NUTREL/SIC

DOCUMENT M-CP, Section 7

TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

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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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCTS

Introduction

toxicological studies and the classification for the plant protection product NUTREL (registration number 11502), containing the active substance hydrolysed proteins, which is included into Annex I of Directive 91/414 (2008/127/EC) 18 December 2008, with extension of approval till 31th August 2019 (please refer to Directive 2008/127/EC) for Hydrolysed proteins.

A full risk assessment according to Uniform Principles is provided which demonstrates that the product is safe for operators, workers and bystanders.

Where appropriate this document refers to the conclusions of the EU review of the hydrolysed proteins compounds. This will be where:

- the active substance data is relied upon in the risk assessment of the formulation; or when
- the EU review concluded that additional data/information should be considered at national re-registration.

This product was not the representative formulation. The product has not been previously evaluated in this country according to Uniform Principles.

The Conclusion on the peer review of the pesticide risk assessment of the active substance hydrolysed proteins (EFSA Journal 2012; 10(2):2545) and the SANCO report for hydrolysed proteins (SANCO/2615/08-rev. 3-27 October 2008) are considered to provide the relevant review information or a reference to where such information can be found. The following table provides the EU endpoints to be used in the evaluation.

Endpoints and related information (Point 5 of Final Review Report for the active substance Hydrolysed proteins; SANCO/2615/08-rev. 3 - 27 October 2008)
In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the Uniform Principles laid down in Annex VI of that Directive, the most important endpoints were identified during the re-evaluation process. These endpoints are listed in volume 1, page 27 and at section 3 of the DAR.

EU End-points

End-Point	**Active Substance**	
	EU agreed endpoints EFSA Journal 2012; 10(2):2545	Endpoints used in risk assessment*
Dermal penetration	No data available*	Not required
AOEL	No data available*	Not required

*Hydrolysed proteins *per se* are considered of low toxicological concern and no risks to human health are expected from its use as a plant protection product. However due to the fact that a specification to include the main components in the active substances is still outstanding a final conclusion cannot be drawn whether the technical specification is of toxicological concern leading to a data gap and issue that cannot be finalized.

CP 7.1 Acute Toxicity

CP 7.1.1 Oral toxicity

Title:	Assessment of acute oral toxicity in rats (acute toxic class method) Test product NUTREL 36% (421g/L) - SL
Document No:	AM687.A1
Guidelines:	OECD 420
GLP	Yes

Material and Methods:
NUTREL (batch No. 4363 DO.LA.05) is a brown liquid containing Hydrolysed proteins (nominal concentration: 421 g/L). A single administration of the undiluted test substance was administered by gavage to 5 fasted female SD (Sprague Dawley) rats at 2000 mg/kg bw. The administration volume was 10 mL/kg bw.

Table: Acute oral toxicity in rats of NUTREL 36

Dose (mg/kg)	**Toxicological results***	**Duration of signs**	**Time of death**	**LD_{50} (mg/kg) (14 days)**
female rats				
2000	0/0/5	24-48h	/	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used

Findings:

- No animals died during the study. During the study in all treated animals were detected piloerection and *addome levrettato* (It is mentioned as a clinical symptom in a research document in which rats are being tested for allergic reactions to a substance).
- The weight gain of the treated animals was compliant species and breed.
- The body weight evolution of the animals remained normal throughout the study, similar between treated and control animals.
- The macroscopical examination of the animals at the end of the study did not reveal treatment related changes (only moderate enteritis mucous). .

Conclusion
Under the experimental conditions, the oral LD_{50} of NUTREL 36 is higher than 2000mg/kg in rats.

Based on the results, interpreted according to the OECD No 420 of 17 December 2001, the product in question NUTREL 36, falls within the CATEGORY 5 of the GHS classification.

CP 7.1.2 Dermal toxicity

Title:	Assessment of acute dermal toxicity in rats. Test product NUTREL 36% (421g/L) - SL
Document No:	AM687.A2
Guidelines:	OECD 402
GLP	Yes

The product NUTREL 36 (batch No. 4363 DO.LA.05), soluble liquid containing 421 g/L of Hydrolysed proteins was applied onto the skin of 10 Sprague Dawley rats (5 males and 5 females) at the single dose of 2000 mg/kg bw according to the experimental protocol established on the basis of the official method as defined in the OECD guideline N° 402 dated February 24th, 1987 and the test method B.3 of directive N° 92/69/EEC dated December 29th, 1992. Animals were then observed for 14 days. The test substance was used as such.

