Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

**PRODUCT ASSESSMENT REPORT OF A BIOCIDAL PRODUCT FOR NATIONAL AUTHORISATION APPLICATIONS**

(submitted by the evaluating Competent Authority)



NYNA D+ AVOINE

Product type 14

Difenacoum

Case Number in R4BP: BC-QT000921-24

Case Number in R4BP: BC-VK068549-07

Evaluating Competent Authority: FR

Date: January 2018

Udated date: November 2021

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**Note to the reader**

This consolidated PAR for the **minor change** application of the product authorisation is based on the PAR of the first authorisation, in which all necessary addenda have been included.

In part 1 and 2 of this consolidated PAR, each section contains the initial assessment and the subsequent successive assessments (minor change, major change, post authorisation data...). The assessments related to the minor change of the product are at the end of each section and are highlighted in grey.

In part 3 of the consolidated PAR: the summary of product characteristics (SPC) is pointed out and corresponds to the decision for the minor change application.

**Disclaimer regarding user category**

For the risk assessment of PT14, two user categories have been addressed depending on the quantity of manipulated product and the possibility of using PPE: non-professional users and professional users.

In France, any professional user needs a dedicated national certificate, hence it is expected that he/she has the required competence to access to biocidal products that are authorized for professional users they are thus considered as « trained professional users ».

Consequently, in the SPC for minor change in Part 3, uses for “professionals” are mentioned according to the agreed standard SPC, but they not relevant in France. It is proposed that each cMS adapts the conditions of authorization of the product according to its own legislation.

1. **History of the dossier**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Application type** | **refMS** | **Case number in the refMS** | **Decision date** | **Assessment carried out (i.e. first authorisation / amendment /renewal)** |
| NA-APP | *FR* | *NA* | 23.02.2012 | Initial assessment : NYNA D+ AVOINE |
| *NA* | *FR* | *NA* | 12.04.2012 | Frame formulation establishment: change of dye-stuff and variation in co-formulants |
| *NA* | *FR* | *NA* | 03.04.2013 | Addition of new uses : user category (non-professionals) and bulk packaging for professional users |
| NA-MIC | *FR* | BC- SU004183-22 | 04.11.2015 | Minor change: addition of field of uses (around buildings, open areas, landfills and wastedump) |
| NA-RNL | *FR* | BC- QT000921-24 | 01.02.2018 | Renewal of the authorisation |
| NA-MIC | *FR* | BC-VK068549-07 |  | Minor change: Packaging modifications, deletion and addition of trade names, modification of biocidal product manufacturers and update of active substance manufacturer address |

**Authorised uses**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Users** | **Target organisms** | **Dose** | **Field of use** | **Packagings** |
| Professionals | Rats (*Rattus rattus* and *Rattus norvegicus*) | 200 g every 5 to 10 meters | In and around buildings, open areas, waste dumps and landfills | Bulk or individual sachets |
| Mice (*Mus musculus*) | 40 g every 1 to 2 meters |
| Non-professionals | Rats (*Rattus rattus* and *Rattus norvegicus*) | 200 g every 5 to 10 meters | Individual sachets |
| Mice (*Mus musculus*) | 40 g every 1 to 2 meters |

**Intended uses for the renewal stage**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Users** | **Target organisms** | **Dose** | **Field of use** | **Packagings** |
| Professionals | Rats (*Rattus rattus* and *Rattus norvegicus*) | 200 g every 5 to 10 meters | In and around buildings, open areas, waste dumps and landfills | Bulk or individual sachets |
| Mice (*Mus musculus*) | 40 g every 1 to 2 meters |

**Intended uses for the minor change stage**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Users** | **Target organisms** | **Dose** | **Field of use** | **Packagings** |
| Professionals | Rats (*Rattus rattus* and *Rattus norvegicus*) | 200 g every 5 to 10 meters | In and around buildings, open areas, waste dumps and landfills | Bulk or individual sachets |
| Mice (*Mus musculus*) | 40 g every 1 to 2 meters |

# General information about the product application – PAR 2012

## 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 |

### Person authorised for communication on behalf of the applicant

|  |  |
| --- | --- |
| **Name:** | Fredy LACROUX |
| **Function:** | Director |
| **Address:** | BP 258 La poste Française |
| **City:** | Andorre la Vieille |
| **00Postal Code:** | AD500 |
| **Country:** | Andorre |
| **Telephone:** | +376 741 445 |
| **Fax:** | +376 741 450 |
| **E-mail address:** | Saida.triplan@andorra.ad |

* **Renewal 2017**

The new e-mail address is triplan@andorra.ad.

