Product Assessment Report

Biocidal product assessment report related to product authorisation under Directive 98/8/EC

FANGA PATE PRO

TRIPLAN S.A.

July 2013

Internal registration n°/authorisation n°:	PB-11-00264 / FR-2014-0130
Authorisation/Registration no:	2012/619/287/FR/APP/7
Granting date/entry into force of authorisation/ registration:	04/08/2014
Expiry date of authorisation/ registration:	04/08/2018
Active ingredient:	Brodifacoum (CAS: 56073-10-0)
Product type:	14

Competent Authority in charge of delivering the product authorisation:
French Ministry of Ecology
Department for Nuisance Prevention and Quality of the Environment
Chemical Substances and Preparation Unit
Grande Arche, Paroi Nord
92 055 La Défense cedex – FRANCE
autorisation-biocide@developpement-durable.gouv.fr

Authority in charge of the efficacy and risk assessment:
Anses – French agency for food, environmental and occupational health and safety
Regulated Products Directorate
253 Avenue du Général Leclerc
94 701 Maisons-Alfort Cedex - FRANCE
biocides@anses.fr

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1 General information about the product application

1.1 Applicant

Company Name:	TRIPLAN SA
Address:	BP258 La Poste Française
City:	Andorre la Vieille
Postal Code:	AD500
Country:	Principauté d'Andorre
Telephone:	+376 741 445
Fax:	+376 741 450
E-mail address:	triplan@andorra.ad

1.1.1 Person authorised for communication on behalf of the applicant

Name:	Fredy Lacroux
Function:	Managing director
Address:	BP258 La Poste Française
City:	Andorre la Vieille
Postal Code:	AD500
Country:	Principauté d'Andorre
Telephone:	+376741 445
Fax:	+376 741 450
E-mail address:	saida.triplan@andorra.ad

1.2 Proposed authorisation holder

Company Name:	TRIPLAN SA
Address:	BP258 La Poste Française
City:	Andorre la Vieille
Postal Code:	AD500
Country:	Principauté d'Andorre
Telephone:	+376 741 445
Fax:	+376 741 450
E-mail address:	triplan@andorra.ad
Letter of appointment for the applicant to represent the authorisation holder provided (yes/no):	No

1.3 Information about the product application

Application received:	02/02/2012
Application reported complete:	16/03/2012
Type of application:	Product authorisation
Further information:	Frame formulation: please refer to the Biocidal Product Assessment Report related to frame formulation establishment.

1.4 Information about the biocidal product

1.4.1 General information

Trade name:	FANGA PATE PRO
Manufacturer's development code number(s), if appropriate:	SOPHY
Product type:	14 - rodenticide
Composition of the product (identity and content of active substance(s) and substances of concern; full composition see confidential annex):	Active substance's identity and content: Brodifacoum 0.005% w/w
Formulation type:	Paste bait
Ready to use product (yes/no):	Yes
Is the product the very same (identity and content) to another product already authorised under the regime of directive 98/8/EC (yes/no); **If yes: authorisation/registration no. and product name:** **or** **Has the product the same identity and composition like the product evaluated in connection with the approval for listing of active substance(s) on to Annex I to directive 98/8/EC (yes/no):**	No No

1.4.2 Information on the intended use(s)

Overall use pattern (manner and area of use):	Indoor environment (public and private buildings, farms.)
Target organisms / stages:	I.1.1 Murids : *Muridae*

	I.1.1.1 Brown rat: *Rattus norvegicus* I.1.1.2 Roof rat, House rat: *Rattus rattus* I.1.1.3 House mouse: *Mus musculus*
Category of users:	V.2 Professional
Directions for use including minimum and maximum application rates, application rates per time unit (e.g. number of treatments per day), typical size of application area:	VI.2 Covered application VI.2.1 in bait stations FANGA PATE PRO is intended to be used for control of mice, brown rats and black rats in buildings included farm buildings. The treatment with FANGA PATE PRO is applied by trained professional users. The product is ready-to-use (paste) so with no dilution and no other substances added for application. FANGA PATE PRO is supplied as 10 g paste wrapped individually in a white heat-sealed paper sachet and is manually applied in secured bait stations. <u>Rats</u> : 180 g grains/secured bait point separated by 5-10 m. <u>Mice</u> : 30 g grains/secured bait point separated by 1-2 m. Over a period of 28 days for application, cleaning, refilling and collect of dead rodents. The control of rats and mice is carried out inside buildings, so the environmental conditions in which rodents are found tend to be similar relating to geographical areas.
Potential for release into the environment (yes/no):	Yes
Potential for contamination of food/feedingstuff (yes/no)	No
Proposed Label:	FANGA PATE PRO is intended to be used for control of mice, brown rats and black rats in buildings included farm buildings. The treatment with FANGA PATE PRO is applied by trained professional users. <u>Rats</u> : 180 g grains/secured bait point separated by 5-10 m. <u>Mice</u> : 30 g grains/secured bait point separated by 1-2 m. Hazard symbol: None Indication of danger : None Risk phrases: None Safety phrases: S1/2: Keep locked up and out of reach of children. S7: Keep container tightly closed. S13: Keep away from food, drink and animal feeding stuffs. S20/21: When using do not eat, drink or smoke. S24: Avoid contact with skin S35: This material and its container must be disposed of in a safe way S36/37: Wear suitable protective clothes and gloves. S46: If swallowed, seek medical advice immediately (show label if

	possible). S49: Keep only in original container
Use Restrictions:	Use only indoors in secured bait stations out of reach of children and domestic animals.

For full details of the intended uses claimed by the applicant, please see Annex 0a.

1.4.3 Information on active substance

Active substance chemical name:	Brodifacoum
CAS No:	56073-10-0
EC No:	259-980-5
Purity (minimum, g/kg or g/l):	950 g/kg
Inclusion directive:	2010/10/CE
Date of inclusion:	9 February 2010
Is the active substance equivalent to the active substance listed in Annex I to 98/8/EC (yes/no):	No
Manufacturer of active substance(s) used in the biocidal product:	PM TEZZA SRL[1]
Company Name:	PM TEZZA SRL
Address:	Via Tre Ponti 22
City:	S. Maria di Zevio (VR)
Postal Code:	37050
Country:	Italy
Telephone:	
Fax:	
E-mail address:	

According to the Assessment Report Revised in November 2010, the technical equivalence between the two sources of the Task Force has not been demonstrated. As the Activa's source is not recognized, only an authorized source must be used.

1.4.4 Information on the substance(s) of concern

There is no substance of concern.

1.5 Documentation

1.5.1 Data submitted in relation to product application

Identity, physico-chemical and analytical method data

[1] Activa is the applicant of the active substance but not the manufacturer. Tezza SRL is the manufacturer of the active substance as mentioned in the Final CAR of brodifacoum of the Activa / PelGar Brodifacoum Task Force.

Physico-chemical properties studies and analytical methods on the biocidal product FANGA PATE PRO were provided by TRIPLAN:

Efficacy data

The following efficacy studies were submitted:

- A free-choice laboratory test was carried out with house mice (***Mus musculus***) and brown rats (***Rattus norvegicus***), with exposure to **FANGA PATE PRO** (0.005 % w/w brodifacoum) for 20 days. The age of the product tested is not known.
- A free-choice laboratory test was carried out with rats (***Rattus norvegicus***), with exposure to a one year aged formulation of **FANGA PATE PRO** (0.005 % w/w brodifacoum) for 4 days.
- A free-choice laboratory test was carried out with house mice (***Mus musculus***), with exposure to a one year aged formulation of **FANGA PATE PRO** (0.005 % w/w brodifacoum) for 4 days.
- A field test was carried out with rats (***Rattus norvegicus***), with exposure to a one year aged formulation of **FANGA PATE PRO** (0.005 % w/w brodifacoum).
- A field test was carried out with house mice (***Mus musculus***), with exposure to a one year aged formulation of **FANGA PATE PRO** (0.005 % w/w brodifacoum).

Toxicology data

The applicant submitted new toxicological data on active substance and studies for the product (see corresponding sections).

Residue data

No new study has been submitted for the biocidal product authorisation.

Ecotoxicology data

No new study has been submitted for the biocidal product authorisation.

1.5.2 Access to documentation

As stated in the letter of access granted by Activa to Triplan:

Activa S.r.l, (via Feltre 32, Milano-Italy), as Notifier and having rights on all the data included in the Dossier for Brodifacoum (CAS No: 56073-10-0) presented by The Activa/Pelgar Brodifacoum and Difenacoum Task Force (composed by: Activa/Tezza S.r.l and Pelgar International Ltd) for Annex I listing to RMS Italy ***authorises*** *the France competent authorities to use these data for authorisation purpose TRIPLAN (BP 258 Poste Francaise - AD500 Andorre la Vieille - PRINCIPAT D'ANDORRA) for the product* ***FANGA PATE PRO*** *(PT14).*

Please refer to the LoA for the complete list of studies for which access has been granted.

2 Summary of the product assessment

The product is to be used in tamper-resistant bait boxes or covered bait stations.

”Tamper-resistant bait boxes” are meant to be tamper-resistant devices, that prevent the access to the baits for children and non-target animals, and that protect the baits from bad weather.

”Covered bait stations” are meant to be devices with the same level of security for the human beings and the environment than the security provided by tamper-resistant bait boxes, fastened to prevent any removal, made in order to avoid direct contact of the bait with the environment. This device must be designed to keep baits out of reach of the general public and non-target animals, and to protect the bait from bad weather

It is considered that professional users only (on the contrary to the general public) are able to design such covered bait stations.

2.1 Identity related issues

The source of the active substance used in the biocidal product FANGA PATE PRO is not the same as the source used for annex I inclusion. The technical equivalence is in progress and evaluated by Italy. Only a recognized source of active substance can be used in the product FANGA PATE PRO[2]. Refer to the confidential annex for more details.

2.2 Classification, labelling and packaging

2.2.1 Harmonised classification of the active substance

Classification - Directive 67/548/EEC		
Class of danger	T+	
	N	
R phrases	R27/28	Very toxic in contact with skin and if swallowed.
	R48/24/25	Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Specific limit concentrations for the environment:

C ≥ 2.5 %	N; R50/53
1 % ≤ C <2.5 %	N; R51/53
0.5 % ≤ C< 1 %	N; R51/53

[2] Assessment Report of Brodifacoum, November 2010, Revision 2 (Italy).

0.25 % ≤ C< 0.5 %	N; R51/53
0.025 % ≤ C< 0.25 %	R52/53

The classification for the environment, under Directive 67/548/EEC, was agreed in April 2006 by the Technical Committee on Classification and Labelling (TC C&L) of Dangerous Substances.

Classification - Regulation (EC) 1272/2008		
Hazard statement	Acute Tox. 1	
	Acute Tox. 2	
	STOT RE 1	
	Aquatic Acute 1	
	Aquatic Chronic 1	
Precautionary statements	H310	Fatal in contact with skin.
	H300	Fatal if swallowed.
	H372	Causes damage to organs through prolonged or repeated exposure.
	H400	Very toxic to aquatic life.
	H410	Very toxic to aquatic life with long lasting effects.

2.2.2 Classification of the biocidal product

Classification - Directive 67/548/EEC	
Class of danger	None
R phrases	None
S phrases	None

Classification - Regulation (EC) 1272/2008	
Hazard statement	None
Precautionary statements	None

2.2.3 Labelling of the biocidal product

Labelling - Directive 67/548/EEC	
Symbols:	None

Indications of danger:	None
Risk phrases:	None
Safety phrases:	None

Labelling - Regulation (EC) 1272/2008	
Pictograms:	None
Signal words:	None
Hazard statements:	None

2.2.4 Packaging of the biocidal product

FANGA PATE PRO is supplied in paper sachet (10g for rats and mice).

Sachets are packed in:

- polypropylene bucket (5, 10, 15, 18 and 20kg);
- plastic bag (laminated film in PET/ PVDC (12µ) and transparent polyethylene (50µ)) with a capacity of 100g to 1kg. Several bags can be packed in a cardboard box with a capacity of 20kg.

2.3 Physico/chemical properties and analytical methods

2.3.1 Active ingredient

2.3.1.1 Identity, origin of active ingredient

The source of the active substance used in the biocidal product FANGA PATE PRO is not the source used for annex I inclusion. The technical equivalence is in progress and evaluated by Italy. Only a recognized source of active substance can be used in the product FANGA PATE PRO. Refer to the confidential annex for more details.

A letter of access to brodifacoum data from Activa has been provided.

2.3.1.2 Physico-chemical properties

Physical and chemical properties of the active substance have already been evaluated at EU level and are presented in the CAR of the active substance brodifacoum (2010). The applicant TRIPLAN has a letter of access to these data.

Source CAR 2010 (Document I):

Brodifacoum is an off-white powder at 20°C and atmospheric pressure, with a relative density of 1.53. It was observed to darken and decompose at 235.8°C, whereas no decomposition or transformation occurred below 150°C.

Brodifacoum is non-volatile, with a Henry's Law Constant value of 2.35E-18 $Pa.m^3.mol^{-1}$. It is essentially insoluble in water at pH 5, but its solubility proved to increase with pH, due to the variation of the ionisation degree of the 4-hydroxycoumarin group in pH range under investigation (5-9). Brodifacoum also turned out to be soluble in organic solvents; results showed that solubility did not vary with temperature, except for dichloromethane.

Brodifacoum dissociation constant was estimated to be 4.50. Log Pow was found to be 4.92 at pH 7 and 20°C. As expected, Log Pow decreased with higher temperature and pH.

Brodifacoum is not highly flammable. Besides, it does not show explosive or oxidising properties. Reaction with container materials (mild steel) has not been observed, either. All results considered, it can be concluded that Brodifacoum does not exhibit hazardous physical-chemical properties.

2.3.1.3 Analytical method for determination of active ingredient and impurities in the technical active ingredient

Analytical method for the determination of pure active substance brodifacoum in the technical active substance as manufactured has already been performed and validated at EU level in the CAR of brodifacoum (2010). The applicant TRIPLAN has a letter of access to these data.

Summary: (source AR November 2010)

	Principle of method
Technical active substance as manufactured:	Brodifacoum is analysed in the technical material by reversed-phased HPLC/UV (254nm) Purity : 96.2-99.4% w/w (mean: 98.1 % w/w)

2.3.1.4 Analytical method for determining relevant components and/or residues in different matrices

Analytical methods for the determination of residues of the active susbtance brodifacoum in the different matrices (plants, soil drinking, ground, surface water, human and animal body fluids and tissues) have already been performed and validated at EU level in the CAR of brodifacoum (2010). No method in air is required since the active substance is non volatile.

Analytical methods are presented in Annex 3 of this document.

The applicant TRIPLAN has a letter of access to these data.

2.3.2 Biocidal product

2.3.2.1 Identity, composition of the biocidal product, packaging

The biocidal product is not the same as the one assessed for the inclusion of the active substance in annex I of directive 98/8/EC.

Trade name: *FANGA PATE PRO*

Type of product: PT14, bait ready to use

Type of formulation: paste bait

The composition of the product is confidential and is presented in a confidential annex. There is no substance of concern.

2.3.2.2 Physico-chemical properties

The tested product is FANGA PATE PRO. Brodifacoum content in tested product is 0.0055% w/w (variation 10%). It is in the range of the FAO tolerance (15%).

The product does not contain more than 10% of hydrocarbon compounds.

Table 1: Physico-chemical properties of the biocidal product

Subsection (Annex Point IIB. 3/TNsG)	Method	Purity/ Specification	Results[3]	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Evaluation FR
3.1 Appearance (IIB3.1/Pt. I-B3.1)		FANGA PATE PRO (brodifacoum 0.0055%) Batch: 308/11/01			Y	1	11-920010-017[4]	Acceptable
3.1.1 Physical state and nature			Paste Bait ready for use (BB)					
3.1.2 Colour	Visual inspection at room temperature		Blue paste					
3.1.3 Odour	Not determinated			An odour should only be recorded it is very apparent				
3.2 Explosive properties (IIB3.2/Pt. I-B3.2)	Determination of exothermic reactions by DSC (internal method)	FANGA PATE PRO (brodifacoum 0.0055%) Batch: 308/11/01	Exothermic peaks were observed but were always below 500J/g. No test on explosive properties with EC A14 is required.		Y	1	11-920010-016[5]	Acceptable. Accordin g to the composition and the DSC results, the product does not contain explosive compounds.
3.3 Oxidising properties (IIB3.3/Pt. I-B3.3)			Based on most recent approach of structural formulas, the product does not contain oxidizing compound, or they are in low content (<1%). Accordingly, the biocidal product is not				11-920010-016	Acceptable. Accordin g to the composition and the type of formulation, the product is not expected to have

[3] Give also data on test pressure, temperature, pH and concentration range if appropriate.
[4] Demangel B. 2012, Physico-chemical tests and chemical stability before and after an accelerated storage procedure for 14 days at 54±2°C on FANGA PATE PRO in compliance with CIPAC MT 46.3 (CIPAC Handbook J -2000). DEFITRACES, report n° 11-920010-017 of 12 March 2012, GLP, unpublished.
[5] Demangel B. 2012. Physico chemical tests on FANGA PATE PRO. DEFITRACES, report n° 11-920010-016 of the 22 February 2012. GLP, unpublished.

