed protein for plants is not considered relevant for the uses intended in EU.

b) No supervised trials were conducted since hydrolysed proteins is exempted from the requirements of data residues.

By default, a MRL of 0.01 mg/kg was set according to Article 18 (1) (b) of the Regulation 396/2005.

CA 6.7.3 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed for imported products (import tolerance)

CA 6.8 Proposed Safety Intervals

CA 6.9 Estimation of the Potential and Actual Exposure through Diet and other Sources

Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

It was not considered necessary the establishment of an ADI for neither the hydrolysed proteins notified.

Acute Reference Dose (ARfD) and Dietary Exposure Calculation

According to the Guidance Document on the setting of an ArfD, there was no need for the establishment of an ArfD for neither the hydrolysed proteins notified.

CA 6.10 Other Studies

CA 6.10.1 Effect on the residue level in pollen and bee products

CA 6 RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED (PHY)

PHYTOPHYL manufactures “Hydrolysed Protein” which is made of Beet molasses and Urea. Both of them are used very widely for many years and have not ever classified as dangerous substances.

Beet molasses are a natural by-product of the sugar industry, defined as the end product of sugar manufacture or refining from which no more sugar may be economically crystallized by conventional means.

Beet molasses mainly used for two purposes, Animal feed additive and Alcohol Production.

There is no evidence in bibliography that Beet molasses are for some reason toxic, irritant or ecologically unsafe.

PHYTOPHYL & FORESTRY COMISSION notified urea according to 91/414 and the substance is now approved under Reg. (EC) No 1107/2009. No toxicity studies were submitted but literature data about the toxicity of urea indicated limited toxicological potential.

During this first notification and inclusion Urea was not registered to ECHA but now has a full registration, the dossier is evaluated and there are 163 active registrants as a high volume chemical (production of 10.000 000 – 100.000.000 TONNES per year).

The annual application rate for urea, or hydrolysed protein in case of ENTOMELA 50SL for 6 applications per year according to the table of intended uses (CP 3.3) is:

Application rate per year for each active substance and total nitrogen content (6 applications/year)	
Hydrolysed protein	1.8kg – 2.08 kg/ha
Urea	0.576 kg – 0.648kg kg/ha
Total nitrogen content	0,288-0.333kg/ha

These rates are very low if we compare them to the annual application rates for urea as fertilizer which are reported to the ECHA site and are 60kg, 120kg, 180kg N/ha.

We can see that the use of Nitrogen fertilizers emits 180-540 times more nitrogen to the environment than the use of ENTOMELA 50SL for bait sprays and the quantities of urea and beet molasses that liberated to the environment are very low in comparison to the use of similar compounds as fertilizer or other uses, or even the quantities of them in wastewater of human origin.

PHYTOPHYL submit a DRR for ENTOMELA 50SL on 2015 according to reg. 1107/2009 and below are the Overall comments of zRMS on Metabolism & Residues section:

Reviewer's comments: IIIA 8	EL: According to EFSA Journal 2012; 10(2):2545, 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. EL: According to EFSA Journal 2012;10(1):2523, Urea can be used as a fungicide to be applied on fresh-cut stumps of conifers in forests. It can also be used as an insect attractant for the control and the suppression of the olive fruit fly and the Mediterranean fruit fly in olive trees as a spot bait spray treatment in combination with an insecticide. The spray application is recommended on the tree trunk and/or on a small area of the tree foliage. Contact with fruits must be avoided. Urea is also used as a mass trapping agent inside liquid traps. When applied under these conditions, insignificant residues of urea are expected on olive fruits. Therefore a quantitative consumer dietary risk assessment is not necessary due to the specific kinds of application.

On EFSA Journal 2017;15(11):5046 we see that EFSA prepared a statement explaining that for these nine active substances a review of MRLs is no longer necessary and refer for urea:

"For urea, EFSA in its opinion (EFSA, 2012a) considered that a quantitative consumer dietary risk assessment was not necessary due to the specific methods of application of that substance. Urea (carbamide) is approved as a food additive in accordance with Regulation (EU) No 1129/2011 of the European Parliament and of the Council.6 In addition, the natural exposure to that substance is far higher than the one linked to the use of urea as a PPP. In view of this, it was considered appropriate to include this substance in Annex IV to Regulation (EC) No 396/2005 via Commission Regulation (EU) 2015/1608."

According to all above mentioned no data submitted in this section for hydrolysed proteins.