Dermal LD50	Males:	> 2000 mg/kg bw
	Females:	> 2000 mg/kg bw
	Combined:	> 2000 mg/kg bw

The body weight evolution of the animals remained normal throughout the study, for the female rats and of the male rats. No macroscopic effects of the test item were seen during necropsy.

Based on the results, interpreted according to the Ministerial Decree April 28, 1997, the test substance should be NUTREL 36 considered NON-TOXIC - NOT HARMFUL DERMAL

CP 7.1.3 Inhalation toxicity

No acute inhalation study is provided as NUTREL 36 - SL, being a soluble liquid formulation containing 421 g/L of Hydrolysed proteins does not require inhalation toxicity to be tested.

An inhalation study is required when the preparation:

- is a smoke generating formulation or fumigant,
- is used with fogging equipment,
- is a vapour releasing preparation,
- is an aerosol,
- is a powder containing a significant proportion of particles or diameter < 50 mm (> 1 % on a weight basis),
- is to be applied from aircraft in cases where inhalation exposure is relevant,
- contains an active substance with a vapour pressure > 1 x 10^{-2} Pa and is to be included in enclosed spaces such as warehouses or glasshouses, or
- is to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 mm (> 1 % on a weight basis)

It is clear that these situations are not applicable to as NUTREL 36 and thus an inhalation study is not required.

CP 7.1.4 Skin irritation

Title:	Assessment of Acute irritant/corrosive effect on the skin, Test product NUTREL 36% (421g/L) - SL
Document No:	AM687.A3
Guidelines:	OECD 404
GLP	Yes

The product NUTREL 36 (soluble liquid containing 4210 g/L of Hydrolysed proteins) was applied, as supplied, at the dose of 0,5 ml, under semi-occlusive dressing during 4 hours on an undamaged skin area of 3 rabbits, according to an experimental protocol established from the OECD guideline N° 404 dated July 17th, 1992 and the method B.4 of the EEC directive N° 92/69 dated December 29th, 1992. Animals were then observed for 72 hours. Irritation was scored using the European scheme and the Draize scheme.

After removal of the patch, it was noted on the treated area, a moderate erythema and absence of oedema. The oedematous reaction was totally reversible between the 5th and the 6th day of the test. On the cutaneous structure, the skin recovered a normal aspect between the 9th and the 13th day of the test.

Based on the results, interpreted according to the Ministerial Decree April 28, 1997, the test substance should be NUTREL 36 considered NOT IRRITATING to the skin.

CP 7.1.5 Eye irritation

Title:	Assessment of Acute eye irritation Test product NUTREL 36% (421g/L) - SL
Document No:	AM688
Guidelines:	OECD 405
GLP	Yes

In a primary eye irritation study, 0,1 ml of the product NUTREL 36 (soluble liquid containing 421 g/L of Hydrolysed proteins), Batch 4362 DO.LA.05, as applied in one eye of each of three young adult New Zealand White rabbits, according to the experimental protocol established on the basis of the official method as defined in the OECD guideline 405 dated February 24th, 1987 and the test method B.5 of the EEC directive n° 92/69 dated December 29th, 1992. Animals were then observed for 7 days. Eye irritation was scored using the European scheme and the Draize scheme for unwashed eyes.

The eyes were examined 1, 24, 48 and 72 hours after application and then at 7, 14 and 21 days. One hour after the single application, a moderate enanthema was noted at the conjunctivae level (totally reversible the 14th day of the test), an important opacity at the corneal level (still noted at the end of the observation time day 21), at the iris level a congestion between the 2nd and the 3rd day of the test and between the 8th and the 10th day as well as an haemorrhage between the 4th and the 7th day of the test. Also noted was a neo-vascularization from the 8th day of the test, this reaction was still noted at the end of the test.

Based on the results, interpreted according to the Ministerial Decree April 28, 1997, the test substance should be NUTREL 36 considered NOT IRRITATING to the eyes.