Subsection (Annex Point IIB. 3/TNsG)	Method	Purity/ Specification	Results[3]	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Evaluation FR
			expected to present a significant hazard, and testing is considered as unnecessary.					explosive properties.
3.4 Flash-point and other indications of flammability or spontaneous ignition (IIB3.4/Pt. I-B3.4)	EC A10	FANGA PATE PRO (brodifacoum 0.0055%) Batch: 308/11/01	Preliminary test: the test was performed twice. Conditions of the test: Humidity: About 39% Room temperature : About 19.5 °C Atmospheric pressure: 97.9 kPa Assay 1: A consumption of the paste was observed at the contact of the flame. Neither propagation nor ignition was observed Assay 2: The same observations as for the assay 1 were recorded. Main test: Taking in account the results obtained during the preliminary test, no main test was performed. The test item was not considered as highly flammable under the experimental conditions of the test**.**		Y		11-920010-016	Acceptable. The product is not auto-flammable and not highly flammable.
Self ignition	**EC** A16		No self ignition temperature of the test item was observed **up to 400°C** (corrected value).					The product is not auto-flammable
3.5Acidity/Alkalinity (IIB3.5/Pt. I-B3.5)	CIPAC MT 75.3	FANGA PATE PRO (brodifacoum 0.0055%) Batch: 308/11/01	The pH mean value of the test item at 1% m/v in standard water D is : 5.22 at 19.4 °C after 1 min. 5.43 at 19.5°C after 2 min. 5.83 at 19.7°C after 10 min. The pH of the test item being higher than 4 and lower than 10, CIPAC MT 191 the test		Y	1	11-920010-017	Acceptable

Subsection (Annex Point IIB. 3/TNsG)	Method	Purity/ Specification	Results[3]	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Evaluation FR
			was not performed.					
3.6 Relative density (IIB3.6/Pt. I-B3.6)	EC A.3	FANGA PATE PRO (brodifacoum 0.0055%) Batch: 308/11/01	Material: stereopycnometer D^{20}_4= 1.322 +/- 0.001		Y		11-920010-016	Acceptable
3.7 Storage stability - stability and shelf life (IIB3.7/Pt. I-B3.7)	14 days at 54°C ± 2 °C CIPAC MT 46.3	FANGA PATE PRO (brodifacoum 0.0055%) Batch: 308/11/01	**Test item during the accelerated storage:** 10 g paper sachets in plastic buckets, carboard box and plastic bag (commercial packaging) **Aspect:** Before the accelerated storage the product looks like a blue paste. After the procedure of storage, the test item looks like a blue paste.		Y	1	11-920010-017	Acceptable. The product is stable after storage at 54°C for 14 days in 10g paper sachets.
Reactivity towards container material			**Packaging of the test item** Before the accelerated storage: White opaque plastic bucket containing bags of blue paste. Weight : 947.5 g After the accelerated storage: White opaque plastic bucket containing bags of blue paste. Weight : 943.4g DW = -0.4% The aspect of the test item was considered to be stable after an accelerated storage procedure for 14 days at 54 ± 2 °C, no					

Subsection (Annex Point IIB. 3/TNsG)	Method	Purity/ Specification	Results[3]	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Evaluation FR
			significant change of weight was observed. The packaging material was considered to be stable after an accelerated storage procedure for 14 days at 54 ± 2 °C.					
			Quantitative analysis of brodifacoum (analytical method validated in report 11-920010019) : The content of brodifacoum before accelerated storage procedure was: Assay 1 (DEF11-0670A): 0.0054%. Assay 2 (DEF11-0671A): 0.0055%. The content of brodifacoum after accelerated storage procedure was: Assay 1 (DEF11-0710B): 0.0053%. Assay 2 (DEF11-0711A): 0.0052% No significant change was observed (-3.6% to -5.45% deviation from T=0 value) after the accelerated storage procedure for 14 days at 54°C ±2°C. The test item is considered to be stable.					Acceptable. Variation of bromadifacoum: -3.6% to -5.45% Variation is above 5% (maximal limit); Variation can be due to analytical deviations. As results are acceptable, a two years shelf life can be granted.
	CIPAC MT 75.3		**Determination of pH values:** The pH mean value of the test item at 1% m/v in standard water D is : Before the accelerated storage procedure: 5.22 at 19.4 °C after 1 min. 5.43 at 19.5°C after 2 min. 5.83 at 19.7°C after 10 min. After the accelerated storage procedure:					Acceptable

Subsection (Annex Point IIB. 3/TNsG)	Method	Purity/ Specification	Results[3]	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Evaluation FR
			5.31 at 20.0 °C after 1 min. 5.35 at 20.1°C after 2 min.					
Effects of light			Not required since the product will be stored protected from light.					Acceptable
Shelf life								No study provided. End of the test: March 2012.
Effect of low temperature								No study provided.
3.8 Technical characteristics (IIB3.8/Pt. I-B3.8)								
Wettability/ Suspensibility				Only solid preparations				Not applicable
Wet sieve analysis				For WPs, SCs, granules, tablets				Not applicable
Emulsifiability				Only forECs and ready for use emulsions				Not applicable
Disintegration time				Only for tablets				Not applicable
Friability of blocks								Not applicable
Persistence of foaming								Not applicable
Flowability/Pourability				Flowability only for				Not applicable

Subsection (Annex Point IIB. 3/TNsG)	Method	Purity/ Specification	Results[3]	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Evaluation FR
				granular preparations, pourability only for suspensions				
Dustability				Only for dustable powders				Not applicable
3.9 Compatibility with other products (IIB3.9/Pt. I-B3.9)								Not applicable
3.10 Surface tension (Pt. I-B3.10)								Not applicable
3.11 Viscosity (Pt. I-B3.10)								Not applicable
3.12 Particle size distribution (Pt. I-B3.11)				Only for powders and granules				Not applicable

Conclusion:

The product FANGA PATE PRO is a ready to use paste bait for mice and rats. The product is not highly flammable and not auto-flammable. It has no explosive or oxidizing properties. The pH of the product at 1%w/v in water after 10 min at 19.7°C is 5.83. The relavite density of the product is 1.322.

After storage at 54°C for 14 days in 10g paper sachets, the content of active substance decreased from 3.6 to 5.4%. The applicant has demonstrated that the product is stable after accelerated storage.

No study has been provided for the long term stability. As the accelerated storage is acceptable, a shelf life of 2 years can be granted. Study are required post registration to confirm the shelf life of the product.

Data requirement:

A long term storage stability study is required post-registration.

2.3.3 Analytical methods for detection and identification

2.3.3.1 Analytical method for determining the active substance and relevant component in the biocidal product

Analytical method for the determination of brodifacoum in the product has been provided.

Principle of the method: brodifacoum is analyzed after extraction from the product with methanol, filtered and quantified by reverse phase HPLC-UV.

Chromatographic conditions:

Colum: Zorbax SB Phenyl, length: 25cm, internal diameter: 3.0mm, granulometry: 5.0µm, Agilent.

Detector: UV, 265nm.

Mobile phase: Eluent A acetonitrile, Eluent B water/acetic acid 34/1.

Time (min)	Eluent% A	Eluent %B	Rate (mL/min)
0	70	30	1.0
15	70	30	1.0

Rate: 1(mL/min).

Oven temperature: 30°C.

Volume injected: 20µL.

Retention times (min): 4.9 for brodifacoum I and 5.4 for brodifacoum II.

Linearity was performed with 5 calibration standards, prepared in methanol, from 0.51to 1.50mg/L. The same linearity was used for the determination of active substance in the product FANGA PATE PRO and FANGA BLOC SP PRO.

Precision was performed by analyzing twice five samples of FANGA BLOC SP PRO. The extraction is the same as for FANGA PATE PRO.

Specificity and accuracy were performed with the formulation FANGA PATE PRO:

Test item: FANGA PATE PRO, Batch 308/11/01.

Blank formulation: (FANGA PATE PRO): Batch 311/11.

Reference item : brodifacoum, purity 99.3%, batch SZB8324XV (supplier: SIGMA Aldrich).

Results are summarized in the following table.

Table 2: Analytical method for the determination of brodifacoum (reverse phase HPLC-UV)

Sample	Test substance	Analytical method	Fortification range/ number of measurements	Linearity	Specificity	Recovery rate (%)			Repeatability	Reference
						range	Mean	St dev.		
FANGA PATE PRO Batch 308/11/01 Blank formulation Batch 311/11	brodifacoum	reverse phase HPLC-UV	Fortification levels: reconstituted sample at 1 concentration level (0.005%, 1mg/L in solution after dilution) two samples prepared and analysed in duplicate	0.51-1.50mg/L Y= 1.4717x -0.09 R^2=0.9965	No interference observed	100-102% two reconstituted sample in duplicate at 0.005% of active substances (1mg/L)	101 %	SD: 0.8 RSD: 0.8%	5 samples (FANGA BLOC PRO) in duplicate Mean: 0.0045% (w/w) SD:0.0001 RSD: 2.90% Horwitz value: 6.04	RICAU hélène, report No. 11-920010-015, May 2012 RICAU Hélène, report No. 11-920010-019, May 2012

Chromatograms were provided for the formulation blank, reference item and test item (at 0.005%). No interference has been observed at the retention time of brodifacoum. Specificity of the method is acceptable.

Linearity has been demonstrated with 5 calibration standards.

According to Sanco/3030/99 rev.4, recoveries should be between 80-120% for active substances with nominal content below 0.01%. Accuracy is acceptable.

RSD is below Horwitz value. Repeatability is acceptable.

It is concluded that the provided method is validated and acceptable for the product FANGA PATE PRO.

2.3.3.2 Analytical methods for determining relevant components and/or residues in different matrices

The analytical methods for determination of residues of active substance in different matrices (soil, air, drinking and surface water, body fluids and tissues, in food and feedstuff) provided in the CAR of the active substance are presented in annex 3 of this document.

Since there is no risk of contact with alimentation, no analytical method is required for the determination of brodifacoum residues in food and feedstuff.

2.4 Risk assessment for Physico-chemical properties

FANGA PATE PRO is a ready-to-use paste bait. The product is not highly flammable, not auto-flammable (up to 400°C), not explosive and does not have oxidizing properties.

The product is stable 14 days at 54°C in paper sachets. A provisional shelf life of 2 years can be granted.

Risk mitigation measures linked to assessment of physico-chemical properties

- Store away from light.

Required information linked to assessment of physico-chemical properties

- A shelf life study (2 years at ambient temperature) with monograph GIFAP n°17.

2.5 Effectiveness against target organisms

2.5.1 Function

MG 03: Pest Control.

Product Type 14: Rodenticide.

2.5.2 Organisms to be controlled and products, organisms or objects to be protected

According to the uses claimed by the applicant, the product FANGA PATE PRO is intended to be used to control rats and mice. The target organisms to be controlled are *Mus musculus*, *Rattus norvegicus and Rattus rattus*.

FANGA PATE PRO is used indoor by professional users. The products, organisms or objects to be protected are public and private buildings, and farms.

The application rates recommended by the applicant are the following (see also Annex 0a):

Rats: 180 g paste/secured bait point separated by 5-10 m.

Mice: 30 g paste/secured bait point separated by 1-2 m.

2.5.3 Effect on target organisms and efficacy

Brodifacoum is a second-generation single dose anticoagulant which prevents blood clotting in the target.

Clinical signs are progressive and occur three days after the ingestion of a toxic dose, leading to the death of target animal within 4 to 9 days after, according to the laboratory tests performed.

The applicant submitted the following studies:

- Study n°: ROD 2012 03: laboratory study:

For brown rats (*Rattus norvegicus*), the mean overestimated palatability percentage is 14.3 % (recalculated to 9.5 %) and the mortality percentage of 90%.

For house mice (*Mus musculus*): the mean overestimated palatability percentage is 8.7 % (recalculated to 5%) and the mortality percentage of 60 %.

Considering the results obtained in these trials, efficacy of the product FANGA PATE PRO is not proved.

Following the applicant's consultation, new efficacy and palatability laboratory studies and also field studies, reported below, have been performed to complete the efficacy part of the dossier.

- Study n° 12 TOX024-1: laboratory study:

For brown rats (*Rattus norvegicus*), the mean palatability percentage was 44 % and the mortality percentage was 90%. Death occurs between day 4 to day 7

- Study n° 12 TOX024-2: laboratory study:

For house mice (*Mus musculus*), the mean palatability percentage was 65 % and the mortality percentage was 100 %. Death occurs between day 4 to day 9.

- Study n°12 TOX24-14: field study:

For brown rats (*Rattus norvegicus*), the assessed bait has been very well accepted and the efficacy was estimated at 100 %.

- Study n°12 TOX24-15: field study:

For house mice (*Mus musculus*), the assessed bait has been very well accepted and the efficacy was estimated at 100 %.

French competent authorities (FR CA) consider that the elements presented in the dossier are sufficient to demonstrate the efficacy of the product against mice (*Mus musculus*) and against brown rats (*Rattus norvegicus)*. However, FR CA considers that for the claim "use against rats", efficacy must be shown on both species *R. norvegicus* and *R. rattus*. Considering that no supporting data on *Rattus rattus* were provided, suitable information (such as a field test) demonstrating the efficacy of FANGA PATE PRO against black rat, will need to be provided in support of the authorisation.

All efficacy studies are presented in annex 9.

2.5.4 Mode of action including time delay

Brodifacoum acts as a vitamin K antagonist. It interferes with the regeneration of prothrombin disturbing the normal blood clotting mechanisms and increasing tendency to bleed.

The main site of its action is the liver, where several of the blood coagulation precursors under vitamin-K dependent post translation processing take place before they are converted into the respective procoagulant zymogens.

Brodifacoum works by blocking the regeneration of vitamin K 2,3-epoxide to vitamin K hydroquinone. Since the amount of vitamin K in the body is finite, the progressive block of the regeneration of vitamin K will lead to an increasing probability of a fatal haemorrhage.

Death of target animal occurs 4 to 9 days after ingestion.

2.5.5 Occurrence of resistance - resistance management / Unacceptable effect

Resistance to the first generation anticoagulants has been widely reported in both *Rattus norvegicus* and *Mus domesticus* since the late 1950's. The incidence of resistance to first generation anticoagulants in areas in which it is established is commonly 25-85%. Some degree of resistance to difenacoum has been reported in the UK, Denmark, France and Germany but this is usually found in certain populations of rodents highly resistant to first generation anti-coagulants (Greaves et al., 1982[6]; Lund, 1984[7]; Pelz et al. 1995[8]). The resistance factor tells how much the anticoagulant dose has to be multiplied to kill resistant individuals compared to sensitive ones. The resistant factors for difenacoum in the brown rats ranged from 1.1 to 8.6 (Greaves and Cullen-Ayres 1988[9]). The study

[6] Greaves J. H.; Shepherd D. S.; Gill, J. E. (1982): An investigation of difenacoum resistance in Norway rat populations in Hampshire. *Annals of Applied Biology* 100, 581–587.
[7] LUND, M. (1984): Resistance to the second generation anticoagulant rodenticides. *In Proceedings of 11th vertebrate pest conference*, Sacramento, Ca. March 6-8, 1984: 89-94.
[8] Pelz H-J, Ha¨nisch D, Lauenstein G (1995) Resistance to anticoagulant rodenticides in Germany and future strategies to control *Rattus norvegicus. Pestic Sci* 43, 61–67.
[9] Greaves J. H.; Cullen-Ayres P. B. (1988): Genetics of difenacoum resistance in the rat. In: J. W. Suttie (Ed.), Current advances in vitamin K research, Elsevier, N.Y., 381–388.

included rats resistant to warfarin and difenacoum. Resistance factors for warfarin ranged from approx. 50 to 2300. Greaves et al. (1982) reported a fivefold difenacoum dose needed to kill difenacoum resistant rats. Considerable doubt exists as to the significance of reports in UK of resistance to second-generation anticoagulants and in the UK control failures with the second-generation products are increasingly being attributed to baiting problems rather than physiological resistance (Greaves and Cullen Ayres, 1988; Quy et al. 1992a,b[10]).

Recent studies carried out in different European countries, in the UK more particularly (Kerins *et al*, 2001; see annex 1) revealed the occasional occurrence of cross-resistances to second-generation anticoagulants, such as difenacoum and bromadiolone on resistant brown rats (*Rattus norvegicus*) populations to coumafene. Moreover, a recent publication (Baer *et al*., 2012) has demonstrated that the majority (91%) of warfarin resistant rat trapped in East and West parts of Belgium were also resistant to bromadiolone. The rats trapped in the region of Flanders (Northern Belgium) carried mutation Y139F. This mutation is found extensively in France where it also confers resistance to bromadionone (Grandemange *et al*., 2009). More recently, the same mutation was also found in UK (Prescott *et al*., 2011) where applications of bromadiolone had been unsuccessful. Difenacoum is also thought to be partially resisted by rats which carry Y139F. So, resistance to second generation anticoagulant rodenticides should not be minimized.

Only an exhaustive study carried out at the French and European levels could enable to point-out resistant areas with first-generation anticoagulants and potential cross-resistances to second-generation anticoagulants. It is one of the actions undertaken since 2010 in France by a group of scientists (Rodent program "*impacts of anticoagulants rodenticides on ecosystems-adaptations of target rodents and effects on their predators*").

Resistance management strategies

The immediate aim of resistance management is to prevent or retard the development of resistance to a given anticoagulant while, as far as is not counterproductive, permitting its continued use. The ultimate aim is to reduce or eliminate the adverse consequences of resistance.

CropLife International has published a strategy for resistant management of rodenticides (RRAC 2003). The habitat management is addressed in the strategy in addition to chemical control. The access of rodents should be restricted by physical barriers and no food should be available for rodents. Rotation between different anticoagulants is not a reliable means of managing the anticoagulant resistance, as all anticoagulants have the same mode of action and the nature of resistance is also similar. The resistant individuals can be identified by conducting a blood clotting response (BCR) test (Gill et al. 1993, RRAC 2003). The problem with the BCR test is that it has proven difficult to standardize and it produces both false positives and negatives (Pelz et al. 2005). In order to follow the occurrence and spread of difenacoum resistance, wild rats should be continuously monitored for resistance in the rodent controlled area. The recommendations of CropLife International are quoted below.

To avoid the development of resistance in susceptible rodent populations:

- When anticoagulant rodenticide is used, ensure that all baiting points are inspected weekly and old bait replaced where necessary.
- Undertake treatment according to the label until the infestation is completely cleared.
- On completion of the treatment remove all unused baits.

[10] Quy R.J., Shepherd D.S., Inglis I.R. (1992): Bait avoidance and effectiveness of anticoagulant rodenticides against warfarin- and difenacoum-resistant populations of Norway rats (Rattus norvegicus). *Crop Protection*, Volume 11, Issue 1, February 1992, Pages 14-20

- Do not use anticoagulant rodenticides as permanent baits routinely. Use permanent baits only where there is a clear and identified risk of immigration or introduction or where protection is afforded to high-risk areas.
- Monitoring of rodent activity should be undertaken using visual survey, through the use of non-toxic placebo monitors or by other effective means.
- Record details of treatment.
- Where rodent activity persists due to problems other than resistance, use alternative baits or baiting strategies, extend the baiting programme or apply alternative control techniques to eliminate the residual infestation (acute or sub-acute rodenticides, gassing or trapping).
- Ensure that complete elimination of the infestation is achieved.
- As appropriate during the rodenticide treatment, apply effective Integrated Pest Management measures (remove alternative food sources, water sources and harbourage and, proof susceptible areas against rodent access).

Treatment of rodent infestations containing resistant individuals:

- Where rodent infestations containing resistant individuals are identified, immediately use an alternative anticoagulant of higher potency. If in doubt, seek expert advice on the local circumstances.
- Alternatively use an acute or sub-acute but non-anticoagulant rodenticide.
- In both cases it is essential that complete elimination of the rodent population is achieved. Where residual activity is identified apply intensive trapping to eliminate remaining rodents. Gassing or fumigation may be useful in specific situations.
- Apply thorough Integrated Pest Management procedures (environmental hygiene, proofing and exclusion).
- Do not use anticoagulant rodenticides as permanent baits as routine. Use permanent baits only where there is a clear and identified risk of immigration or introduction or where protection is afforded to high risk areas.
- Record details of treatment.