CA 6.1 Storage stability of Residues

CA 6.2 Metabolism, Distribution and Expression of Residues

CA 6.2.1 Metabolism, distribution and expression of residues in plants

CA 6.2.2 Poultry

CA 6.2.3 Lactating ruminants

CA 6.2.4 Pigs

CA 6.2.5 Fish

CA 6.3 Magnitude of Residues Trials in Plants

CA 6.3.1 Crop 1

CA 6.3.2 Crop 2

CA 6.3.3 Crop 3

Add additional data points as required

CA 6.4 Feeding Studies

CA 6.4.1 Poultry

CA 6.4.2 Ruminants

CA 6.4.3 Pigs

CA 6.4.4 Fish

CA 6.5 Effects of Processing

CA 6.5.1 Nature of the residue

CA 6.5.2 Distribution of the residue in inedible peel and pulp

CA 6.5.3 Magnitude of residues in processed commodities

CA 6.6 Residues in Rotational Crops

CA 6.6.1 Metabolism in rotational crops

CA 6.6.2 Magnitude of residues in rotational crops

CA 6.7 Proposed Residue Definitions and Maximum Residue Levels

CA 6.7.1 Proposed residue definitions

CA 6.7.2 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed

CA 6.7.3 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed for imported products (import tolerance)

CA 6.8 Proposed Safety Intervals

CA 6.9 Estimation of the Potential and Actual Exposure through Diet and other Sources

Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

Acute Reference Dose (ARfD) and Dietary Exposure Calculation

CA 6.10 Other Studies

CA 6.10.1 Effect on the residue level in pollen and bee products

CA 6 RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED (SIC)

Hydrolysed proteins are used also as foliar fertiliser and does not cause negative transformations in the environment, if it is used following the suggested dosages and the suggested conditions.

The product is constituted by natural substances and consequently is completely biodegradable.

Reasonably there are not negative effects on the environment.

CA 6.1 Storage stability of Residues

The stability of residues is not applicable

CA 6.2 Metabolism, Distribution and Expression of Residues

No metabolisms studies are necessary.

CA 6.2.1 Metabolism, distribution and expression of residues in plants

CA 6.2.2 Poultry

CA 6.2.3 Lactating ruminants

CA 6.2.4 Pigs

CA 6.2.5 Fish

CA 6.3 Magnitude of Residues Trials in Plants

Metabolism studies in plants are not considered necessary

CA 6.3.1 Crop 1

CA 6.3.2 Crop 2

CA 6.3.3 Crop 3

Add additional data points as required

CA 6.4 Feeding Studies

Based on the intended uses supported in the context of inclusion of Hydrolysed protein in Annex I of Directive 91/414/EEC, no potential feedingstuffs are expected to result and be fed to livestock.

Furthermore, it would not be possible to distinguish the proteins brought in an artificial way from the ones already existing in the same animal tissues. Therefore, it is not expected that livestock will be exposed to significant hydrolysed protein residues through diet.
Consequently, metabolism studies are not considered necessary.

CA 6.4.1 Poultry

CA 6.4.2 Ruminants

CA 6.4.3 Pigs

CA 6.4.4 Fish

CA 6.5 Effects of Processing

Hydrolysed proteins are completely biodegradable. Residues are not expected to be found in harvested products.

CA 6.5.1 Nature of the residue

CA 6.5.2 Distribution of the residue in inedible peel and pulp

CA 6.5.3 Magnitude of residues in processed commodities

CA 6.6 Residues in Rotational Crops

There is no risk for significant residues of Hydrolysed proteins in succeeding crops given the rapid degradation of this substance in soil. Therefore, no metabolism studies are required.

CA 6.6.1 Metabolism in rotational crops

CA 6.6.2 Magnitude of residues in rotational crops

CA 6.7 Proposed Residue Definitions and Maximum Residue Levels

A residue definition of Hydrolysed protein for plants and for products of animal origin is not considered relevant for the uses intended in EU.

CA 6.7.1 Proposed residue definitions

CA 6.7.2 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed

CA 6.7.3 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed for imported products (import tolerance)

CA 6.8 Proposed Safety Intervals

The product itself does not require any PHI. PHI (days) depends on the insecticide to be mixed with the attractant.
No re-entry period for livestock to area to be grazed need to be set, as the representative crops are not grazed.

No re-entry period for man to crops, buildings or spaces treated needs to be established. No withholding period needs to be established for animal feedstuff since the representative used of hydrolysed proteins is not for animal feeding stuffs. Nor Waiting period before sowing or planting succeeding crops, nor Waiting period before sowing or planting crop to be protected need to be established.

CA 6.9 Estimation of the Potential and Actual Exposure through Diet and other Sources

Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

No data available

Acute Reference Dose (ARfD) and Dietary Exposure Calculation

No data available.

CA 6.10 Other Studies

None.

CA 6.10.1 Effect on the residue level in pollen and bee products