## Current authorisation holder[[1]](#footnote-1)

|  |  |
| --- | --- |
| **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 |

## 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 |

## Information about the product application

|  |  |
| --- | --- |
| **Application received:** | 31/03/2010 |
| **Application reported complete:** | 30/08/2010 |
| **Authorisation granted:** |  |
| **Type of application:** | Product authorisation |
| **Further information:** | - |

## Information about the biocidal product

### General information

|  |  |
| --- | --- |
| **Trade name:** | NYNA D+ AVOINE |
| **Manufacturer’s development code number(s), if appropriate:** | Not reported |
| **Product type:** | PT14 - 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: Difenacoum 0.005% w/w  No substance of concern |
| **Formulation type:** | Cereal grains |
| **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 |

### Information on the intended use(s)

|  |  |
| --- | --- |
| **Overall use pattern (manner and area of use):** | NYNA D+ AVOINE is intended to be used for control of mice, brown rats and black rats inside buildings (private and public including farm buildings |
| **Target organisms:** | 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.1 Non Professional/general public  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 Covered application in bait stations.  The product is a ready to use grain bait and contains 0.005% w/w of difenacoum  Professional/Non professional :  Rat: 180-200 g grains (secured bait point separated by 5-10 m).  Mice: 30-40 g grains (secured bait point separated by 1-2 m).  For professional and non professional, the product is supplied in sachets of 25, 50 or 100 g and for professional users only, in bulk of 20 or 25 kg bags  Secondary packaging:   * For non professional: cardboard boxes or in buckets : from 400 g to 3 kg * For professional: cardboard boxes or in buckets from 5 kg to 20 kg and bulk in bags of 20 and 25 kg. |
| **Potential for release into the environment (yes/no):** | Yes |
| **Potential for contamination of food/feedingstuff (yes/no)** | No |
| **Proposed Label:** | Control of rats (*Rattus norvegicus* and *Rattus rattus*) and mice (*Mus musculus*) inside buildings.  Non professional (sachet of 25 g):  Rat: 8 sachets/secured bait point separated by 5-6 m.  Mice: 2 sachets/secured bait point separated by 1-2 m.  Professional (bulk and sachet of 25 g):  Sachet:  Rat: 8 sachets/secured bait point separated by 5-6 m.  Mice: 2 sachets/secured bait point separated by 1-2  Bulk:  Rat: 200 g secured bait point separated by 5-6 m.  Mice: 40 g grains/secured bait point separated by 1-2  Over a period of 28 days for application, cleaning, refilling and collect of dead rodents |
| **Use Restrictions:** | Use only inside buildings in secured bait stations out of reach of children and domestic animals. |

### Information on active substance(s)[[2]](#footnote-2)

|  |  |
| --- | --- |
| **Active substance chemical name:** | Difenacoum |
| **CAS No:** | 56073-07-5 |
| **EC No:** | 259-978-4 |
| **Purity (minimum, g/kg or g/l):** | 960 g/kg |
| **Inclusion directive:** | [2008/81/EC](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32008L0081:EN:NOT) |
| **Date of inclusion:** | 01/04/2010 |
| **Is the active substance equivalent to the active substance listed in Annex I to 98/8/EC (yes/no):** | Yes |
| **Manufacturer\* of active substance(s) used in the biocidal product:** |
| **Company Name:** | PM TEZZA SRL |
| **Address:** | Via Tre Ponti 22 |
| **City:** | Maria di Zevio (VR) |
| **Postal Code:** | 37050 |
| **Country:** | Italy |
| **Telephone:** | Not reported |
| **Fax:** | Not reported |
| **E-mail address:** | Not reported |

\*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 difenacoum of the Activa / PelGar Brodifacoum and Difenacoum Task Force.

* **Renewal 2017**

Difenacoum does meet the exclusion criteria laid down in Article 5(1)(c) of Regulation (EU) No 528/2012. Difenacoum does meet the conditions laid down in Article 10(1)(a) and (e) of Regulation (EU) No 528/2012 if approved, and is therefore considered as a candidate for substitution.