Application of rodent control in area or block to eliminate resistance:

- Where individual infestations are found to be resistant or contain resistant individuals it is possible that the resistance extends further to neighboring properties.
- Where there are indications that resistance may be more extensive than a single infestation, apply control rodent programs in the whole area or block.
- The area under such management should extend at least to the boundaries of the area known resistance and ideally beyond.
- These programmes must be effectively coordinated and should encompass the procedures identified above.

The authorisation holder should report any observed resistance incidents to the Competent Authorities (CA) or other appointed bodies involved in resistance management every two years.

2.5.6 Evaluation of the label claim

French competent authorities (FR CA) assessed that the product FANGA PATE PRO has shown a sufficient efficacy for the control of house mice (*Mus musculus*) and brown rats (*Rattus norvegicus)*.

But for the claim ”use against rats”, efficacy must also be shown on black rats (*R. Rattus)*. So, in the absence of supporting data on *Rattus rattus*, suitable information (such as a field test) demonstrating the efficacy of FANGA PATE PRO against black rat will need to be provided in support of the authorisation.

Label has to be revised as following:

- Inspections of bait points have to be made 3 days after the first application then weekly for use in building.

The application rates validated are the following (see also Annex 0b):

House mice (*Mus musculus*): 30 g pasta/secured bait point separated by 1-2 m.

Rats (*Rattus norvegicus* and *Rattus rattus*): 180g pasta/secured bait point separated by 5-10 m

The product FANGA PATE PRO is supplied in 10g sachets. The amount of bait per bait station or bait points must not exceed the recommended application rates.

2.5.7 Conclusion of the efficacy assessment

The product FANGA PATE PRO has shown a sufficient efficacy and can be used for the control of house mice (*Mus musculus*) and brown rats (*Rattus norvegicus*).

French competent authorities (FR CA) assessed that the product FANGA PATE PRO has shown a sufficient efficacy for the control of *Rattus norvegicus*. But for the claim ”use against rats”, efficacy must be also shown on *R. Rattus*. Consequently, in the absence of supporting data on *Rattus rattus*, suitable information (such as a field test) demonstrating the efficacy against black rat of FANGA PATE PRO will need to be provided in support of the authorisation. Field tests against all the target organisms (*Rattus rattus, Rattus norvegicus and Mus musculus)* performed with a 2 years old product must be submitted to support the storage duration of 2 years.

The authorisation holder should report any observed resistance incidents to the Competent Authorities (CA) or other appointed bodies involved in resistance management every two years.

Conditions of use linked to efficacy assessment

- Adapt the number of bait points to the infestation level.
- Inspect and resupply the bait points, 3 days after application then once a week as long as the bait is consumed.
- Remove all bait points after the end of treatment.
- The amount of bait per bait point and distances between bait points must be respected. Products have always to be used in accordance with the label.
- The users should inform is the treatment is ineffective and report straightforward to the registration holder any alarming signals which could be assumed to be resistance development.
- To avoid resistance, professional users must:
    - use the treatment alternately with other kinds of active substances having different modes of action;
    - adopt integrated pest management methods such as the combination of chemical, physical control methods and other public health measures;

- monitor the level of efficacy (periodic check), and investigate the case of reduced efficacy for possible evidence of resistance;
- not use the product in areas where resistance is suspected or established.

Recommandations to be taken into account by the applicant

- Adapt the amount of bait per bait point to the validated effective dose.
- The product label has to contain information on resistance management for rodenticides.

Required information linked to efficacy assessment

- The authorisation holder has to monitor the resistance phenomenon of rodent populations toward the active substance brodifacoum, and resistance strategies management must be put in place. Results of the resistance monitoring must be submitted to the Competent Authorities (CA) or other appointed bodies involved in resistance management every 2 years.
- Field tests against all the target organisms (*Rattus rattus, Rattus norvegicus and Mus musculus)* performed with a 2 years old product must be submitted to support the storage duration of 2 years.

2.6 Description of the intended use

The product FANGA PATE PRO is intended to be used for the control of rodents indoor by professional users. The target species claimed by the applicant are mice and rats.

Efficacy is demonstrated at the following dosage:

Rats: 180 g paste/secured bait point separated by 5-10 m. (indoor only)

House mice: 30 g paste/secured bait point separated by 1-2 m. (indoor only)

The product is a ready-to-use paste bait with no dilution nor other substances added for application. The mode of application claimed by the applicant is a manual application by professional users in secured bait point (bait stations).

2.7 Risk assessment for human health

2.7.1 Hazard potential

2.7.1.1 Toxicology of the active substance

The toxicology of the active substance was examined extensively according to standard requirements.

The results of this toxicological assessment can be found in the **combined Assessment Report**. Brodifacoum (CAS no. 56073-10-0) was notified as an existing active substance, by Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force[11], hereafter referred to as the "AS applicants", in product-type 14. A combined assessment report was available on December 2010.

The following corresponds to the summary of the effect assessment available in the combined assessment report of brodifacoum.

- **Toxicokinetics**

Data from Syngenta:

Brodifacoum (0.21 mg/kg bw) administered orally to rats was rapidly absorbed (T_{max} =8h; C_{max} 16.1 ng/ml whole blood). The levels declined slowly and about 10% (1.3 ng/ml) was still present at 10 days after dosing. Almost all (82.5 %) the radioactivity in whole blood was found to be associated with the plasma. Based on the radioactivity still associated to the animal tissues, 10 days after the treatment, the **oral absorption was > 75%.** After a single oral dose of 10 mg/kg of *Brodifacoum* about 64.0% was absorbed and could be accounted for in the liver, carcass and bile 48h after dosing. The rest was recovered in the faeces, as unabsorbed material.

After absorption the product was widely distributed. 10 days after dosing the proportion of the retained dose was highest in the liver (22.8 %), followed by the pancreas (2.3 %), and then the kidney (0.8 %), heart (0.1 %) and spleen (0.2 %). The remainder of the dose (≅50%) was in the carcass and skin.

Brodifacoum was only partially metabolised. 31.3% and 19.6% of the residues in the carcass and liver, respectively, was unchanged *Brodifacoum*. Two more polar metabolites were detected in the bile, the major one being identified as the glucuronide.

Brodifacoum shows a high potential for bioaccumulation: in all studies undertaken and at all dose levels tested, the liver retained the largest % of the dose, even very long time after dosing.

Analyses of the rat livers from the 90 day feeding study, indicate a non-linear accumulation of *Brodifacoum* vs dose and time.

A small amount (11 – 14%) of the radioactivity was slowly eliminated in urine and faeces over 10 days following a single oral dose of 0.25 mg/kg. Biliary and renal routes are of equal significance in the elimination of *Brodifacoum*. The rate of elimination as given by the biological half-life, was calculated to be 150 – 200 days.

The elimination from the liver was biphasic at higher doses. There was a rapid phase (days 1-4) which also corresponded to a reduction in clotting factor synthesis, followed by a slower terminal phase (days 28-84) during which blood clotting function was normal. The half-life of elimination from the liver during the rapid and the slow phase was ≅4 and 128 days, respectively. At low dose levels, clotting factor synthesis was unaffected indicating that probably only the slow elimination phase was

[11] Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force Combined Assessment Report according to the procedure of Directive 98/8/EC, active substance in biocidal products, brodifacoum CAS n°56073-10-0, product type 14 (rodenticides), RMS Italy, Revision2: November 2010.

present in the liver. The half-life of *Brodifacoum* in the liver was calculated in the range of 282-350 days.

Dermal absorption was assessed by using a formulation (ready-for-use pellet bait) containing 0.0048% *Brodifacoum* w/w tested in vitro test on human skin samples. Over the entire 24 h exposure *Brodifacoum* (determined by LC-MS-MS) was found below the LOQ in the receptor fluid (<3.53% of the applied dose) and in the epidermis (<1.64%), after tape stripping. The applied dose was readily removed by mild skin washing and recovered (108 ±6.25%) in the washing fluid. **A 'surrogate value' of 5% dermal absorption was calculated** by summing up the amount in the receptor fluid and in the epidermis after tape stripping, which can be considered as systemically available material. This value has been taken forward to the risk characterization as the worst case, also taking into account that the exposure period exceeds the usual time (*i.e.* 8 hours) of professional handling.

***Data from Activa/PelGar*:**

Read across to data from some related 2nd generation anticoagulants (*i.e. Difenacoum*, *Flocoumafen*) is requested for ADME data, including dermal absorption, and has been applied for other end-points by the RMS.

Beside the similar mode of action, the read across is supported by bridging studies demonstrating the similarity in physico-chemical and toxicological properties of these substances which are presented up-front to Doc. IIA- Section 3.

Anticoagulant rodenticides including *Brodifacoum* are rapidly absorbed via the gastro-intestinal tract and oral absorption is assumed to be 100%, on the basis of amount of radioactivity recovered in the excreta and retained in the tissues. The major route of elimination after oral administration is via the faeces, both as polar metabolites and parent compound. *Brodifacoum* is widely distributed and bioaccumulates in the liver with minor concentrations in the kidney.

Elimination processes are very slow with 50-75% of the administered dose being retained in the liver ($t_{1/2}$ for hepatic residues more than 200 days).

The metabolism of *Brodifacoum* is limited, although in repeated dose studies evidence of induction of metabolism was reported, with increasing levels of radioactivity associated to polar metabolites recovered in the urine. The toxicologically relevant chemical species is the parent compound.

No study on dermal absorption of *Brodifacoum* has been presented. *Brodifacoum* is expected to be slowly absorbed through the skin, due to the lipophylicity of the molecule, allowing passive transport through the membrane. The read across principle can be applied, based on the close structural relationship, the similar physico-chemical properties and the same mode of action displayed by *Brodifacoum* towards other 2nd generation anticoagulants, such as *Difethialone* and *Difenacoum*. A dermal absorption value =4% has been adopted for *Difethialone*, whereas in the case of *Difenacoum* two different values have been used for risk characterisation depending on the type of formulation, that is 3% (pellets and grains) or 0.047% (wax block bait).

In the CAR, by applying the read across from data on a structurally related 2nd generation anticoagulant *Difenacoum*, a 3% dermal absorption value was adopted for the exposure calculation. This value was calculated from a dermal absorption study testing a pellet formulation containing *Difenacoum* as active substance.

Conclusion on toxicokinetics:

An almost complete oral absorption can be considered, on the basis of amount of radioactivity recovered in the excreta and retained in the tissues. *Brodifacoum* is widely distributed and bioaccumulates mainly in the liver with lower concentrations in the kidney. Hepatic bioaccumulation of *Brodifacoum* is a non-linear *vs* dose and time. The elimination kinetic from the liver was biphasic, with an half-life in the range of 282-350 days. The excretion after oral administration is very slow (11 – 14% in 10 days), occurring via the urine and the bile, both as polar metabolites (glucuronide) and

parent compound. The metabolism of *Brodifacoum* is limited and the toxicologically relevant chemical species is the parent compound.

Concerning the dermal absorption value to be used in the risk characterisation for wax block bait, in the Combined Assessment Report for *Difenacoum* (September 2009) a value of 0.047% was proposed. Therefore, on the basis of the available study and reading across from data on other 2nd generation anticoagulant rodenticides, two different values should be used for risk characterisation depending on the type of formulation: 5% (pellets and grains) or 0.047% (wax block bait).

- **Acute effects**

Data from Syngenta:

Brodifacoum was very toxic to rats and mice with similar oral LD_{50} of about 0.4 mg/kg bw to the male rat and mouse. *Brodifacoum* is also acutely toxic by the dermal and inhalation routes. Death was the result of internal haemorrhage.

Brodifacoum does not fulfil the EU criteria for classification as a skin or eye irritant, but is able to cause skin sensitization in guinea pig and fulfils the EU criteria for classification as a skin sensitizer.

***Data from Activa/PelGar*:**

Brodifacoum is very toxic if swallow (oral LD_{50} <5 mg/kg bw) or in contact with skin (dermal LD_{50}= 7.48 mg/kg bw in rat females; even lower in males).

The waiving for the inhalation toxicity study has been accepted due to low vapour pressure of *Brodifacoum* and data on dustiness and particle size, indicating that the potential for inhalation is limited in addition to ethical and animal welfare reasons. However, based on data with structurally related compounds with the same mechanism of action (*i.e.* 2nd generation anticoagulants), it is expected that the substance is also highly toxic after inhalation.

Brodifacoum is not irritant to the skin or eyes of rabbits and showed no sensitizing potential in a LLNA study in mice.

Conclusion on acute effects:

Brodifacoum is very toxic after oral administration and also via the dermal and inhalation routes. Death was the result of internal haemorrhage. Classification with T+; R26/27/28; 'Very toxic by inhalation, in contact with skin and if swallowed' is warranted.

Brodifacoum does not fulfil the EU criteria for classification as a skin or eye irritant. Although showed no sensitizing potential in a LLNA study in mice, it was able to cause skin sensitization in guinea pig and fulfils the EU criteria for classification as a skin sensitizer.

- **Repeated Dose Effects**

Data from Syngenta:

Repeated dose oral studies show that in the rat and in the dog, the clinical signs, haematological and post mortem data were consistent with the known pharmacological action of *Brodifacoum*: impairment of the clotting cascade and increased prevalence of haemorrhage leading to death. There were no indications of other secondary toxicities: any of the other parameters including histopathological analysis revealed no treatment related alterations.

The subchronic 90-day oral toxicity allowed the derivation of the lowest repeated toxicity NOEL= 0.001 mg/kg bw/day. In this study, no treatment related effects on haematological parameters were evidenced at any dose, after 45 days, but statistically significant increases in both the kaolin-cephalin time (KCT) and the prothrombin time (PT) were measured at the highest dose level, 0.004 mg/kg bw/day after 90 days. Based upon this effect on prothrombin times and based on

haemorrhagic changes seen at necropsy, the NOEL was set at the next lowest dose, 0.001 mg/kg bw/day.

Classification with T; R48/23/24/25 “Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed” is warranted based on these data plus extrapolation from the acute data for the dermal and inhalation route of exposure.

***Data from Activa/PelGar*:**

Repeated oral exposure to *Brodifacoum* resulted in clinical signs and toxicity consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent (lethal haemorrhages). The overall NOAEL for subchronic oral toxicity is 0.04 mg/kg/day.

No data have been submitted on dermal repeated toxicity On the basis of both physico-chemical properties and *Brodifacoum* mode of action it can be anticipated that subchronic effect due to prolonged skin contact should not be disregarded.

No data on repeated inhalation toxicity have been submitted. As indicated by the low vapour pressure, dustiness and particle size, the potential for inhalation is low and the request for a repeated dose inhalation toxicity study is not considered justified also based on ethical and animal welfare reasons.

However, based on the results of the acute dermal and inhalation toxicity studies, route-to-route extrapolation, consistently with the decision adopted for *Difenacoum* (being the read across accepted for other end-points), it is justified to assume a similar concern for serious damage to health by prolonged exposure through dermal and inhalation routes also.

- **Genotoxicity**

Data from Syngenta:

Brodifacoum was tested in *Salmonella typhimurium* strains TA 1535, TA 1537,TA 98, TA 100, TA 1538. with and without S9-mix, up to 5000 mg/plate, with negative results. No clastogenic activity was observed in the *in-vitro* cytogenetic assay in human lymphocytes, performed with and without metabolic activation, up to cytotoxic doses. The *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y cells also resulted negative, with and without S9-mix, while cytotoxic effects was observed at the highest doses. The AS applicant submitted also an *in vitro* UDS test and in an *in vitro* cell transformation assay, but because of several methodological and reporting shortcomings, they were considered of limited scientific significance. An *in vivo* mouse micronucleus test gave negative results. The studies submitted were rather dated, therefore they were not always compliant with the current guidelines. However a genotoxic potential of the active substance can be reliably ruled out.

***Data from Activa/PelGar*:**

Brodifacoum was tested for genotoxic activity in the bacterial reverse mutation test in *Salmonella thyphimurium* in strains TA 98, TA 100, TA 102, TA 1535 and TA 1537, up to 5000 □g/plate, with and without metabolic activation (S9-mix). No genotoxic activity was observed in any bacterial strain. The substance resulted negative up to cytotoxic concentration also in the gene mutations assay in L5178Y mouse lymphoma cells, with and without S9-mix, and in the *in vitro* mammalian chromosome aberration test in human lymphocytes (50% mitotic inhibition at the maximum dosage tested).

- **Carcinogenicity/chronic toxicity**

Carcinogenicity and long-term toxicity studies were waived as infeasible and unnecessary.

- **Reproductive and developmental toxicity**

Data from Syngenta:

Brodifacoum did not induce developmental effects in two adequate prenatal toxicity studies

in the rat and rabbit, respectively.

In particular, in the rat studies maternal hemorrhages were observed at dose levels > 0.01 mg/kg bw (NOEL 0.001 mg/kg bw) whereas no effects on conceptuses were detected up to the top dose level of 0.02 mg/kg bw. In the rabbit study, the top dose of 0.005 mg/kg b.w caused a high proportion of maternal deaths, whereas no significant effects on litters were observed. In spite of these findings, a provisional decision has been made at the Technical Meeting of Classification and Labelling that [R61] should be applied to all anticoagulant active substances on the basis of analogy to *Warfarin*.

***Data from Activa/PelGar*:**

There was no evidence of developmental toxicity effects up to the dose levels of 0.04 and 0.004 mg/kg bw in rats and rabbits, respectively. In rabbit dams an increase in kaolin-cephalin and prothrombin time was present at 0.004 mg/kg bw (NOAEL 0.002 mg/kg).

Whereas it is suggested that two-generation studies may not be need for anticoagulant rodenticides, a two-generation study on rat was submitted: findings confirmed those of developmental toxicity, both qualitatively (parental toxicity with haemorrhages, no reproductive or developmentakl effects in the absence of general toxicity) and quantitatively (NOAEL: 0.001 mg/kg bw).

Since the conventional OECD Guideline 414 may have limitations in the detection of possible developmental effects of coumarin related compounds, and in spite of these findings, a provisional decision has been made at the Technical Meeting of Classification and Labelling that [R61] should be applied to all anticoagulant active substances on the basis of analogy to *Warfarin.*

- **Neurotoxicity**

Data from Syngenta:

None of the acute or subchronic performed tests gave any indication for a potential neurotoxic effect of *Brodifacoum*

***Data from Activa/PelGar*:**

The toxicological studies do not indicate any neurotoxic effects.