CP 7.1.6 Skin sensitization

Title:	Assessment of Sensitising Properties on Albino Guinea Pig (Maximisation test according to Magnusson and Kligman). Test product NUTREL 36% (421g/L) - SL
Document No:	AM687.A5
Guidelines:	OECD 406
GLP	Yes

After induction (intradermic injection and topical application) of 10 female Guinea pigs of the group treated with the test product NUTREL 36 and a 18 days rest phase, the challenge phase, under occlusive dressing for 24 hours, consisted to a single topical application of the test product at 25% and diluted at 12,5% in distilled water, according to the experimental protocol established from the OECD guideline 406 dated July 17th, 1992 and the method B.6 of the European directive N° 96/54 dated July 30th, 1996. The treatment regime involved induction of sensitisation by intradermal injection on day 1, induction of sensitisation by topical administration on day 12 and challenge by topical administration on day 30.

No macroscopic cutaneous reactions attributable to allergy were recorded during the examination following the removal of the occlusive dressing (challenge phase) from the animals of the treated group with the test product. No cutaneous intolerance reaction was recorded in animals from the negative control group.

Based on the results, interpreted according to the Ministerial Decree April 28, 1997, the test substance should be NUTREL 36 considered NOT SENSITIZING.

CP 7.1.7 Supplementary studies on the plant protection product

Not required

CP 7.1.8 Supplementary studies for combinations of plant protection product

Not available

CP 7.2 Data on Exposure

CP 7.2.1 Operator exposure

The Plant Protection Product NUTREL (formulation type SL) contains 378 g/L of hydrolysed proteins. NUTREL is intended to be used on orchards as an insect attractant and insect bait and it is applied in combination with insecticides.

NUTREL can be used by normal volume spraying of high pressure in combination with an insecticide or by suitable containers for the trapping of flies without combination with an insecticide. Usage information pertinent to operator exposure is summarised in Table 7.2-1.

Table 7.2-1 Summary of critical use patterns (i.e. worst case)

Crop (field)	Application rate (kg as/ha)	Spray dilution (L/ha)	Application method
Orchards (olive, pome fruits, stone fruits, walnut, citrus, kiwi, blueberries)	1.0	100	Normal volume spraying / high pressure
	8.5	Not available	Product in Traps

According to EFSA, the hydrolysed proteins *per se* are derived by the hydrolysis of tissues from organisms that can be of plant or animal origin. Although the information provided by the applicants were very limited, hydrolysed proteins *per se* are likely to be of low toxicological concern provided hydrolysed proteins of animal origin are pathogen-free and hydrolysed proteins from plant origin do not have sensitisation potential. On this basis no risks to human health could be expected from its use as a plant protection product and data waivers for specific toxicological studies were initially supported.

Considering that no AOEL of hydrolysed proteins is available, a quantitative risk assessment of the operator exposure is not possible.

Conclusion

Taking into account all the available data on the toxicity potential of the formulation and on the recommended uses the following conclusions are reached:
1st intended use: The use by normal volume spraying of high pressure in combination with and insecticide is considered safe for the operator, based on lack of any significant toxicity potential of the formulation and since use of suitable gloves, clothing and suitable respiratory protective equipment is recommended during application.

2nd intended use: The use into suitable containers for the trapping of flies (not combined with an insecticide) is considered safe for the operator, based on lack of any significant toxicity potential of the formulation and since use of suitable gloves and clothing is recommended.

Risk assessment for operator

CP 7.2.1.1 Estimation of operator exposure

No estimation is required. Justification has been carried out in point 7.2.1

Measurement of operator exposure

No measurement is required. Justification has been carried out in point 7.3.

CP 7.2.2 Bystander and resident exposure

Risk assessment for bystander and resident

CP 7.2.2.1 Estimation of bystander and resident exposure

Estimates of bystander exposure have not been performed. Nevertheless, no risk is anticipated for the bystanders in the areas of application of the plant protection product NUTREL

CP 7.2.2.2 Measurement of bystander and resident exposure

No measurement is required. Justification has been carried out in point 7.3.

CP 7.2.3 Worker exposure

Risk assessment for worker

CP 7.2.3.1 Estimation of worker exposure

Estimates of worker exposure have not been performed. Nevertheless, based on the argumentation presented in section 7.3 no risk is anticipated for the worker entering the application area directly after treatment when the same personal protective equipment with the operator is used.

CP 7.2.3.2 Measurement of worker exposure

No measurement is required. Justification has been carried out in point 7.3.

CP 7.3 Dermal Absorption

This is not an EC data requirement/ not required by Directive 91/414/EEC

CP 7.4 Available Toxicological Data Relating to Co-Formulants

Not available