***Comparative assessment***

A comparative assessement has been carried out at the European level. According to Article 1 of Commission Implementing Decision (EU) 2017/1532 of 7 September 2017 addressing questions regarding the comparative assessment of anticoagulant rodenticides in accordance with Article 23(5) of Regulation (EU) No 528/2012 of the European Parliament and of the Council. In the absence of anticoagulant rodenticides, the use of rodenticides containing other active substances would lead to an inadequate chemical diversity to minimize the occurrence of resistance in the target harmful organisms.

In summary it can be concluded that the criteria according Article 23(3) a), b) BPR are not fulfilled.

Therefore, the authorisation of this product will be renewed for 5 years.

### Information on the substance(s) of concern[[3]](#footnote-3)

NYNA D+ AVOINE does not contain any substance of concern according to the Technical Notes for Guidance on data requirements[[4]](#footnote-4).

* **Renewal application (2017)**

NYNA D+ AVOINE does not contain any substance of concern according to the Guidance on the BPR Volume III Human Health – Part B Risk Assessment[[5]](#footnote-5).

## Documentation

### Data submitted in relation to product application

**Identity, physicochemical and analytical method data**

Physico-chemical properties were provided by Triplan. Some data have been provided using product with old composition and some other with the new composition:

* Most of physico-chemical properties were performed on NYNA D+ AVOINE, current formulation.
* Explosive properties are on another difenacoum-based formulation, NYNA D+ BLE, old formulation. These properties have been extrapolated for the current formulation NYNA D+ AVOINE.

An analytical method to determine the active substance in the formulation NYNA D+ AVOINE has been provided by Triplan.

Data on the active substance required at the product authorization stage as stated in the Assessment Report of the active substance and provided by Activa:

- Analytical data to prove the isomeric composition and impurity profile of the active substance,

- Appearance of the active substance,

- A validated method for the analysis of difenacoum in animal and human tissues,

- Validation data for the determination of residues of difenacoum in meat and in oil-seed rape (food/feeding stuffs),

- Validation data for the determination of difenacoum in sediment.

* **Renewal application (2017)**

In the frame of the initial active substance approbation (2009), post approbation data as listed above were required.

Those data were provided in the frame of the renewal assessment report.

* **Minor change application (2021)**

New packaging claims were submitted, the section 2.3 packaging of the biocidal product has been updated with packagings considered as acceptable for product’s supply.

A mitigation measure should be added: “Store away from humidity”.

**Efficacy data**

The following efficacy studies were submitted:

* Efficacy laboratory study of cereal rodenticide containing 0.005% difenacoum with albino house mice (*Mus musculus).*
* Efficacy field study of cereal rodenticide containing 0.005% difenacoum with brown rats (*Rattus norvegicus).*
* Acceptance comparison study between hulled oat and wheat with albino house mice *(Mus musculus).*

These studies were performed with another difenacoum-based formulation NYNA D+ BLE (see detailed composition in confidential document). This formulation is different from NYNA D+ AVOINE because of the type of grain, the pigment, and it also contains fewer appetent agents. But as it is also a grain formulation containing 0.005% of difenacoum and as it is the same rate of bittering agent, then the results can be taken into account in order to support the product authorization of NYNA D+ AVOINE.

Moreover, in order to support the resistance information, new data carried out with literature references were submitted during the evaluation.

* **Renewal application (2017)**

Field tests with the formulation NYNA CEREALES A 25, have been submitted on house mice (*M.musculus*), brown rats (*R.norvegicus*) and black rats (*R.rattus*). NYNA CEREALES A 25 differs only from the product NYNA D+ AVOINE by the content of the active substance difenacoum. (0.0025 % w/w instead of 0.005% w/w).

**Toxicology data**

The applicant did not submit new toxicological data on active substance. Acute oral and dermal toxicity, skin and eye irritation and skin sensitisation studies have been provided on the old formulation of another difenacoum-based formulation, NYNA D+ BLE. A dermal penetration study was submitted with another difenacoum-based formulation, NYNA D+ CEREALES. Extrapolation to NYNA D+ AVOINE was accepted since it is expected that the differences do not impact the toxicity.

* **Assessment of new uses’ addition (2013)**

The study ” ACTIPELLET-DIFE: *In vitro* dermal delivery with human skin,” was supplied in the dossier.

* **Renewal application (2017)**

No additional data was provided in the frame of the product authorisation renewal.

**Ecotoxicology data**

The applicant has not provided ecotoxicological study with the biocidal product. The environmental risk assessment, part 2.8, has been done by the authority in charge of the risk assessment, using the difenacoum CAR of the Task Force Activa/Pelgar.