Conclusion on repeated dose effects:

Repeated oral exposure to *Brodifacoum* resulted in clinical signs and toxicity consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent (lethal haemorrhages). The NOEL for subchronic oral toxicity is in the range 0.04 -0.001 mg/kg/day (the lowest values identified with sensitive end-points, such as increases in both the kaolin-cephalin time and the prothrombin time). Based on results from the acute dermal and inhalation toxicity studies, route-to-route extrapolation, consistently with the decision adopted for *Difenacoum*, it is justified to assume serious damages associated to prolonged exposure through dermal and inhalation routes also. Therefore, classification with T; R48/23/24/25 “Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed” is warranted.

Conclusion on Genotoxicity and Carcinogenicity:

Brodifacoum displayed no mutagenic activity in a standard range of genotoxicity tests. No long-term carcinogenicity study was submitted by the two AS applicants. In fact, chronic toxicity studies were not considered to be technically feasible due to the specific action of the active substance on the

test/target species. However, the anticoagulant action is apparently the only pharmacological action of *Brodifacoum*. The active substance has no structural alerts for carcinogenicity and no concern about possible non-genotoxic carcinogenic potential can be derived from the toxicological studies. Therefore the justifications of both AS applicants for not-submission of carcinogenicity data was considered acceptable.

Conclusion on Reproductive toxicity:

Reproductive and developmental toxicity studies on *Brodifacoum* did not reveal any specific effects. General toxicity effects were consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent. The lowest NOAELs for rabbits and rats were 0.002 and 0.001 mg/kg bw.

In spite of these findings, a provisional decision has been made at the Technical Meeting of Classification and Labelling that [R61] should be applied to all anticoagulant active substances on the basis of analogy to *Warfarin*.

None of the acute or subchronic performed tests gave any indication for a potential neurotoxic effect of *Brodifacoum*.

The harmonised classification of the active substance is the following:

Classification under directive 67/548/EEC	**Classification under regulation (EC) 1272/2008**
T+ R27/28 T ; R48/24/25 No specific limit concentrations.	Acute Tox 1 H310 Acute Tox 2 H300 STOT RE Cat 1 H372 No specific limit concentrations.

The following corresponds to the summary of the derivation of the AELs from the combined Assessment Report of brodifacoum:

Data from Syngenta:

The Acceptable Exposure Level for acute exposure (AEL_{acute}) was based on the maternal NOEL from developmental study of 0.001 mg/kg bw/day (rat, maternal effect). A safety factor of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{acute} results to be of 3.3×10^{-6} mg/kg/day.

The Acceptable Exposure Level for repeated exposure (AEL_{chr}) was based on a subchronic NOEL from a 90-day oral rat study of 0.001 mg/kg bw/day. A safety factor of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{chr} results to be of 3.3×10^{-6} mg/kg/day.

***Data from Activa/PelGar*:**

The Acceptable Exposure Level for acute exposure (AEL_{acute}) was based on NOAEL from a developmental study (female rabbit) of 0.002 mg/kg bw/day. A safety factor of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{acute} results to be of 6.7×10^{-6} mg/kg bw/d.

The Acceptable Exposure Level for repeated exposure (AEL_{chr}) was based on NOAEL for females from the reproductive 2-generation study in rat of 0.001 mg/kg bw/day. A safety factor of 300 (10 for

intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{chr} results to be of 3.3×10^{-6} mg/kg bw/day.

TMIII09 agreed to derive $AEL_{medium\ term}$ consistently with what decided for the other AVK rodenticides. Therefore, $AEL_{medium\ term}$ was calculated from the NOAEL of 0.002 mg/kg bw/day (developmental oral toxicity study in rabbit) divided by an Assessment Factor of 300 (10 for interspecies x 10 for intraspecies x 3 additional factor for severity of effects). The $AEL_{medium\ term}$ results to be of 6.7×10^{-6} mg/kg bw/day.

***Conclusions**:*

The following AELs should be considered in the risk characterization for *Brodifacoum*:

- AEL_{acute} of 3.3×10^{-6} mg/kg/day based on the maternal NOEL from a teratogenicity study of 0.001 mg/kg bw/day (rat, maternal effect)
- $AEL_{medium\ term}$ of 6.7×10^{-6} mg/kg bw/day based on the NOAEL from a developmental study (female rabbit) of 0.002 mg/kg bw/day
- AEL_{chr} of 3.3×10^{-6} mg/kg bw/day based on the NOAEL for females from the reproductive 2-generation study in rat of 0.001 mg/kg bw/day

2.7.1.2 Toxicology of the substance(s) of concern

Considering the following definition of a substance of concern set in the TNsG on data requirement chapter 4 (2000), "*the substance is regarded as a substance of concern if [...] it is classified as dangerous and its concentration in the product exceeds the classification limit set in the Council Directive 88/379/EEC, as amended by Directive 1999/45/EC, for a particular dangerous property or the other classification limit indicated for the substance in a preparation set in Annex I of Council Directive 67/548/EEC or causes that the overall sum of the concentrations of dangerous substances in the product exceeds the limit for classification of the preparation set in Council Directive 88/379/EEC, as amended by Directive 1999/45/EC, for a particular dangerous property*", the biocidal product FANGA PATE PRO contains no substance of concern.

2.7.1.3 Toxicology of the biocidal product

The toxicology of the biocidal product was examined appropriately according to standard requirements. The product was a dummy product in the EU- review program for inclusion of the active substance in Annex I of Directive 98/8/EC.

The basis for the health assessment of the biocidal product is laid out in Annex 5 "Toxicology – biocidal product".

Acute oral and dermal toxicity, skin and eye irritation and skin sensitisation studies have been performed with the product FANGA BLOC SP PRO, a block formulation containing 0.005% of brodifacoum. The compositions of FANGA BLOC SP PRO and FANGA PATE PRO are considered similar.

2.7.1.3.1 Percutaneous absorption

A default value of 0.047% was considered for FANGA PATE PRO, as mentioned in the brodifacoum assessment report.

2.7.1.3.2 Acute toxicity

Oral route

No mortality occurred during the study (daily examination during 14 days).

No clinical signs related to the administration of the test item were observed.

The body weight evolution of the animals remained normal throughout the study.

The macroscopically examination of the animals at the end of the study did not reveal treatment-related changes.

LD_{50} of the test item is higher than 2000 mg/kg/bw.

Route	Method	Species	Dose level	LD50
Oral	OECD 423	Rat 3 males and 3 females	2000mg/kg bw	>2000 mg/kg bw

Dermal route

No mortality occurred during the study.

The body weight evolution of the animals remained normal throughout the study.

Neither cutaneous reactions nor systemic clinical signs related to the administration of the test item were observed.

The macroscopically examination of the animals at the end of the study did not reveal treatment-related changes.

LD_{50} of the test item is higher than 2000 mg/kg/bw.

Route	Method	Species	Dose level	LD50
Dermal	OCDE 402	Rat 5 males and 5 females	2000 mg/kg bw	>2000 mg/kg bw

Based on the above-mentioned results, no classification is required for FANGA PATE PRO.

2.7.1.3.3 Irritation and corrosivity

Based on the results of the irritation assays on rabbit's skin and eye, no classification is required for FANGA PATE PRO.

Route	Method	Species	Dose level	
Skin	OECD 404	Rabbit NZ 3 females	0.5 g	Not irritant
Eye	OCDE 405	Rabbit NZ 3 females	0.1 g	Not irritant

2.7.1.3.4 Sensitisation

Based on the results of the irritation assays on rabbit's skin and eye (LLNA), no classification is required for FANGA PATE PRO.

Route	Method	Species	Dose level	
Skin	OECD 429	Mice16 (12 for the treated groups)	Topical way of induction: 5, 10, 25% of the test item	Not skin sensitizing

2.7.1.3.5 Other studies

No other studies are performed on FANGA PATE PRO.

2.7.2 Human exposure assessment

FANGA PATE PRO (PT14) is a ready-to-use rodenticide containing 0.005 % of brodifacoum (pure: 950 g/kg). Baits are packaged in sachet for professional users.The baits are placed in bait stations (tamper-resistant bait boxes or covered bait stations) out of reach of children and domestic animals.

No new human exposure studies have been submitted.

2.7.2.1 Identification of main paths of human exposure towards active substance from its use in biocidal product

The potential for exposure to brodifacoum paste baits is summarised in the table below:

Table 3: Main paths of human exposure

Exposure path	Industrial use	Professional use	General public	*via* the environment
Inhalation	Not relevant	Potentially significant	Negligible	Negligible
Dermal	Not relevant	Potentially significant	Potentially significant	Negligible
Oral	Not relevant	Negligible	Potentially significan	Negligible

2.7.2.2 Direct exposure as a result of use of the active substance in biocidal product

2.7.2.2.1 Exposure of professional users

In Annex 6 „Safety for professional operators", the results of the exposure calculations for the active substance and the substance of concern for the professional user are laid out.

FANGA PATE PRO is used for the control of rats and mice for use indoors, with the purpose of protecting human food and animal feedstuffs, and for human hygiene.

The product is only supplied in sachets. Considering the nature of the sachets (paper), a dermal exposure during loading is taken into account. Exposure assessment has been performed with the dose of 180 g of product for the control of rats. This assessment covers the assessment for mice as the intended doses are lower.

In the dossier, TRIPLAN assessed the human exposure based on the TNsG on human exposure, section 7.2 of part 3 – June 2002. This document only contains a series of examples for human exposure assessment and should not be considered as reference data. Therefore, since TRIPLAN provided a letter of access for the unpublished CEFIC study "*Chambers J.G. and Snowdon P.J. Study to determine potential exposure to operators during simulated use of anticoagulant rodenticide baits*", the FR CA decided to base the human exposure assessment for professionals on this study as done by the RMS (Italy) of the active substance in the Assessment report on brodifacoum. This study examined the inhalation and dermal exposures associated with all activities involved in using a paste bait (filling and placing bait points, and clean-up and disposal of bait points). The used paste bait containing flocoumafen was selected as a worst case representative product of all block rodenticide baits. In this study, 10 replicates were performed at 1, 5 and 10 manipulations. Therefore, the FR CA decided to use the exposure estimations issued from the CEFIC study for the assessment of FANGA PATE PRO

Additionally, the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant), agreed at TMIII 2010 and the HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants) agreed at TMII 2011 were taken into account for the estimation of exposure for professionals.

Loading phase:

Based on the CEFIC study and taking into account the HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants) agreed at TMII 2011, the amount of product on fingers/hands **during the loading** of 5 wax blocks of 20g per manipulation was 27.79 mg of product. The following parameters were taken into account:

- active substance in product: 0.005 %,(w/w);
- number of blocks per bait site[12]: 18 for control of rats
- dermal absorption: 0.047 %,
- body weight: 60 kg.

Thus, the systemic dose of brodifacoum per placing of one bait site is 3.9×10^{-8} mg/kg bw/event for control of rats and mice.

The harmonised number of manipulations for rodenticides anticoagulant set in the HEEG opinion agreed at TMIII 2010 was used to assess the overall exposure systemic dose. Considering 60 loadings are done per day, the systemic dose via skin is 2.4×10^{-6} mg a.s/kg bw/day for the control of rats.

Cleaning phase:

Based on the CEFIC study and taking into account the HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants) agreed at TMII 2011, the amount of product on fingers/hands **during the cleaning** of one bait site is 5.70 mg of product. The following parameters were taken into account:

- active substance in product: 0.005 %,(w/w);

[12] Although the block weights 10 g and not 20 g as in the CEFIC study, it was considered that the important parameter is the number of blocks loaded rather than the weight of the block

- dermal absorption: 0.047 %,
- body weight: 60 kg.

Thus, the systemic dose of brodifacoum per cleaning of one bait site is $2.2x10^{-9}$ mg/kg bw/event for control of rats and mice (because the amount of disposed bait is not taken into account).

The harmonised number of manipulations for rodenticides anticoagulant set in the HEEG opinion agreed at TMIII 2010 was used to assess the overall exposure systemic dose. Considering 15 cleaning are done per day, the systemic dose via skin is $3.4x10^{-8}$ mg a.s/kg bw/day for the control of rats and mice, because the amount of disposed bait is not taken into account during cleaning.

In conclusion, the total systemic dermal exposure is set at $2.4x10^{-6}$ mg/kg bw/day without PPE for the control of rats and mice.

2.7.2.2.2 Exposure of non-professional users

The product is for professional use only.

2.7.2.3 Indirect exposure as a result of use of the active substance in biocidal product

Handling of dead rodents (adult, child, infant) – acute scenario

Exposure can occur during handling of dead rodents by professionnal and general public. However, this scenario is excluded and considered of low relevance due to unrealistic assumptions (TNsG on human exposure (2007)). Gloves are recommended to help prevent rodent-borne disease, therefore exposure due to this senario is considered negligible.

Oral exposure by ingesting bait (infant) – acute scenario

Besides, exposure of non users can occur during ingestion of poison baits. For the scenario "*oral exposure by ingesting bait*", a reverse scenario was calculated. Based on the acute AEL of 3.3×10^{-6} mg a.s/kg bw/day, a body weight of 10 kg and an oral absorption of 75% (as stated in the Assessment report of brodifacoum), ingestion of more than 0.88 mg of product per day by an infant is needed to exceed the AEL.

2.7.2.4 Exposure to residues in food

The intended uses description of the product FANGA PATE PRO indicates that these uses are not relevant in terms of residues in food and feed. The product is to be used as rodenticide and does not come in direct or indirect contact with food and feedstuff. No further data are required concerning the residue behaviour.

2.7.2.5 Combined exposure

Not relevant.

2.7.3 Risk assessment for human health

The estimated exposures for the professional users are compared to the systemic AEL of brodifacoum set in the Assessment Report ($3.3x10^{-6}$ mg/kg bw/day for short-term and long-term exposures).

2.7.3.1 Risk for direct exposure

2.7.3.1.1 Professional users

Based on the risk assessment of the active substance, the risk for professional users resulting from the intended use is acceptable for FANGA PATE PRO, even if gloves are not worn (%AEL at 72.3%) for the control of rats and, by extension, of mice.

Gloves are anyway recommended to help prevent rodent-borne disease. Moreover, the mention “do not open the sachet” has to be added in the label of the product.

Table 4: Summary of risk characterisation for professionals for the control of rats and mice

Scenario	AEL (mg/kg bw/d)	Exposure (mg/kg bw/d)	%AEL	Risk
Sachet formulation (exposure during loading and cleaning phases)				
Professionnal (without gloves)	$3.3x10^{-6}$	$2.4x10^{-6}$	72.3	Acceptable

2.7.3.1.2 Non-professional users

The product is for professional use only.

2.7.3.2 Risk for indirect exposure

Based on a reverse scenario, more than 0.88 mg of product per day should be ingested by an infant to exceed the AEL. This indicates that infants are at significant risk of poisoning. Therefore, even if FANGA PATE PRO contains a bittering agent which reduces the likelihood of ingestion, the baits should be unattainable for children.

Product label (“do not open the sachet”) and good practice advise users to prevent access to bait by children and infants.

2.7.3.3 Risk for consumers via residues

Considering the intended uses, no dietary risk assessment is necessary.

2.7.3.4 Risk for combined exposure

Not relevant.

2.7.3.5 Conclusion on human health risk assessment

Based on the risk assessment of the active substance, the risk for professional users resulting from the intended use is acceptable for FANGA PATE PRO for the control of rats and mice.

Risk of secondary poisoning to infants and children is considered as relevant. Therefore, even if the product FANGA PATE PRO contains a bittering agent which reduces the likelihood of ingestion, the baits should be unattainable for children. Product label ("do not open the sachet") and good practice advise users to prevent access to bait by children and infants.

The intended uses description of the product FANGA PATE PRO indicates that these uses are not relevant in terms of residues in food and feed. The product is to be used as rodenticide and does not come in direct or indirect contact with food and feedstuff.

Risk mitigation measures linked to risk assessment for human health

- Gloves have to be worn to help prevention against rodent-borne disease.
- Do not open the sachets.
- Apply strict hygiene measures: do not eat, drink or smoke during handling of the product and wash hands after use of the product.
- Use in tamper-resistant bait boxes or in covered bait stations.
- Tamper-resistant bait boxes should be clearly marked to show that they contain rodenticides and that they should not contain other products than rodenticides.
- Covered bait stations must be placed only in areas not accessible to the general public and non-target animals.
- Baits must be unattainable to children, pets or other non-target animals in order to minimize the risk of poisoning.
- Do not place tamper-resistant bait boxes and covered bait stations on surfaces in contact with food, feed or drinks and beverages.
- Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations and dead rodents, during and after treatment.
- Remove all bait points after the end of treatment.

Emergency *(information provided in the product Safety Data Sheet)*

Inhalation: no action should be necessary.

Ingestion: if swallowed, seek medical advice immediately and show container or leaflet. A treatment with vitamin K1 should be necessary during a long period.

Skin or eye contact: wash immediately with plenty of water.

Disposal considerations

- Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations and dead rodents, during and after treatment.
- Remove all bait points after the end of treatment.

Required information linked to risk assessment for human health

None.

2.8 Risk assessment for the environment

2.8.1 Fate and distribution in the environment of the active substance brodifacoum

The summary of information about the active substance brodifacoum is carried out with the data from the combined AR of brodifacoum owned by Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force[11].

2.8.1.1 Degradation

2.8.1.1.1 Abiotic degradation

2.8.1.1.1.1 Hydrolysis in function of pH

Brodifacoum is considered stable to hydrolysis. It was concluded that the hydrolytic half-life (DT_{50}) was above one year at environmentally relevant pH. The hydrolytic degradation is deemed negligible.

2.8.1.1.1.2 Photolysis in water

Brodifacoum photolytically degrades in aqueous solution with a half-life (DT_{50}) < 1 day. Photolysis of brodifacoum was fast with 38 % of removal in the first hour of exposure. Greater than 89 % of photolysis has occurred by around three hours. No degradation products were detected.

2.8.1.1.1.3 Photolysis in soil

Not relevant for a use inside buildings of products containing Brodifacoum.

2.8.1.1.1.4 Photodegradation in air

The photo-oxidative degradation of brodifacoum in air was estimated by a structural activity relationship (QSAR) method using the Atmospheric Oxidation Program v1.90 (AOPWIN). Brodifacoum is predicted to undergo rapid indirect photolysis with OH radicals and ozone (DT_{50}= approximately 2 hours). According to TGD the half-live has been recalculated considering C_{OH} = 0.5 * 10^6 molec/cm^3; corresponding to a DT_{50} of 0.217 days). There are no predicted effects on the atmosphere.

2.8.1.1.2 Biotic degradation

2.8.1.1.2.1 Aquatic compartment

- Ready biodegradation / inherent biodegradation

Brodifacoum is not readily biodegradable under OECD 301B Test (0% after 28 days). Brodifacoum is not inherently biodegradable under the conditions of the ‘Inherent – Concawe Test’ (OECD 302D) performed (0% after 56 days).

- Degradation in water/sediment system

No study on water/sediment system of the active substance has been submitted in the combined AR of brodifacoum.

Moreover it is not relevant for a use inside buildings of products containing brodifacoum.

2.8.1.1.2.2 Degradation in STP

No study on water/sediment system of the active substance has been submitted in the combined AR of brodifacoum.

Moreover it is not relevant for a use inside buildings of products containing brodifacoum.

2.8.1.1.2.3 Terrestrial compartment

Brodifacoum is persistent in soil with a DT_{50} value of 157 days (The Pesticide Manual 13th Edition).

Moreover it is not relevant for a use inside buildings of products containing brodifacoum.

2.8.1.2 Distribution

Based on literature data, the Koc value (50 000 L/kg, The Pesticide Manual 13th Edition) indicates that the active substance would not be mobile in soil and is not expected to contaminate groundwater. A laboratory study carried out by another applicant show that with Koc values which ranged from 17.8 (pH 8.46) to 426 579 (pH 3.29) with a Koc value of 9155 L/kg at pH7.1-7.6, brodifacoum can be considered immobile in soil. Under basic conditions (high pH), Brodifacoum is not likely to be adsorbed onto soils or sewage sludge due to the ionisation of the molecule; whereas under acidic conditions (low pH), Brodifacoum is likely to be adsorbed onto soils or sewage sludge as the molecule is in its neutral or non-ionised form.

Brodifacoum is not expected to move from soil into water.

2.8.1.3 Accumulation

Brodifacoum has a log Kow > 6 (6.12) and is highly adsorptive; consequently these properties indicate that brodifacoum is likely to bioaccumulate in aquatic or terrestrial species.

The aquatic BCF has been estimated with calculation method for substances with a K_{ow} > 6:

BCF_{fish} = 35 645 L/kg (according to Equation 75; TGD).

The terrestrial BCF has been estimated with calculation method:

$BCF_{earthworm}$ = 15 820 L/kg (according to Equation 82d; TGD).

These BCF values confirm the high bioaccumulation of Brodifacoum in aquatic and terrestrial species.

2.8.1.4 Behaviour in air

The vapour pressure of brodifacoum has been determined to be << 1 x 10^{-6} Pa (OECD 104, EC methods A.4). Furthermore, Henry's law constant for brodifacoum has been calculated to be << 2.18 x 10^{-3} $Pa.m^3.mol^{-1}$ at pH 7 (based on a water solubility of 0.24 mg/L). Based on these data brodifacoum is not expected to partition into atmosphere to a relevant extent.

In addition, brodifacoum is predicted to undergo rapid indirect photolysis with OH radicals and ozone (DT_{50}= approximately 2 hours) and undergoes rapid direct photodegradation (DT_{50} = 0.217 days).

2.8.2 Effects on environmental organisms for active substance brodifacoum

The summary of information about the active substance brodifacoum is carried out with the data from the combined AR of brodifacoum owned by Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force.

2.8.2.1 Aquatic compartment (including water, sediment and STP)

2.8.2.1.1 Aquatic organisms

Based on the results of acute toxicity studies submitted in the combined AR by Activa / PelGar Brodifacoum and Difenacoum Task Force, brodifacoum is very acute toxic to aquatic organisms. No long-term tests have been performed. One study was performed on each of the two trophic levels (daphnia and algae) and two studies were performed on fish. *Selenastrum capricornutum* is the most sensitive species with a 72h E_rC_{50} of 0.04 mg a.s./L.

Table 5: Toxicity to freshwater aquatic organisms

Guideline / Test method	Species	Endpoint	Results (mg a.s./L)	Reference
OECD 203	*Oncorhynchus mykiss* - fish	LC_{50} – 96h	0.042	Activa / PelGar Brodifacoum and Difenacoum Task Force CAR a.s. Doc III-A 7.4.1.1
OECD 202	*Daphnia magna* - invertebrate	EC_{50} – 48h	0.25	Activa / PelGar Brodifacoum and Difenacoum Task Force CAR a.s. Doc III-A 7.4.1.2
OECD 201	*Selenastrum capricornutum* - algae	E_bC_{50} – 72h E_rC_{50} – 72h	0.016 0.04	Activa / PelGar Brodifacoum and Difenacoum Task Force CAR a.s. Doc III-A 7.4.1.3

All Concentrations are expressed on measured concentrations.

Justification of $PNEC_{water}$:

According to the TGD, the $PNEC_{water}$ is derived from the 72h E_rC_{50} value (0.04 mg a.s./L) for *Selenastrum capricornutum* divided by an assessment factor of 1000. Therefore,

PNECwater = 0.04 µg a.s./L.

2.8.2.1.2 Sediment dwelling organisms

No experimental data are available for sediment dwelling organisms. A $PNEC_{sediment}$ (0.043 mg/kg_{wwt}) is derived through the Equilibrium Partitioning Method. However, due to the absence of measured data for the determination of a $PEC_{sediment}$ and according to the TGD a quantitative risk characterization cannot be carried out. Therefore the risk for the sediment compartment will be covered by the risk for the aquatic compartment.

According to the TGD and considering the log Kow > 5, the PEC/PNEC ratio for the aquatic compartment is increased by a factor of 10 to take into account the possible additional uptake via sediment ingestion.

2.8.2.1.3 STP micro-organisms

The toxicity to microorganisms in a sewage treatment plant (STP) was estimated by a respiration inhibition test (OECD 209) submitted by Activa / PelGar Brodifacoum and Difenacoum Task Force . No effects of Brodifacoum on aerobic biological sewage treatment processes was expected. Due to the lack of measured values of test substance concentration, the EC_{10} was conservatively set greater than Brodifacoum' water solubility (0.058 mg a.s/L).

Table 6: Toxicity to STP microorganisms

Guideline/Test method	Species / Inoculums	Endpoint / Type of test	Duration	Results [mg a.s/L]				Reference
				EC_{10}	EC_{20}	EC_{50}	EC_{80}	
OECD 209	Activated sludge	Respiration Inhibition	3h	> 0.058*				Activa / PelGar Brodifacoum and Difenacoum Task Force CAR a.s. Doc III-A 7.1.4

* corresponding to the water solubility at pH=7 and T=20°C

Justification of $PNEC_{micororganisms:}$

According to TGD (2003) when an EC_{10} from a respiration inhibition test is used an assessment factor of 10 should be applied.

$PNEC_{STP}$ microorganisms > 0.0058 mg a.s/L

Additional endpoints:

According to the combined AR of brodifacoum owned by Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force, a lower PNEC value for sewage treatment microorganisms is provided: **PNEC STP microorganisms > 0.0038 mg a.s/L**. Therefore, as the data set are considered equivalent, the worst case PNEC from the combined AR is used in the risk assessment.

2.8.2.2 Atmosphere

Brodifacoum has a low volatility and is not intended to be sprayed or fumigated. It is formulated into a non volatile solid consequently its occurrence in air is highly unlikely. Moreover, significant phototransformation in air due to hydroxyl radicals would be expected. Brodifacoum is not expected to contribute to global warming, ozone depletion in the stratosphere, or acidification on the basis of its physical or chemical properties.

2.8.2.3 Terrestrial compartment

No effects of brodifacoum, in soil concentration ranging up to 994 mg/kg dw, were found on earthworms in a test conducted according to the guideline OECD 207. LC_{50} was determined to be > 994 mg/kg dw, corresponding to a LC_{50} >879.6 mg/kg in wet weight.

Table 7: Toxicity to soil organisms

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results (mg a.s/kg wwt soil)		Reference
			design	duration	NOEC	LC_{50}	
OECD 207	*Eisenia foetida*	LC_{50}	soil exposure	14days	879.6	>879.6	Activa / PelGar Brodifacoum and Difenacoum Task Force CAR a.s. Doc IIIA 7.5.1.2

Justification of $PNEC_{soil}$:

Since LC_{50} was determined to be >879 mg/kg ww, when corrected for soil humidity, an assessment factor of 1000 was used in accordance with TGD (2003).

$PNEC_{soil}$ > 0.88 mg/kg wet weight

As additional information, brodifacoum-based products are intended for indoor use only, no exposure to soil and groundwater is expected.

2.8.2.4 Non compartment specific effect relevant to the food chain

The exposure of brodifacoum directly to non-target birds and mammals (primary poisoning) and indirectly via target rodent carcasses (secondary poisoning) is considered in the risk assessment.

Table 8: Toxicity to birds and mammals (key studies)

Guideline / Test method	Species	Endpoint / Type of test / Duration	Results NOEC/NO(A)EL	Results LD_{50}	Reference
OPPTS 850.2100	Japanese quail	LD_{50}/ acute oral Single dose followed by 14 days oservation		LD_{50} = 19 mg a.s/kg bw	Activa / PelGar Brodifacoum and Difenacoum Task Force CAR a.s. Doc IIIA 7.5.3.1.1
OECD 416	Rat Wistar	High dose F1: haemorrhagic diathesies 2-generation	NO(A)EL Parental (females) = 0.001 mg/kg bw/day)		Morris, 1995

2.8.2.4.1 Primary poisoning

Acute/short-term qualitative assessment

Acute primary toxicity for birds and mammals is assessed only qualitatively in accordance with the decision from TMIII-06.

For mammals the acute toxicity to rat: a LD_{50} value =< 5 mg a.s. /kg bw is provided.

Additional endpoints:

According to the combined AR of brodifacoum, a lower **LD_{50}** value of **0.4 mg a.s. /kg bw** is provided by another applicant. Therefore, as the data set are considered equivalent, the worst case LD_{50} value from the combined AR is used in the qualitative assessment for comparisons with estimated daily uptakes of brodifacoum (ETE, mg a.s. /kg bw).

For birds the acute toxicity to Japanese quail: **LD_{50} = 19 mg a.s. /kg bw** is provided.

Additional endpoints:

According to the combined AR of brodifacoum, a lower LD_{50} value of **0.31 mg a.s. /kg bw** is provided by another applicant. Therefore, as the data set are considered equivalent, the worst case LD_{50} value from the combined AR is used in the qualitative assessment for comparisons with estimated daily uptakes of brodifacoum (ETE, mg a.s. /kg bw).

Long-term quantitative assessment

For **mammals**, in a two-generation fertility study with rats, a NOAEL of 0.001 mg/kg bw/day was estimated. According to the TGD, the NOAEL is transformed into a NOEC using a conversion factor of 20, and the AF_{oral} of 90 is applied to this NOEC, which results in a

$PNEC_{oral}$ (mammal) = 0.001/90 = 1.1E-05 mg/kg bw/day

equivalent to

$PNEC_{oral}$ (mammal) = 0.001*20/90 = 2.22E-04 mg/kg food

For **birds** the NOEC for Brodifacoum is based on the results of the chronic toxicity study with Difenacoum (with Japanese Quail), chosen as reference chemical for second generation anticoagulants (NOEC > 0.1 mg Difenacoum /kg diet). An extrapolation factor of 8.05 was applied to correct for differences in toxicity based on the acute test results for Difenacoum (LD_{50} = 66 mg/kg, male and females) and Brodifacoum (LD_{50} = 19 mg/kg bw), both related to Japanese quail. Brodifacoum results very toxic to birds, with NOEC = 0.012 mg Brodifacoum/kg diet (obtained as NOEC > 0.1 mg Difenacoum /kg diet / 8.05) and NOEL = 0.0012 mg Brodifacoum/kg bw/d.

According to TGD, an assessment factor of 30 is applied to derive the PNEC:

$PNEC_{oral}$ for birds (dose) = 0.0012/30 = 4E-05 mg/ kg bw/ day

equivalent to

$PNEC_{oral}$ for birds (conc. In food) = 0.012/30 = 43E-04 mg/kg food

Additional endpoints: According to the combined AR of brodifacoum, a lower **$PNEC_{oral}$ for birds** is provided by another applicant. The long-term toxicity was extrapolated by read across to reproduction toxicity of Difenacoum to Japanese Quail (NOEC > 0.1 mg Difenacoum /kg diet), selected as representative compound of the second generation anticoagulants. A factor of 26 was applied to take into account differences in toxicity between the two compounds, with the brodifacoum more toxic than difenacoum. A NOEC = 0.0038 mg Brodifacoum /kg/ diet and a NOEL = 3.85E-04 mg Brodifacoum/kg bw/d are derived.

According to TGD, an assessment factor of 30 is applied to derive the PNEC:

$PNEC_{oral}$ for birds (dose) = 1.3E-05 mg/ kg bw/ day

equivalent to

$PNEC_{oral}$ for birds (conc. In food) = 1.3E-04 mg/kg food

Therefore, as the data set are considered equivalent, the worst case PNEC from the combined AR is used in the risk assessment.

2.8.2.4.2 Secondary poisoning

Acute/short-term qualitative assessment

Acute primary toxicity for birds and mammals is assessed only qualitatively in accordance with the decision from TMIII-06.

For mammals the acute toxicity to rat: LD_{50} = 0.4 mg a.s. /kg bw recalculated into **LC_{50} = 8 mg/kg food**, using the conversion factor bw/dfi of 20 from table 22 in the TGD II is the lowest value for the acute toxicity.

For birds a LD_{50} value of **0.72 mg a.s. /kg food** is provided by another applicant in the combined AR. No data about the dietary toxicity to birds was submitted by Activa / PelGar Brodifacoum and Difenacoum Task Force in the combined AR.

Long-term quantitative assessment

For **mammals**, in a two-generation fertility study with rats, a NOAEL of 0.001 mg/kg bw/day was estimated. According to the TGD, the NOAEL is transformed into a NOEC using a conversion factor of 20, and the AF_{oral} of 90 is applied to this NOEC, which results in a

$PNEC_{oral}$ (mammal) = 0.001*20/90 = 2.22E-04 mg/kg food

equivalent to

$PNEC_{oral}$ (mammal) = 0.001/90 = 1.1E-05 mg/kg bw/day

For **birds** the NOEC for Brodifacoum is based on the results of the chronic toxicity study with Difenacoum (with Japanese Quail), chosen as reference chemical for second generation anticoagulants (NOEC > 0.1 mg Difenacoum /kg diet). An extrapolation factor of 8.05 was applied to correct for differences in toxicity based on the acute test results for Difenacoum (LD_{50} = 66 mg/kg, male and females) and Brodifacoum (LD_{50} = 19 mg/kg bw), both related to Japanese quail.

Brodifacoum results very toxic to birds, with NOEC = 0.012 mg Brodifacoum/kg diet (obtained as NOEC > 0.1 mg Difenacoum /kg diet / 8.05) and NOEL = 0.0012 mg Brodifacoum/kg bw/d.

According to TGD, an assessment factor of 30 is applied to derive the PNEC:

$PNEC_{oral}$ for birds (conc. In food) = 0.012/30 = 43E-04 mg/kg food

equivalent to

$PNEC_{oral}$ for birds (dose) = 0.0012/30 = 4E-05 mg/ kg bw/ day

Additional endpoints: according to the combined AR of brodifacoum, a lower **$PNEC_{oral}$ for birds** is provided by another applicant. The long-term toxicity was extrapolated by read across to reproduction toxicity of Difenacoum to Japanese Quail (NOEC > 0.1 mg Difenacoum /kg diet), selected as representative compound of the second generation anticoagulants. A factor of 26 was applied to take into account differences in toxicity between the two compounds, with the brodifacoum more toxic than difenacoum. A NOEC = 0.0038 mg Brodifacoum /kg/ diet and a NOEL = 3.85E-04 mg Brodifacoum/kg bw/d are derived.

According to TGD, an assessment factor of 30 is applied to derive the PNEC:

$PNEC_{oral}$ for birds (conc. In food) = 1.3E-04 mg/kg food

equivalent to

$PNEC_{oral}$ for birds (dose) = 1.3E-05 mg/ kg bw/ day

Therefore, as the data set are considered equivalent, the worst case PNEC from the combined AR is used in the risk assessment.

2.8.2.5 Summary of PNECs of the active substance Brodifacoum

Table 9: Summary of the brodifacoum (a.s.) PNECs used for risk assessment

Compartment		Test Value	AF	PNEC	Source
Aquatic	PNECwater	72h E_rC_{50} = 0.04 mg a.s./L	1000	0.04 µg a.s./L	Combined AR
	$PNEC_{STP}$	EC_{10} > 0.0038 mg a.s. /L	100	> 0.0038 mg a.s/L	combined AR
Terrestrial	$PNEC_{soil}$	14-d LC_{50} > 879.6 mg a.s. /kg ww soil	1000	> 0.88 mg/kg wet weight	Combined AR
Primary and secondary poisoning	$PNEC_{oral\ for\ birds}$	NOEC = 0.0038 mg/kg food NOEL = 3.85E-04 mg/kg bw/day	30	1.3E-04 mg/kg food 1.3E-05 mg/ kg bw/ day	Combined AR
	$PNEC_{oral\ for\ mammals}$	NO(A)EL=0.001mg a.s/kg bw/day NOEC= (0.001*20)=0.02 mg a.s/kg food	90	1.1E-05 mg/kg bw/day 2.22E-04 mg/kg food	Combined AR

PNEC values of other applicant of brodifacoum from the combined AR are indicated when they represent worst-case value in comparison with the PNEC values of Activa / PelGar Brodifacoum and Difenacoum Task Force presented in the combined AR. **The lowest PNEC values is used in the risk assessment.**

2.8.2.6 PBT Assessment

Persistence

According to results given in the combined AR, brodifacoum is not readily, inherently or anaerobically biodegradable. In addition, Brodifacoum resulted hydrolytically stable, but undergoes rapid photolysis in water. These results indicate according to screening criteria, that brodicaoum can be considered as potentially persistent (P) very persistent (vP).

Bioaccumulation

Based on log Kow = 6.12 and BCFfish = 35 645 $L.Kg^{-1}$ (according to Equation 75; TGD), brodifacoum potentially fulfils the B criterion and vB criterion.

Toxicity

Brodifacoum is proposed to be classified as T+; R27/28, T; R48/24/25, N; R50/53. According to the TGD, brodifacoum fulfils the T criterion.

Brodifacoum is considered a potential PBT, according to the TGD on Risk Assessment (2003).