* **Renewal application (2017)**

No additional data was provided in the frame of the product authorisation renewal.

### Access to documentation

In the frame of the authorization of NYNA D+ AVOINE supported by TRIPLAN SA, the applicant Activa Srl has submitted a letter of access to all data on difenacoum submitted by the Activa/Pelgar Brodifacoum and Difenacoum Task Force under directive 98/8/EC for the purpose of Annex I listing.

# Summary of the product assessment

## Identity related issues

Data on the active substance were required at the product authorization stage as stated in the AR about the active substance and were provided by Activa:

- Analytical data to prove the isomeric composition and impurity profile of the active substance

The assessment of the technical equivalence of the source of difenacoum from Activa versus the reference source of Pelgar used for annex I inclusion has been performed. The conclusion is that the source of Activa used in NYNA D+ AVOINE is technically equivalent to the source of Pelgar assessed for annex I inclusion. The confidential document is attached to this PAR as the addendum to the CAR of difenacoum is not available yet. See the confidential appendix “Technical equivalence Difenacoum Activa” for detailed information.

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

## Classification, labelling and packaging – PAR 2012, updated 2017

### Harmonised classification of the biocidal product

No classification is required for NYNA D+ AVOINE.

* **Renewal application (2017)**

| **Classification** | |
| --- | --- |
| Hazard category | Repr. 1B  STOT RE 2 |
| Hazard statement | H360D: May damage the unborn child  H373: May cause damage to organs through prolonged or repeated exposure |

### Labelling of the biocidal product

No labelling is required for NYNA D+ AVOINE.

* **Renewal application (2017)**

|  |  |
| --- | --- |
| **Labelling** | |
| Signal words | Danger    GHS 08 |
| Hazard statements | H360D: May damage the unborn child  H373: May cause damage to organs through prolonged or repeated exposure |
| Precautionary statements | P201: Obtain special instructions before use.  P202: Do not handle until all safety precautions have been read and understood.  P260: Do not breathe dust/fumes/gas/mist/vapours/spray.  P280: Wear protective gloves/protective clothing/eye protection/face protection.  P308 + P313: If exposed or concerned: Get a medical advice/attention  P314: Get medical advice/attention if you feel unwell.  P405: Store locked up.  P501: Dispose of contents/container to … [*… in accordance with local/regional/national/international regulation]* |

### Packaging of the biocidal product

Primary packaging:

NYNA D+ AVOINE is supplied in white opaque or transparent polyethylene (PE) film sachets (of 25, 50 or 100 g) for professional and non-professional users and in bulk in 20 or 25 kg bags (in several paper layers + PE film) for professional users, only.

Secondary packaging:

The sachets are put in cardboard boxes or in buckets of different capacities (from 400 g to 3 kg for non-professionals and from 5 kg to 20 kg for professionals).

* **Assessment of new uses’ addition (2013)**

**Primary packaging**

NYNA D+ BLE / NYNA D+ AVOINE / NYNA D+ CEREALES are supplied in white opaque or transparent polyethylene (PE) film sachets (of 25, 50 or 100 g) for professional and non-professional users and in bulk in 20 or 25 kg bags (in several paper layers + PE film) for professional users, only.

**Secondary packaging**

The sachets are put in cardboard boxes or in buckets of different capacities (from 400 g to 3 kg for non-professionals and from 5 kg to 20 kg for professionals).

* **Renewal application (2017)**

Only packaging for professionnal user are maintained.

Primary packaging:

NYNA D+ AVOINE is supplied in white opaque or transparent polyethylene (PE) film sachets (25-50-100 g) or in bulk.

Secondary packaging:

The sachets are put in cardboard boxes (5-10-15-20 kg), paper bags with PE layer inside (20-25 kg) or in PE buckets (5-10-15-18-20 kg).

Bulk is packed in paper bags with PE layer inside (20 or 25 kg).

Bulk can also be packed in buckets (PE) of 5-10-15-18-20 kg.

* **Minor change application (2021)**

NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.