2.8.3 Effects on environmental organisms for biocidal product

It is important to notice that the applicant did not provide ecotoxicological data about the biocidal product FANGA PATE PRO. Consequently, all the effects assessment is based on the data obtained from the active substance brodifacoum (Combined Assessment Report According to Directive 98/8EC, Active substance in Biocidal Products, Brodifacoum CAS 56073-10-0, Product Type 14 (Rodenticides), RMS Italy, Revision 2: November 2010).

Denatonium benzoate is used in the biocidal product as bittering agent. This substance is classified as “Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment” in the frame of the Directive 91/414/EEC. Nevertheless at the concentration used in FANGA PATE PRO, the substance does not contribute to the classification of the biocidal product.

No other substance used in the biocidal product is classified for the environment.

Therefore, considering that the product contains no substances of concern except brodifacoum, environmental effects following the use of FANGA PATE PRO can be extrapolated from the environmental effects of the active substance brodifacoum only.

2.8.3.1 Aquatic compartment (including water, sediment and STP)

2.8.3.1.1 Aquatic organisms

Refers to section 2.8.2.1.

2.8.3.1.2 Sediment dwelling organisms

Refers to section 2.8.2.1

2.8.3.1.3 STP micro-organisms

Refers to section 2.8.2.1.

2.8.3.2 Atmosphere

Refers to section 2.8.2.2.

2.8.3.3 Terrestrial compartment

Refers to section 2.8.2.3.

2.8.3.4 Non compartment specific effect relevant to the food chain

Refers to section 2.8.2.4.

2.8.3.5 Summary of PNECs

Refers to section 2.8.2.5.

2.8.4 Environmental exposure assessment

As the product contains no substances of concern except brodifacoum, it is considered that risks posed to environment following the use of the product FANGA PATE PRO can adequately be assessed based on the evaluation conducted for the active substance. Therefore the exposure assessment is carried out with the data obtained from the active substance brodifacoum only.

The product FANGA PATE PRO is a ready-to-use rodenticidal bait containing 0.005% brodifacoum (0.05 g/kg). The product is in the form of a paste supplied in sachet for professional users. The product is used at 30 g for mouse and 180 g for rat / bait point. According to the applicant, the sachets containing the paste are placed in secured bait stations, inside domestic, industrial, and farm buildings. The secured bait points are refilled 4 times over 28 days. Dead rodents and unconsumed baits are removed each week.

As the product is applied indoor only, no environmental compartment is exposed to FANGA PATE PRO. Nevertheless primary and secondary poisoning cannot be excluded. Indeed, pets living in treated buildings could be exposed directly to the product. Moreover even if the product is applied inside buildings, rats can live some days before dying. Therefore, they have the time to escape outside buildings and to be eaten by predators.

2.8.4.1 Aquatic compartment (surface water, sediment, STP)

Exposure of the aquatic compartment *via* the STP after the treatment with rodenticides is only relevant for indoor application of liquid poisons, residues from mixing and cleaning (ESD PT14). As FANGA PATE PRO is a solid form and is intended to be used indoor only, indirect or direct exposure of the aquatic compartment may be considered negligible.

2.8.4.2 Atmospheric compartment

Due to its physico-chemical properties (low vapour pressure of 2.6 x 10^{-22} Pa at 20°C and low Henry's law constant of 2.35 x 10^{-18} $Pa.m^3.mol^{-1}$), brodifacoum is not expected to be present in the atmosphere in significant quantities. The exposure of air is therefore considered negligible for the application of FANGA PATE PRO biocidal product.

2.8.4.3 Terrestrial compartment (soil and groundwater)

As FANGA PATE PRO is intended to be used indoor only, no exposure to soil and groundwater is expected.

2.8.4.4 Non-compartmental-specific exposure relevant to the food chain (secondary poisoning)

2.8.4.4.1 Primary poisoning

As stated in the ESD (Larsen, 2003), primary poisoning hazard to mammals and birds (both wild and domestic) can be considered small when rodenticides are applied according to the label instructions. In the scenario "in and around buildings" when the product is placed in protected bait point, the risk for primary poisoning is mainly for birds and mammals of equal size or smaller as the target rodents, which may be able to enter into the bait stations. Another exposure of non-target animals may arise when target rodents carry bait away from bait stations.

Worst case exposure estimations are based on the equations and default values proposed by the ESD (Larsen, 2003). Some defaults parameters may be replaced by product-specific properties.

2.8.4.4.1.1 Primary poisoning – Tier 1 assessment

The Tier 1 assessment assumes that the whole day's food requirement is satisfied by consumption of baits and therefore the concentration in food will be the same as the concentration of the active substance in the bait: 50 $mg.kg^{-1}$ (0.005% w/w of brodifacoum in FANGA PATE PRO).

Hence, **the worst case Tier 1 PEC_{oral} is 50 $mg.kg^{-1}$**.

2.8.4.4.1.2 Primary poisoning – Tier 2 assessment, acute exposure

According to ESD (Larsen, 2003), a Tier 2 assessment can be done estimating a daily uptake of a compound (ETE, $mg.kg^{-1}_{bw}.d^{-1}$) by non-target animals according to the equation 19 of ESD:

$$ETE = (FIR/BW) \times C \times AV \times PT \times PD$$

With:

FIR: food intake rate of the indicator species ($g.d^{-1}$),

BW: indicator species body weight (g),

C: concentration of the active substance in fresh diet ($mg.kg^{-1}$),

AV: avoidance factor (-),

PT: fraction of diet obtained in treated area (-),

PD: the fraction of the food type in the diet (-).

In Tier 2 Step 1 (worst case) AV, PT and PD are all set at 1. In Step 2 (realistic worst case) AV and PT are refined to 0.9 and 0.8, respectively.

Table 10: Expected concentrations of brodifacoum in non-target animals in the worst case (Step 1) and realistic worst case (Step 2) for acute situations.

Non-target animal	BW (g)[a]	FIR ($g_{dry\ weight}.day^{-1}$)	C ($mg.kg^{-1}$)	ETE = concentration of brodifacoum after one meal ($mg.kg^{-1}_{bw}.d^{-1}$)	
				Step 1	Step 2
Dog	10 000	456[b]	50	2.28	1.64
Pig	80 000	600[a]	50	0.38	0.27
Pig young	25 000	600[a]	50	1.20	0.86
Tree sparrow	22	7.6 [a]	50	17.27	12.44
Chaffinch	21.4	6.42 [a]	50	15.00	10.80
Wood pigeon	490	53.1 [a]	50	5.42	3.90
Pheasant	953	102.7 [a]	50	5.39	3.88

[a] From EUBEES 2, Table 3.1, section 3.2.1

[b] From EUBEES 2, using the equation log FIR = 0.822 log BW - 0.629 (for mammals)

2.8.4.4.1.3 Primary poisoning – Tier 2 assessment, long-term exposure

The long-term risks of brodifacoum are determined by the expected concentrations (EC) in the animal after metabolisation and elimination, which is regarded as PEC. The EC values are calculated on the basis of the actual dose of the substance consumed by a non-target animal each day (ETE) using the realistic worst case scenario (Step 2), calculated above. Calculations are performed according to the equation 20 of the ESD.

$$EC = ETE \times (1 - El)$$

According to the ESD, a default value of 0.3 for daily uptake eliminated (El) can be used if no studies are submitted. The EC values are the expected concentrations of active substance brodifacoum in non-target animals in primary poisoning scenarios after one meal followed by a 24 hour elimination period.

Table 11: Expected concentrations of brodifacoum in non-target animals in realistic worst case (Step 2) for long-term situation.

Non-target animal	EC, conc. of brodifacoum after one day of elimination ($mg.kg^{-1}_{bw}$)
	Step 2
Dog	1.15
Pig	0.19
Pig young	0.60
Tree sparrow	8.71
Chaffinch	7.56
Wood pigeon	2.73
Pheasant	2.72

2.8.4.4.2 Secondary poisoning

Secondary poisoning via the aquatic food chain

As no exposure of the aquatic compartment is foreseen with the use of FANGA PATE PRO inside buildings, no risk assessment for secondary poisoning through the aquatic food chain is required.

Secondary poisoning via the terrestrial food chain

As no exposure of the terrestrial compartment is foreseen with the use of FANGA PATE PRO inside buildings, no risk assessment for secondary poisoning through the terrestrial food chain is needed.

Secondary poisoning for the rodent-eating mammal or the rodent-eating bird

According to the ESD (Larsen, 2003) document, for uses 'in and around buildings' it is assumed that predators among mammals and birds may occur inside buildings or they may hunt rats in the immediate vicinity of buildings (parks and gardens or further away). Scavengers may also search for food close to buildings.

Therefore secondary poisoning through poisoned rats exists, even in case of an indoor use. Secondary poisoning hazard can only be ruled out completely when the rodenticide is used in fully enclosed spaces so that rodents cannot move to outdoor areas or to (parts of) buildings where predators may have access.

2.8.4.4.2.1 Secondary poisoning - Tier 1 assessment, acute

Calculations of the risk for secondary poisoning of scavengers and predators are done by determining the concentration of brodifacoum in their food, i.e. the poisoned rodents. This PEC_{oral} is then compared to the LC_{50} values for a qualitative risk assessment in accordance with the decision from TM III-06. According to the ESD section 3.3.1, the consumption of rodenticides makes up at least 20 % of total consumptions in a choice test and could in a worst case be up to 100 %, whilst 50 % would be considered as the normal situation. Therefore, in the calculations the fractions of the food type in the diet (PD) are set to 0.2, 0.5 and 1.0. The FIR/BW quotient (food intake rate of the indicator species/indicator species body weight) is a default value set to 0.1, i.e. it is assumed that the rats eat 10 % of their bodyweight each day. The avoidance factor (AV) and the fraction of diet (PT) obtained in the area are both set to 1.

The calculations are done according to equation 19 in the ESD:

$$ETE = (FIR/BW) \times C \times AV \times PT \times PD \text{ (mg.kg}^{-1}_{bw}\text{.d}^{-1}\text{)}$$

This equation gives the concentration of brodifacoum in rodent (PEC_{oral}) after the first meal. Considering the elimination rate and the mean time to death (seven days), the concentrations in rodents can be calculated each day by the equation 21 in the ESD:

$$ECn = \sum_{n-1} ETE \times (1 - EI)n$$

For the active substance brodifacoum, the default value of 0.3 is used for elimination (El).

Table 12: Residues of brodifacoum in target animals at specific points in time and varying bait consumption

	Residues in target animal (mg.kg^{-1}bw)		
	20%	**50%**	**100%**
Day 1 after the first meal	1.0	2.5	5.0
Day 2 before new meal	0.7	1.8	3.5
Day 5 after the last meal	2.8	6.9	13.9
Day 7 mean time to death	1.4	3.4	6.8

According to the ESD, the concentrations of brodifacoum in rats are at peak after consuming bait during 5 days; thereafter the concentrations in rodents are decreasing until day 7 due to excretion and metabolisation of the rodenticide in rodents. The values from day 5 (after the meal) are used as worst case PEC_{oral}.

2.8.4.4.2.2 Secondary poisoning - Tier 1 assessment, long-term

To assess the risk of long-term secondary poisoning to mammals, the PEC in rodents after 1 day and after 5 days are used considering that the consumption of rodenticides makes up 100% of total consumptions (refer to Table 12).

Table 13: Residues of brodifacoum in target animals at specific points in time and varying bait consumption used in the long term assessment

	PEC_{oral} **Brodifacoum conc. in target rodent (mg.kg^{-1} bw), ESD default values**
Birds	**13.9**
Mammals	**13.9**

2.8.4.4.2.3 Secondary poisoning - Tier 2 assessment, long-term

For the Tier 2 assessment, the average food intake for each species and the average weight of the species have been considered, according to the Table 3.5 in the ESD. The calculations are based on the expected values for uptake of active substance by a mammal predator after a single day of exposure presented as an illustrative example in the ESD.

The amount of a.i. consumed by the non-target animal is 13.9 mg.kg^{-1} bw for rodents caught on day 5 and 16.6 mg.kg^{-1} bw for resistant rodents caught on day 14, also assuming that the non-target

animals feed to 50 % on the rodents, all in accordance with the ESD. By knowing the amount of a.i. consumed by the non-target animal and the weight of the animal, the PEC (concentration in non-target animal) after one day consumption of rodents can be calculated. The results are presented in Table 14.

Table 14: Expected concentrations of brodifacoum in non-target animals (predators/carnivores) due to secondary poisoning after a single day of exposure (concentration of brodifacoum in rodenticide bait 0.005%). Rodents fed 100% on rodenticide and predators/carnivores fed 50% on poisoned rodents.

			Normal susceptible rodents caught on day 5		Resistant rodents caught on day 14	
Species	**Body weight (g)**	**Daily mean food intake ($g.d^{-1}$)**	**Amount a.i. (mg)[1]**	**Conc. ($mg.kg^{-1}$)[2]**	**Amount a.i. (mg)[1]**	**Conc. ($mg.kg^{-1}$)[2]**
Barn owl *(Tyto alba)*	295	72.9	0.51	1.7	0.60	2.1
Kestrel *(Falco tinnunculus)*	209	78.7	0.55	2.6	0.65	3.1
Little owl *(Athene noctua)*	164	46.4	0.32	2.0	0.38	2.3
Tawny owl *(Strix aluco)*	426	97.1	0.67	1.6	0.80	1.9
Fox *(Vulpes vulpes)*	5700	520.2	3.61	0.6	4.31	0.8
Polecat *(Mustela putorius)*	689	130.9	0.91	1.3	1.08	1.6
Stoat *(Mustela erminea)*	205	55.7	0.39	1.9	0.46	2.3
Weasel *(Mustela nivlis)*	63	24.7	0.17	2.7	0.20	3.3

[1] Amount a.i. consumed by non-target animal
[2] Conc. in non-target animal

2.8.5 Risk characterisation for the environment

2.8.5.1 Primary poisoning

Risk characterization for the environment is done quantitatively by comparing predicted environmental concentrations (PEC) and the concentrations below which effects on organism will not occur (PNEC and/or LD_{50}) according to the guidance in Technical guidance document (TGD, 2003) and "Emission Scenario document for biocides used as rodenticides" (Larsen, 2003, ESD PT14).

The environmental risk characterization has been carried out for brodifacoum.

2.8.5.1.1 Tier 1 assessment

The PEC value for Tier 1 assessment is compared to the long-term PNEC for mammals and birds.

Table 15: Tier 1 risk characterization of primary poisoning – Long-Term

	PEC[1] mg.kg food $^{-1}$	PNEC[1] mg.kg food $^{-1}$	PEC/PNEC
Birds	50	1.3E-04	384 615
Mammals	50	2.22E-04	225 225

[1] Concentration of brodifacoum in food.

For mammals and birds, the resulting PEC/PNEC ratios reveal high risks of long-term primary poisoning.

Tier 2 assessment – acute

For the acute situation of primary poisoning, only a qualitative risk assessment is carried out in accordance with the decision from TM III-06. In this Tier 2 acute qualitative assessment, the PEC values are compared to the LD_{50} values.

Table 16: Tier 2 acute qualitative risk assessment of primary poisoning

	PEC_{oral}[1] mg.kg^{-1} $_{bw}$		LD_{50} dose mg.kg^{-1} $_{bw}$ d^{-1}	$PEC_{oral} > LD_{50}$ (y/n)	
	Step 1	**Step 2**		**Step 1**	**Step 2**
Dog	2.28	1.64	0.40	y	y
Pig	0.38	0.27		n	n
Pig young	1.20	0.86		y	y
Tree sparrow	17.27	12.44	0.31	y	y
Chaffinch	15.00	10.80		y	y
Wood pigeon	5.42	3.90		y	y
Pheasant	5.39	3.88		y	y

[1] PEC_{oral} = ETE, concentration of brodifacoum after one meal

This comparison indicates that the situation for mammals is uncertain. Dogs and young pigs are at risk while pigs are not at risk but very close to the trigger value. On the other hand, this comparison indicates that all birds are at risk for acute primary poisoning.

Tier 2 assessment – long-term

The PEC values are compared to the PNEC values.

Table 17: Tier 2 long-term risk assessment of primary poisoning

	PEC_{oral}[1] $mg.kg^{-1}_{bw}$	PNEC $mg.kg^{-1}_{bw}\ d^{-1}$	PEC /PNEC
	Step 2		
Dog	1.15	1.1E-05	**104 545**
Pig	0.19		**17 273**
Pig young	0.60		**54 545**
Tree sparrow	8.71	1.3E-05	**670 000**
Chaffinch	7.56		**581 538**
Wood pigeon	2.73		**210 000**
Pheasant	2.72		**209 231**

[1] PEC_{oral} = EC, concentration of brodifacoum after one day of elimination

The risk characterization indicates a very high risk to non-target mammals and birds from direct eating of bait. Primary poisoning incidents can be minimized by preventing the access of non-target animals to the baits. It is assumed in the ESD that if the rodenticide baits are use according to the label instructions, the risk for primary poisoning is negligible. However, it is stated at the EU level that it may not be possible to exclude exposure of all non-target animals, as the baits have to be accessible to target rodents, they may as well be accessible to non-target mammals birds of equal or smaller size than the target rodents.

Nevertheless, as the product FANGA PATE PRO is intended to be used indoor and in bait stations only, primary poisoning can therefore be considered negligible as domestic animals can be kept away from the product, and wild animals other than rats and mice are not expected to be found inside buildings.

2.8.5.2 Secondary poisoning

The only relevant scenario of secondary poisoning in the case of an indoor application only is for the rodent-eating mammal or bird.

2.8.5.2.1 Tier 1 assessment, acute

The PEC_{oral} are compared to the LC_{50} value presented in the section above for qualitative risk assessment in accordance with the decisions taken at the TMII-06.

Table 18: Tier 1 long-term risk assessment of secondary poisoning

Non-target animal	PECoral $mg.kg^{-1}_{bw}$			LC_{50} dose $mg.kg^{-1}_{food}$	$PEC_{oral} > LC_{50}$ (y/n)		
	PD=0.2	PD=0.5	PD=1		PD=0.2	PD=0.5	PD=1
Birds	2.8	6.9	13.9	8	n	n	y
Mammals	2.8	6.9	13.9	0.72	y	y	y

PEC_{oral} = Expected concentration in rodent caught on day 5 after meal

PD = fraction of the food type in the diet

This qualitative risk assessment indicates risk for birds with a fraction of the food type in the diet of 1 and with a PEC in rodent caught on day 5 after meal, and indicates risk for mammals at all fractions of food type in the diet and with a PEC in rodent caught on day 5 after meal.

Tier 1 assessment, long-term

To assess the risk of long-term secondary poisoning, the PEC in rodents after 5 days is used and compared to the long-term PNECoral for birds and mammals.