Sachets are packed in:

- Buckets (PE/PP) (5-10-15-18-20-25-30 kg)

- Bags (paper/PE/PP) (5-10-15-20-25-30 kg)

- Cardboards (carton) (5-10-12-15-20-25-30-50 kg)

- Metal box (metal) (5-10-15-20-25 kg)

- Bait box PET/PP/PE/PVC

The product is supplied in bulk in:

- Buckets (PE/PP) (5-10kg)

- Bags (paper/PE/PP) (5-10 kg)

- Cardboards (carton) (5-10 kg)

- Metal box (metal) (5-10 kg)

- Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg)

## Physico/chemical properties and analytical methods – PAR 2012, updated 2017

Data on the active substance difenacoum were required at the product authorization stage as stated in the Assessment Report of the active substance and were provided by Activa:

- Appearance of the active substance

Results of the assessment: for appearance, the data provided are acceptable. The results are reported in 2.3.1.

### Physico-chemical properties

Table 1: Physico-chemical properties of the active substance

|  | Method/ Guideline | Purity/Specification | Result | Reference |
| --- | --- | --- | --- | --- |
| Physical state | Visual examination | 99.5% w/w difenacoum  Batch number 03090205 | Solid powder at ca. 22°C | CH-082/2010 |
| Colour | Visual examination | 99.5% w/w difenacoum  Batch number 03090205 | Faint beige (Sigma-aldrich Color Chart) |
| Odour | Olfactory test | 99.5% w/w difenacoum  Batch number 03090205 | Characteristic |

Other physico-chemical properties are presented in the CAR of difenacoum of the Activa / Pelgar Brodifacoum and Difenacoum Task Force. Triplan has a letter of access to these data.

Table 2: Physico-chemical properties of the biocidal product

For the studies performed on NYNA D+ BLE old formulation, results from these studies could be extrapolated to the current formulation of NYNA D+ AVOINE. The differences in composition between the two formulations were evaluated and considered as acceptable for each property under consideration.

|  | Method | Purity/Specification | Results | Reference |
| --- | --- | --- | --- | --- |
| Physical state and nature | Visual inspection at room temperature | 0.049 g/kg difenacoum | Cereal grains  Bait ready for use (RB) | 10-920010-015 |
| Colour | Heterogeneous dark turquoise-blue |
| Odour |  |  | Not determined |  |
| Explosive properties | Internal method with DSC | 0.043 g/kg  difenacoum  NYNA D+ BLE (old formulation) | Not explosive | 09-920010-13 |
| Oxidizing properties | Statement |  | No oxidizing properties |  |
| Flash point | Not applicable |  |  |  |
| Autoflammability | EC A16 | 0.043 g/kg  difenacoum  NYNA D+ BLE (old formulation) | Not auto-flammable up to 400°C | 09-920010-13 |
| Other indications of flammability | EC A10 | 0.050 g/kg difenacoum  NYNA D+ CEREALES | Not highly flammable  See comment below the table | 10-920010-019 |
| Acidity / Alkalinity | CIPAC MT 75.3 | 0.049 g/kg difenacoum | 1% m/v in standard water D  6.44 at 21.3°C after 1 min.  6.43 at 21.5°C after 10 min.  The measured pH value is higher than 4 and lower than 10, therefore no further testing is required. | 10-920010-016 |
| Relative density / bulk density | EC A3 | 0.049 g/kg difenacoum | The relative density mean value of the test using the gas comparison method with the stereopycnometer was:  D (19.6°C/4.0°C) = 1.393 ± 0.007.  See comment and conclusion below the table | 10-920010-015 |
| Storage stability – stability and shelf life | 2-year storage stability |  | See conclusion below the table |  |
| Effects of temperature | CIPAC MT 46.3 | 0.049 g/kg difenacoum | After the accelerated storage procedure, the aspect of the test item was considered to be stable.  No significant change was observed in the difencoum content (-4.1% deviation from T=0) after the accelerated storage for 14 days at 54°C  See comment and conclusion below the table | 10-920010-016 |
| Effects of light |  |  | Not required since the product will be stored protected from light. |  |
| Reactivity towards container material |  | 0.049 g/kg difenacoum Material: colourless plastic bag (PE) | After the accelerated storage procedure, the packaging was considered to be stable (loss of weight of the two bags tested:  DWBag 2 = -4.5%  DWBag 3 = -4.8%  See conclusion below the table | 10-920010-016 |
| Technical characteristics in dependence of the formulation type | Dust content  CIPAC MT 58.2 |  | See comment below the table |  |
| Compatibility with other products |  |  | The product is never used with other products including biocidal products. |  |
| Surface tension | Not applicable |  |  |  |
| Viscosity | Not applicable |  |  |  |
| Particle size distribution | CIPAC MT 58.2 | 0.049 g/kg difenacoum | See comment and conclusion below the table | 10-920010-16 |

Other indications of flammability:

For the flammability property, no study was submitted and FR CA used the flammability study performed on NYNA D+ CEREALES as results from this study could be extrapolated to the current formulation of NYNA D+ AVOINE. The differences in composition between the two formulations were evaluated and considered as acceptable for the property under consideration.