Table 19: Tier 1 long-term risk assessment of secondary poisoning

Non-target animal	PECoral $mg.kg^{-1}_{bw}$	PNEC $mg.kg^{-1}_{food}$	PEC /PNEC
Birds	13.9	1.3E-04	106 923
Mammals	13.9	2.22E-04	62 613

PEC_{oral} = Expected concentration in rodent caught on day 5 after meal

The tier 1 long-term assessment indicates very high risks of long-term secondary poisoning for birds and mammals.

Tier 2 assessment, long-term

Table 20: Tier 2 long-term risk assessment of secondary poisoning

Species	PEC (mg/kg bw)		PNEC (mg/kg bw)	PEC/PNEC	
	day 5	day 14		day 5	day 14
Barn owl ***(Tyto alba)***	1.7	2.1	1.3E-05	**130 769**	**161 538**
Kestrel ***(Falco tinnunculus)***	2.6	3.1		**200 000**	**238 462**
Little owl ***(Athene noctua)***	2.0	2.3		**153 846**	**176 923**
Tawny owl ***(Strix aluco)***	1.6	1.9		**123 077**	**146 154**
Fox ***(Vulpes vulpes)***	0.6	0.8	1.1E-05	**54 545**	**72 727**
Polecat ***(Mustela putorius)***	1.3	1.6		**118 182**	**145 455**
Stoat ***(Mustela erminea)***	1.9	2.3		**172 727**	**209 091**
Weasel ***(Mustela nivlis)***	2.7	3.3		**245 455**	**300 000**

The tier 2 risk characterisation shows very high risks for secondary poisoning at long-term for birds and mammals.

However, considering the fact that FANGA PATE PRO is intended to be used indoor only, it can be assumed that, applying use restrictions (such as collecting dead rodents), the risk for secondary poisoning will be lower.

Nevertheless, in order to reduce the risk of secondary poisoning, it is very important to follow the use instructions of the rodenticide baits. The risk reduction measures are considered in the following section.

2.8.5.3 Conclusion of the risk assessment for the environment

No studies were conducted with the product FANGA PATE PRO for the environment part; therefore the environmental risk assessment has been carried out with data from the Combined AR of brodifacoum. The environmental risk is considered as limited for the indoor use by professionals, in strict compliance with the specific use instructions of rodenticidal baits and the use restrictions to reduce the risk for primary and secondary poisoning.

Risk mitigation measures linked to risk assessment for environment

- Use in tamper-resistant bait boxes or in covered bait stations. The bait stations must be placed only in areas not accessible to the general public and non-target animals.
- Tamper-resistant bait boxes should be clearly marked to show that they contain rodenticides and that they should not contain other products than rodenticides.
- Never wash the tamper-resistant bait boxes and covered bait stations with water.
- Place the tamper-resistant bait boxes and covered bait stations in areas non-liable to floodings.
- Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations and dead rodents, during and after treatment[13].
- Baits must be unattainable to children, pets or other non-target animals in order to minimize the risk of poisoning.
- Dispose of the tamper-resistant bait boxes and covered bait stations, packaging, uneaten baits and dead rodents in accordance with local requirements.
- Remove all bait points after the end of treatment.
- Do not throw the product on the ground, into a water course, into the sink or down the drain and into the environment.

Disposal considerations

- Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations and dead rodents, during and after treatment[13].
- Dispose of the tamper-resistant bait boxes and covered bait stations, packaging, uneaten baits and dead rodents in accordance with local requirements.
- Never wash the tamper-resistant bait boxes and covered bait stations with water.
- Do not throw the product on the ground, into a water course, into the sink or down the drain and into the environment.
- Remove all bait points after the end of treatment.

Required information linked to risk assessment for environment

None.

2.9 Measures to protect man, animals and the environment

See Summary of Product Characteristics (SPC).

[13] If the dead rodents, uneaten bait and bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations are not entirely collected, primary and secondary poisoning risks remain unacceptable.

3 Proposal for decision to be adopted by the French CA (Ministry of Ecology)

This section is a proposal from the authority in charge of the risk assessment (Anses) for the decision to be adopted by the competent authority in charge of the decision (French Ministry of Ecology).

In case of inconsistency between the risk assessment and the decision, only the original and signed decision has a legal value. The decision specifies the terms and conditions to the making available on the market and use of the biocidal product.

The source of the active substance used in the biocidal product FANGA PATE PRO is not the same as the source used for annex I inclusion. The technical equivalence is in progress and evaluated by Italy. Only a recognized source of active substance can be used in the product FANGA PATE PRO.

Conclusions of efficacy and risk assessment

Risk assessment for Physico-chemical properties

FANGA PATE PRO is a ready-to-use paste bait. The product is not highly flammable, not auto-flammable (up to 400°C), not explosive and does not have oxidizing properties.

The product is stable 14 days at 54°C in paper sachets. A provisional shelf life of 2 years can be granted.

Summary of efficacy assessment

The product FANGA PATE PRO has shown a sufficient efficacy and can be used for the control of house mice (*Mus musculus*) and brown rats (*Rattus norvegicus*).

French competent authorities (FR CA) assessed that the product FANGA PATE PRO has shown a sufficient efficacy for the control of *Rattus norvegicus*. But for the claim ”use against rats”, efficacy must be also shown on *R. Rattus*. Consequently, in the absence of supporting data on *Rattus rattus*, suitable information (such as a field test) demonstrating the efficacy against black rat of FANGA PATE PRO will need to be provided in support of the authorisation. Field tests against all the target organisms (*Rattus rattus, Rattus norvegicus and Mus musculus)* performed with a 2 years old product must be submitted to support the storage duration of 2 years.

The authorisation holder should report any observed resistance incidents to the Competent Authorities (CA) or other appointed bodies involved in resistance management every two years.

Summary of risks characterisation of the product for human health

Based on the risk assessment of the active substance, the risk for professional users resulting from the intended use is acceptable for FANGA PATE PRO for the control of rats and mice.

Risk of secondary poisoning to infants and children is considered as relevant. Therefore, even if the product FANGA PATE PRO contains a bittering agent which reduces the likelihood of ingestion, the baits should be unattainable for children. Product label (“do not open the sachet”) and good practice advise users to prevent access to bait by children and infants.

Summary of risks characterisation of the product for consumer

The intended uses description of the product FANGA PATE PRO indicates that these uses are not relevant in terms of residues in food and feed. The product is to be used as rodenticide and does not come in direct or indirect contact with food and feedstuff.

Summary of risks characterisation of the product for the environment

No studies were conducted with the product FANGA PATE PRO for the environment part; therefore the environmental risk assessment has been carried out with data from the Combined AR of brodifacoum. The environmental risk is considered as limited for the indoor use by professionals, in strict compliance with the specific use instructions of rodenticidal baits and the use restrictions to reduce the risk for primary and secondary poisoning.

Risk mitigation measures and conditions of use

The product is to be used in tamper-resistant bait boxes or covered bait stations.

”Tamper-resistant bait boxes” are meant to be tamper-resistant devices, that prevent the access to the baits for children and non-target animals, and that protect the baits from bad weather.

”Covered bait stations” are meant to be devices with the same level of security for the human beings and the environment than the security provided by tamper-resistant bait boxes, fastened to prevent any removal, made in order to avoid direct contact of the bait with the environment. This device must be designed to keep baits out of reach of the general public and non-target animals, and to protect the bait from bad weather

It is considered that professional users only (on the contrary to the general public) are able to design such covered bait stations.

Conditions of use linked to efficacy assessment

- Adapt the number of bait points to the infestation level.
- Inspect and resupply the bait points, 3 days after application then once a week as long as the bait is consumed.
- Remove all bait points after the end of treatment.
- The amount of bait per bait point and distances between bait points must be respected. Products have always to be used in accordance with the label.
- The users should inform is the treatment is ineffective and report straightforward to the registration holder any alarming signals which could be assumed to be resistance development.
- To avoid resistance, professional users must:
    - use the treatment alternately with other kinds of active substances having different modes of action;
    - adopt integrated pest management methods such as the combination of chemical, physical control methods and other public health measures;
    - monitor the level of efficacy (periodic check), and investigate the case of reduced efficacy for possible evidence of resistance;
    - not use the product in areas where resistance is suspected or established.

Recommandations to be taken into account by the applicant

- Adapt the amount of bait per bait point to the validated effective dose.
- The product label has to contain information on resistance management for rodenticides.

Risk mitigation measures

- Store away from light.
- Gloves have to be worn to help prevention against rodent-borne disease.
- Do not open the sachets.
- Apply strict hygiene measures: do not eat, drink or smoke during handling of the product and wash hands after use of the product.
- Use in tamper-resistant bait boxes or in covered bait stations.
- Tamper-resistant bait boxes should be clearly marked to show that they contain rodenticides and that they should not contain other products than rodenticides.
- Covered bait stations must be placed only in areas not accessible to the general public and non-target animals.
- Baits must be unattainable to children, pets or other non-target animals in order to minimize the risk of poisoning.
- Do not place tamper-resistant bait boxes and covered bait stations on surfaces in contact with food, feed or drinks and beverages.
- Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations and dead rodents, during and after treatment[13].
- Remove all bait points after the end of treatment.
- Never wash the tamper-resistant bait boxes and covered bait stations with water.
- Place the tamper-resistant bait boxes and covered bait stations in areas non-liable to floodings.
- Dispose of the tamper-resistant bait boxes and covered bait stations, packaging, uneaten baits and dead rodents in accordance with local requirements.
- Do not throw the product on the ground, into a water course, into the sink or down the drain and into the environment.

Emergency *(information provided in the product Safety Data Sheet)*

Inhalation: no action should be necessary.

Ingestion: if swallowed, seek medical advice immediately and show container or leaflet. A treatment with vitamin K1 should be necessary during a long period.

Skin or eye contact: wash immediately with plenty of water.

Disposal

- Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes or covered bait stations and dead rodents, during and after treatment[13].
- Remove all bait points after the end of treatment.
- Dispose of the tamper-resistant bait boxes and covered bait stations, packaging, uneaten baits and dead rodents in accordance with local requirements.
- Never wash the tamper-resistant bait boxes and covered bait stations with water.
- Do not throw the product on the ground, into a water course, into the sink or down the drain and into the environment.

Information required post-authorisation

Required information linked to assessment of physico-chemical properties

- A shelf life study (2 years at ambient temperature) with monograph GIFAP n°17 must be submitted no later than 6 months post-registration.

Required information linked to efficacy assessment

- The authorisation holder has to monitor the resistance phenomenon of rodent populations toward the active substance brodifacoum, and resistance strategies management must be put in place. Results of the resistance monitoring must be submitted to the Competent Authorities (CA) or other appointed bodies involved in resistance management every 2 years.
- Field tests against all the target organisms (*Rattus rattus, Rattus norvegicus and Mus musculus),* performed with a 2 years old product, must be submitted no later than 6 months post-registration to support the efficacy of FANGA PATE PRO and storage duration of 2 years.

4 Appendices

Annex 0a: Practical use claimed by the applicant

Name of the product and type of formulation (grains, powder, paste, block…)	Target organism (rat, mice…)*	User category (professional/non professional)*	Area of use (sewers, in and around buildings, indoor only, open areas, waste dumps,…)*	Dosage claimed expressed in g/bait point, for high and low infestation (if appropriate)	Time delay of the action of the product	Frequency and method of controls	Size(s) of the bait (g/block, g/grain, g/sachet, g/paste …)	Distance between 2 bait points, for high and low infestation (if appropriate)	Methods of application of the bait (ex: pre-filled secured bait box)	Package details : Individual packaging (yes/no)**	Primary packaging : type : bulk, individual wrapping…/ nature: bucket, bottle, sachet…/ material: paper, polyethylene…/ sizes	Secondary packaging
FANGA PATE PRO Formulation: paste bait	Brown rat : *Rattus norvegicus*	Profes-sional	Indoor only	Rats: 180 g / secured bait point	3 to 10 days	4 refilling of bait stations Over 28 days Interval between applications (min): one week	10 g sachet	5-10 meters	Manual application of baits in bait stations	yes	Paper sachet	Bucket; carton
	Black rat : *Rattus rattus*	Profes-sional	Indoor only	Rats: 180 g / secured bait point	3 to 10 days	4 refilling of bait stations Over 28 days Interval between applications (min): one week	10 g sachet	5-10 meters	Manual application of baits in bait stations	yes	Paper sachet	Bucket; carton
	Mice: *Mus musculus*	Profes-sional	Indoor only	Mice: 30 g / secured bait point	3 to 10 days	4 refilling of bait stations Over 28 days Interval between applications (min): one week	10 g sachet	1-2 meters	Manual application of baits in bait stations	yes	Paper sachet	Bucket; carton

Annex 0b: Proposed uses for authorisation

This table reflects the results of the risk assessment. In case of differences between the uses suggested by Anses to be authorised and the uses contained in the decision taken by the French ministry, only the original and signed decision has a legal value.

Name of the product and type of formulation (grains, powder, paste, block…)	Target organism (rat, mice…)	User category (professional/ non professional)	Area of use (sewers, in and around buildings, indoor only, open areas, waste dumps…)	Dosage validated expressed in g/bait point, for high and low infestation (if appropriate)	Methods of application of the bait (ex: pre-filled secured bait box)	Primary packaging : type : bulk, individual wrapping…	Authori-sation
FANGA PATE PRO Formulation: paste bait	Brown rat : *Rattus norvegicus*	Professional	Indoor only	Rats: 180 g / secured bait point	Manual application of baits in tamper-resistant bait boxes or in covered bait stations	Sachet (paper) in bucket, carton	
	Black rat* : *Rattus rattus*	Professional	Indoor only	Rats: 180 g / secured bait point	Manual application of baits in tamper-resistant bait boxes or in covered bait stations	Sachet (paper) in bucket, carton	
	Mice: *Mus musculus*	Professional	Indoor only	Mice: 30 g / secured bait point	Manual application of baits in tamper-resistant bait boxes or in covered bait stations	Sachet (paper) in bucket, carton	

** Provided a field test on Rattus rattus is submitted within 6 months after product authorisation.*

Annex 1: Summary of product characteristics

See separated file.

Annex 2: List of studies reviewed

4.1.1.1.1 List of new data[14] submitted in support of the evaluation of the active substance

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
						☐	☐	☐	☐
Add rows as necessary									

4.1.1.1.2 List of new data submitted in support of the evaluation of the biocidal product

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
B3	B3.1-3.5-3.7	Demangel B	2012	Physico-chemical tests and chemical stability before and after an accelerated storage procedure for 14 days at 54±2°C on FANGA PATE PRO in compliance with CIPAC MT 46.3 (CIPAC Handbook J -2000). DEFITRACES, Report n° 11-920010-017 of xx January 2012, GLP, unpublished.	TRIPLAN	☐	☒	☒	☐

14 Data which have not been already submitted for the purpose of the Annex I inclusion.

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
B3	B3.1-3.5-3.7	Demangel B	2012	Physico-chemical tests and chemical stability before and after an accelerated storage procedure for 14 days at 54±2°C on FANGA PATE PRO in compliance with CIPAC MT 46.3 (CIPAC Handbook J -2000). DEFITRACES, Report n° 11-920010-017 of 12 March 2012, GLP, unpublished.	TRIPLAN	☐	☒	☒	☐
B3	B3.2 – B3.3-B3.4 – B3.6	Demangel B	2012	Physico chemical tests on FANGA PATE PRO DEFITRACES, Report n° 11-920010-016 of the 22 February 2012. GLP, non published	TRIPLAN	☐	☒	☒	☐
B4	B4.1.01	Ricau H	2012	Analytical method validation for the determination of brodifacoum in the FANGA BLOC SP PRO in compliance with SANCO/3030/99 rev.4 from 11/07/00. DEFITRACES, Report n° 11-920010-015 of 23 January 2012, GLP, unpublished	TRIPLAN	☐	☒	☒	☐

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
B4	B4.1.01	Ricau H	2012	Analytical method validation for the determination of brodifacoum in the FANGA BLOC SP PRO in compliance with SANCO/3030/99 rev.4 from 11/07/00. DEFITRACES, Amended report n° 11-920010-015 of 04 May 2012, GLP, unpublished.	TRIPLAN	☐	☒	☒	☐
B4	B4.1.02	Ricau H	2012	Analytical method validation for the determination of brodifacoum in the FANGA PATE PRO in compliance with SANCO/3030/99 rev.4 from 11/07/00. DEFITRACES, Report n° 11-920010-019 of 8 January 2012, GLP, unpublished.	TRIPLAN	☐	☒	☒	☐
B4	B4.1.02	Ricau H	2012	Analytical method validation for the determination of brodifacoum in the FANGA PATE PRO in compliance with SANCO/3030/99 rev.4 from 11/07/00. DEFITRACES, Amended report n° 11-920010-019 of 18 May 2012, GLP, unpublished.	TRIPLAN	☐	☒	☒	☐

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
B5	B5.10.2	De Proft M	2012	Palatability of “FANGA PATE PRO” (50 ppm brodifacoum) ready-to-use bait targeting brown rat (*Rattus norvegicus*) and house mouse (*Mus musculus*). Walloon Agricultural Research Centre, Department Pesticide Research, report n° ROD 2012 02 of the 6 March 2012, not GLP, unpublished	TRIPLAN	☐	☒	☒	☐
B5	B5.10.2/01	Guicherd A	2013	Study on the palatability and efficacy of a bait containing 0.005% (w/w) brodifacoum in brown rats (*Rattus norvegicus*). Biolytics, Study n° 12-TOX024-1 of 24 January 2013, not GLP (unpublished).	TRIPLAN	☐	☒	☒	☐
B5	B5.10.2/02	Guicherd A	2013	Study on the palatability and efficacy of a brodifacoum paste bait containing 0.005% in house mouse (*Mus musculus*). Biolytics, Study n° 12-TOX024-2 of 24 January 2013, not GLP (unpublished).	TRIPLAN	☐	☒	☒	☐

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
B5	B5.10.2/03	Guicherd A	2013	Evaluation of the efficacy of a paste rodenticide (FANGA PATE PRO) containing 0.005% brodifacoum for the control of brown rat infestations. One trial, 1 site: Rhone, France, 2012-2013. Biolytics, Final Report, Study n° 12-TOX024-14 of 24 January 2013, not GLP (unpublished).	TRIPLAN	☐	☒	☒	☐
B5	B5.10.2/04	Guicherd A	2013	Evaluation of the efficacy of a paste rodenticide (FANGA PATE PRO) containing 0.005% brodifacoum for the control of mouse infestation. One trial, 1 site: Rhone, France, 2012-2013. Biolytics, Final Report, Study n° 12-TOX024-15 of 24 January 2013, not GLP (unpublished).	TRIPLAN	☐	☒	☒	☐
B6	B6.1.1	Colas S	2012	FANGA BLOC SP PRO evaluation of acute oral toxicity in rats – acute toxic class method. PHYCHER BIO DEVELOPPEMENT, study n°: TAO423-PH-11/0402 of 5 January 2012, GLP (unpublished).	TRIPLAN	☐	☒	☒	☐

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
B6	B6.1.2	Colas S	2012	FANGA BLOC SP PRO evaluation of acute dermal toxicity in rats. PHYCHER BIO DEVELOPPEMENT, study n°: TAD-PH-11/0402 of 5 January 2012, GLP (unpublished).	TRIPLAN	☐	☒	☒	☐
B6	B6.2.1	Colas S	2012	FANGA BLOC SP PRO assessment of acute dermal irritation. PHYCHER BIO DEVELOPPEMENT, study n°: IC-OCDE-PH-11/0402 of 5 January 2012, GLP (unpublished).	TRIPLAN	☐	☒	☒	☐
B6	B6.2.2	Colas S	2012	FANGA BLOC SP PRO assessment of acute eye irritation. PHYCHER BIO DEVELOPPEMENT, study n°: IO-OCDE-PH-11/0402 of the 5 January 2012, GLP (unpublished).	TRIPLAN	☐	☒	☒	☐
B6	B6.3	Colas S	2012	FANGA BLOC SP PRO assessment of the skin sensitization potential in the mouse using the local lymph node assay (LLNA). PHYCHER BIO DEVELOPPEMENT, study n°: LLNA-PH-11/0402, report n° : LLNA-PH-11/0402-R1 of the 16 January 2012, GLP (unpublished).	TRIPLAN	☐	☒	☒	☐

Section No	Reference No	Author	Year	Title	Owner of data	Letter of Access		Data protection claimed	
						Yes	No	Yes	No
Add rows as necessary									

Annex 3: Analytical methods residues – active substance

Brodifacoum

Date: 25.04.2013

Methods suitable for the determination of residues (monitoring methods)

Extract from document IIA of final CAR of brodifacoum.

Table 21: Analytical methods for the determination of brodifacoum residue

Sample	Test substance	Analytical method	Fortification range / Number of measurements	Linearity	Specificity	Recovery rate (%)			Limit of determination	Reference
						Range	Mean	RSD		
Soil	*Brodifacoum*	RP-HPLC/DAD (detection at 264 nm)	0.016÷-0.16 mg/kg in soil, with 4 replicates per level	0.256÷-12.8 µg/ml (0.006÷-0.32 mg/kg in soil), single determinations at 8 concentrations levels. r2 = 0.9999 No matrix-matched calibration	Not highly specific LC/MS method for confirmation (only experimental conditions provided)	88.5÷-95.4 (overall)	92.9 (overall)	2.2 (overall)	LOQ = 0.016 mg/kg in soil (lowest validated concentration level)	**IIIA4.2 (a)**
Drinking water *(natural mineral water Fiuggi)*	*Brodifacoum*	RP-HPLC with MS/MS detection. Molecular ion (SIM): 521 (m/z), daughter ion (SRM): 187 (m/z) Quantification by calibration curve, except for spiking level 0.05 µg/l (quantification with the lowest standard calibration level)	0.05 µg/l (n=5) 0.5 µg/l (n=5) 5.0 µg/l (n=5) 50 µg/l (n=5)	0.1÷-0.5 µg/ml (0.05÷-0.25 µg/l in water), 4 determinations at 5 concentration levels r = 0.995 (SIM mode) r = 0.997 (SRM mode)	Highly specific	83.5÷-92.0 77.7÷-94.1 72.3÷-94.6 83.2÷-107.7	87.8 82.5 81.7 97.8	3.8 7.2 9.8 10.6	LOQ = 0.05 05 µg/l in drinking and ground water; 0.5 µg/l in surface water (lowest validated concentration level) LOD = 0.025 µg/l in water	**IIIA4.2 (c)**
Ground water *(Well SB1 I.Pi.Ci)*			0.05 µg/l (n=5) 0.5 µg/l (n=5) 5.0 µg/l (n=5) 50 µg/l (n=5)			80.4÷-100.6 82.6÷-94.4 80.1÷-94.6 81.3÷-101.2	90.5 98.7 87.3 92.5	9.3 5.6 7.3 7.0		
Surface water *(sampled at Desenzano, Garda lake)*			0.05 µg/l (n=5) 0.5 µg/l (n=5) 5.0 µg/l (n=5) 50 µg/l (n=5)			116÷-124.3 79.5÷-88.0 78.7÷-98.6 104.6÷-117	120.6 84.5 87.3 110.8	2.9 4.5 7.8 3.6		
Blood serum (*from Rabbit, lyophilized powder from clotted whole blood)*	*Brodifacoum*	RP-HPLC with MS/MS detection. Molecular ion (SIM): 523 (m/z), daughter ion (SRM): 187 (m/z) Quantification by calibration curve at 0.06 mg/l , quantification with the lowest standard calibration level at 0.3 mg/l	0.06 mg/l (n=5) 0.3 mg/l (n=6)	0.05-0.40 µg/ml (0.05-0.40 mg/l in blood serum), 4 determinations at 5 concentration levels r = 0.99679 (SIM mode) r = 0.99623 (SRM mode	Highly specific	80.8-96.6 86.2-109.1	92.1 101.7	6.5 8.6	LOQ = 0.06 mg/l (lowest validated concentration level)	**IIIA4.2 (d)(2)**

Sample	**Test substance**	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of determination**	**Reference**
						Range	Mean	RSD		
Cucumber	*Brodifacoum*	LC/MS/MS. Internal standard: Difenacoum Linear calibration curve for all determinations, except for both spiking levels in lemon and for the validation in meat at 0.1 mg/kg (multi-level calibration standards used) Brodifacoum precursor ion 1: 521; product ion 1: 79; precursor ion 2: 523; product ion 2: 81 *Coumatetralyl* precursor ion 1: 291; product ion 1: 143; precursor ion 2: 291; product ion 2: 141 Product ion 1 used for measurements	0.01 mg/kg (n=5) 0.1 mg/kg (n=5)	0.03-1.2 µg/ml, 2 determinations at 4 concentration levels. Matrix-matched calibration solutions used r2: 0.9095÷-0.9963	Highly specific	82-103 86-106	91 94	9 9	LOQ = 0.01 mg/kg in all 5 matrices (lowest validated concentration level)	**IIIA4.3 [also IIIA4.2(d)(1) for Meat only]**
Wheat			0.01 mg/kg (n=5) 0.1 mg/kg (n=5)			88-126 71-90	107 84	13 9		
Meat			0.01 mg/kg (n=5) 0.1 mg/kg (n=5)			62-86 45-87	73 61	13 29		
Oil-seed rape			0.01 mg/kg (n=5) 0.1 mg/kg (n=5)			75-99 110-134	86 119	10 8		
Lemon			0.01 mg/kg (n=5) 0.1 mg/kg (n=5)			74-93 62-89	84 76	10 13		

Annex 4: Toxicology and metabolism –active substance

Brodifacoum

Threshold Limits and other Values for Human Health Risk Assessment

Date: 31/07/2012

Summary			
	Value	Study	SF
AEL long-term	3.3 x 10^{-6} mg/kg bw/d	Develomental toxicity study in rats	300
AEL medium-term	6.67 x 10^{-6} mg/kg bw/d	Maternal toxicity from developmental study in rabbits	300
AEL acute	3.3 x 10^{-6} mg/kg bw/d	Reproductive 2-generation study in rats	300
ADI	3.3 x 10^{-6} mg/kg bw/d	Reproductive 2-generation study in rats	
ARfD	Not applicable		

Inhalative absorption	100%
Oral absorption	75%
Dermal absorption	0.047%

Classification	
with regard to toxicological data (according to the criteria in Dir. 67/548/EEC)	T+ R27/28 T ;R48/24/25 No specific limit concentrations
with regard to toxicological data (according to the criteria in Reg. 1272/2008)	Acute Tox 1 H310 Acute Tox 2 H300 STOT RE Cat 1 H372 No specific limit concentrations

Annex 5: Toxicology – biocidal product

FANGA PATE PRO

Date: 31/07/2012

General information

Formulation Type	Paste bait
Active substance(s) (incl. content)	Brodifacoum (0.005% m/m)
Category	

Acute toxicity, irritancy and skin sensitisation of the preparation (Annex IIIB, point 6.1, 6.2, 6.3)	
Rat LD50 oral (OECD 420)	> 2 000 mg/kg bw
Rat LD50 dermal (OECD 402)	> 2 000 mg/kg bw
Rat LC50 inhalation (OECD 403)	No data submitted
Skin irritation (OECD 404)	Non irritant
Eye irritation (OECD 405)	Non irritant
Skin sensitisation (OECD 429; LLNA)	Non sensitizing

Additional toxicological information (e.g. Annex IIIB, point 6.5, 6.7)	
Short-term toxicity studies	None
Toxicological data on active substance(s) (not tested with the preparation)	None
Toxicological data on non-active substance(s) (not tested with the preparation)	None
Further toxicological information	None

Classification and labelling proposed for the preparation with regard to toxicological properties (Annex IIIB, point 9)	
Directive 1999/45/EC	None
Regulation 1272/2008/EC	None

Annex 6: Safety for professional operators

FANGA PATE PRO

Date: 31/07/2012

Exposure assessment

Exposure scenarios for intended uses (Annex IIIB, point 6.6)

Primary exposure of professionals– FANGA PATE PRO (exposure during loading and cleaning considered) – Control of rats

	Component	CAS	Actual Dermal Total [mg/kg/d]	InhalationExposure [mg/m³]	Model
Control of rats and mice					
Professionnal rat (without gloves)	Brodifacoum	56073-10-0	$2.4x10^{-6}$	Not applicable	CEFICstudy

Risk assessment– Control of rats and mice

Scenario	Component	CAS	AEL [mg/kg/d]	Absorption [%]		Total syst exposure [mg/kg bw/d]		Risk
				inh	derm	Expo	%AEL	
Control of rats and mice								
Professionnal rat (without gloves)	Brodifacoum	56073-10-0	$3.3x10^{-6}$	100	0.047	$2.4x10^{-6}$	72.3	Acceptable

Annex 7: Safety for non-professional operators and the general public

FANGA PATE PRO

General information	
Formulation Type:	Paste bait
Active substance(s) (incl. content):	Brodifacoum (0.005% m/m)
Category	
Authorisation number	

Brodifacoum

Data base for exposure estimation	
according to	Appendix: Toxicology and metabolism – active substance/CAR

Exposure scenarios for intended uses (Annex IIIB, point 6.6)	
Primary exposure	Not applicable
Secondary exposure, acute	Infant ingesting bait
Secondary exposure, chronic	None

Conclusion:

The accidental ingestion of baits poses a risk to infants since the AEL is exceeded when infant ingests more than 0.88 mg of product per day.

Annex 8: Residue behaviour

Brodifacoum

The intended uses description of the product FANGA PATE PRO indicates that these uses are not relevant in terms of residues in food and feed. No further data are required concerning the residue behaviour.

Annex 9: Efficacy of the active substance from its use in the biocidal product

Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*	RI
FANGA PATE PRO 0.005% brodifacoum	House mice (*Mus musculus)* Brown rat *(Rattus norvegicus)*	Laboratory test House mice: 10 animals (5 males and 5 females) Brown rat: 10 animals (6 males and 4 females) Intoxication duration: 20 days with daily measurement of mortality and food consumption.	Acclimation: 7 days in individual cage. D0-D5: routine food has been given: 40.0 g for rats, 10.0 g for mice. D5-D20: routine food and tested baits have been given in different feeding dishes. 40.0 g of routine food and 40.0 g of tested baits for rats 10.0 g of routine food and 10.0 g of tested baits for mice. Food and bait consumption were measured and mortality was observed during 20 days after the first day of intoxication.	<u>For brown rats</u>: Every rat tasted at least very little quantity of the proposed bait since the very first day. Some rats ate large quantities (> 20 g). 2 or 3g was sufficient to kill the rat. Only one rat did not eat bait enough to be killed (0.3 g). Mean palatability percentage on brown rat = 14.31 % Mortality percentage on brown rat = 90 % Efficacy can be considered as satisfying for brown rats. <u>For house mice</u>: Four mice were still living at the end of the test. In this test, palatability level is overestimated, because it was observed that mice often gnawed the bait and dispersed it in small crumbs, but did not eat all what they took away. This was impossible to measure (a part was mixed with water wheat and urine). This behavior is observed especially when products have a poor palatability. Mean palatability percentage on house mouse = 8.73 % Mortality percentage on house mouse = 60 %. For mice, the studied bait did not appear as palatable enough for obtaining good performance against mice.	ROD 2012 02[15] IIIB5.10.2	3
FANGA	Brown rats	Laboratory test	Acclimatization: 4 days in individual cage at room	The FANGA PATE PRO bait	Guicherd A.	1

[15] De Proft M. 2012 ; Palatability of « FANGA PATE PRO » (50 ppm brodifacoum) ready-to-use bait targeting brown rat (*Rattus norvegicus*) and house mouse (*Mus musculus*). Walloon Agricultural Research Centre – Department Pesticide Research, Report n° ROD 2012 02 of the 6 March 2012, not GLP, unpublished.

PATE PRO 0.005% brodifacoum	*(Rattus norvegicus)*	Brown rats: 5 males and 5 females. Intoxication duration: 4 days with daily measurement of mortality and consumption.	temperature. Day 0: reference food and bait biocidal product have been given: - 50 g per animal of reference food for the assessment of palatability, - 50 g per animal of paste bait for the assessment of efficacy during 4 consecutive days with daily consumption measurements. Mortality was observed during 21 days every 24 hours.	containing 50 ppm brodifacoum given to brown rats (5 males and 5 females) during 4 days has demonstrated: - A palatability equivalent to 0.44 - A good consumption for all rats between day 0 and day 4 - A very good efficacy with a mortality of 90% in a period from day 4 to day 7	Study n°12-TOX024-1[16] IIIB5.10.2-01	
FANGA PATE PRO 0.005% brodifacoum	House mice *(Mus musculus)*	Laboratory test House mice: 10 males and 10 females. Intoxication duration: 4 days with daily measurement of mortality and consumption.	Acclimatization: 4 days in separate cages (10 males in a cage and 10 females in a second cage) at room temperature. Day 0: reference food and bait biocidal product have been given during 4 consecutive days with daily consumption measurements. Mortality was observed during 21 days every 24 hours or until the death of all animals.	The FANGA PATE PRO bait containing 50 ppm brodifacoum given to house mice (10 males and 10 females) during 4 days has demonstrated: - A palatability equivalent to 0.65 - A good consumption for all mice between day 0 and day 4 - A very good efficacy with a mortality of 100 % in a period from day 4 to day 9	Guicherd A. Study n° 12-TOX024-2[17] IIIB5.10.2-02	1
FANGA PATE PRO 0.005% brodifacoum	Brown rats *(Rattus norvegicus)*	Field test The rodenticide was evaluated using the census baiting technique, which involved the following phases: Pre-treatment census Pre-treatment lag phase Treatment census Post-treatment lag phase Post-treatment census During each assessment the food/bait at each station was weighed and replenished, and the consumption in grams was calculated. During the treatment census, searches were conducted for dead and dying rats	Acclimatization: 15 days (150-200 g of wheat per station per day) Treatment : 40 to 160 g of paste bait in each lockable bait station per day (total 10 bait stations) during15 days Post-baiting: 3 days (150-200 g of wheat per station per day) Mortality was observed from the first day of intoxication and noted about every 2 days until the end of the trial.	The FANGA PATE PRO bait containing 50 ppm brodifacoum given to brown rats has demonstrated: The efficacy was total (100 %). - Pre-baiting plateau = 531 g/day - Post-baiting = 0 g - Assessed efficacy = 100 % The assessed bait has been very well accepted by brown rats and effective and the results are consistent with laboratory ones. No secondary poisoning occurred at the baited site.	Guicherd A. Study n° 12-TOX024-14[18] IIIB5.10.2-03	1

[16] Guicherd A. 2013. Study on the palatability and efficacy of a bait containing 0.005% (w/w) brodifacoum in brown rats (*Rattus norvegicus*). Biolytics. Study n° 12-TOX024-1 of 24 January 2013, not GLP (unpublished).
[17] Guicherd A. 2013. Study on the palatability and efficacy of a brodifacoum paste bait containing 0.005% in house mouse (*Mus musculus*). Biolytics, Study n° 12-TOX024-2 of 24 January 2013, not GLP (unpublished).
[18] Guicherd A. 2013. Evaluation of the efficacy of a paste rodenticide (FANGA PATE PRO) containing 0.005% brodifacoum for the control of brown rat infestations. One trial, 1 site: Rhone, France, 2012-2013. Biolytics, Final Report, Study n° 12-TOX024-14 of 24 January 2013, not GLP (unpublished).

		around the sites.				
FANGA PATE PRO 0.005% brodifacoum	House mice *Mus musculus*	Field test: The rodenticide was evaluated using the census baiting technique, which involved the following phases: Pre-treatment census Pre-treatment lag phase Treatment census Post-treatment lag phase Post-treatment census During each assessment the food/bait at each station was weighed and replenished, and the consumption in grams was calculated. During the treatment census, searches were conducted for dead and dying mice around the sites.	Acclimatization: 14 days (150-200 g of semolina per station per day) Treatment : 40 g of paste bait in each lockable bait station (total 10 bait stations) during11 days Post-baiting: 3 days (150-200 g of semolina per station per day) Mortality was observed from the first day of intoxication and noted about every 2 days until the end of the trial.	The FANGA PATE PRO bait containing 50 ppm brodifacoum given to House mice has demonstrated: The efficacy was total (100 %). - Pre-baiting plateau = 154 g/day - Post-baiting = 0 g - Assessed efficacy = 100 % The assessed bait has been very well accepted by House mice and effective and the results are consistent with laboratory ones (100 % efficacy). No secondary poisoning occurred at the baited site.	Guicherd A Study n° 12-TOX024-15[19] IIIB5.10.2-04	1

[19] Guicherd A. 2013. Evaluation of the efficacy of a paste rodenticide (FANGA PATE PRO) containing 0.005% brodifacoum for the control of mouse infestation. One trial, 1 site: Rhone, France, 2012-2013. Biolytics, Final Report, Study n° 12-TOX024-15 of 24 January 2013, not GLP (unpublished).