Relative density / bulk density:

The relative density measured using method EC A3 is not well adapted. The method CIPAC MT 186 would have been more suitable with measure of tap and pour density. Nevertheless results of method EC A3 can be used to characterize the product.

Storage stability:

The pH was measured after 14 days at 54°C and no significant changes were observed.

Reactivity toward container material:

The reactivity toward colourless plastic bag (PE) has been tested. The reactivity toward white opaque PE film sachet and 20-25 kg bags (several paper layers + PE film) has not been tested.

Dust content:

The CIPAC method 58.2 is not adapted. The CIPAC method 171 would have been more suitable. The CIPAC method 58.2 allows to conclude that 0.04% of particles are lower than 150µm.

Particle size distribution:

The CIPAC MT 58.2 method is not well adapted. But the study shows that 99.92% of grains have a size higher than 850µm.

**Conclusion – PAR 2012**

A 2-year storage stability study is missing and is required in post registration. The study shouldbe performed with test items in quantity sufficient to overcome the heterogeneity problem. Intermediate results at 1 year have to be provided also.

The reactivity toward white opaque PE film sachet of 25g is missing and is required in post registration. The tested material should be clearly identified in the study. The reactivity toward 20-25 kg bags (several paper layers + PE film) is not required as this packaging is not accepted due to the risk assessment.

The pour and tap density (CIPAC MT 186) and the particle size distribution (CIPAC MT 59.4 (ii)) are required in post registration.

* **Assessment of frame formulation establishment (2012)**

**Physico-chemical comparison**

Data submitted:

* Variations of compositions within the frame formulation.
* Safety data sheet of new formulant used.

The biocidal product Nyna D+ Avoine is a rodenticid product (TP14) made of grain bait (AB) containing 0.005% of Difenacoum.

Evaluation of the reference NYNA D+ Avoine Product Authorization dossier was performed using read acrosses with other formulations for explosive and flammability properties. These read-acrosses are still acceptable for the frame formulation establishment.

No study was submitted for this frame formulation establishment dossier. None of the formulant is classified in physicochemistry.

Considering the small changes of composition and the non Phys-Chem classification of formulants, the physicochemical properties initially assessed for the reference product NYNA D+ AVOINE can be considered as valid for the frame formulation.

No data were submitted on the packaging of products covered by the frame formulation. The allowed packaging will be those allowed for the reference product.

**Conclusion**

Considering the small changes of composition and the non Phys-Chem classification of formulants, the physicochemical properties initially assessed for the reference product NYNA D+ AVOINE can be considered as valid for the frame formulation. The allowed packaging will be those allowed for the reference product.

* **Renewal application (2017)**

**Assessment of the submitted post-registration data (2017)**

Post-authorisation data required in the frame of the initial product authorisation (2012) were assessed for the renewal application.

**Table 3: Physico-chemical properties of the biocidal product**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Property** | **Guideline and Method** | **Purity of the test substance (% (w/w)** | **Results** | **Reference** |
| Density / Bulk density | CIPAC MT 186 | NYNA D + AVOINE  (0.005% w/w of difenacoum)  Batch No. 12/13 | The mean pour density of the test item was 0.682 ± 0.001 g/mL.  The mean tap density of the test item was 0.742 ± 0.002 g/mL. | DEMANGEL, B. (2013), Study No. 13-920010-003 |
| Storage stability test – **long term storage at ambient temperature** | CIPAC 46.3  2-years storage stability | NYNA D + AVOINE  (0.005% w/w of difenacoum)  Batch No. 48/10 | Determination of physico-chemical properties and storage stability test packed in PE film bag:   |  |  |  |  | | --- | --- | --- | --- | |  | Initial | After 12 months at rt | After 24 months at rt | | Appearance | Heterogeneous blue-green oat grains | Heterogeneous blue-green oat grains | Heterogeneous blue-green oat grains | | Appearance of packaging | Transparent thermofused PE bag | Transparent thermofused PE bag | Transparent thermofused PE bag | | Content of AS | 0.0049% | 0.0047% | 0.0049% | | Variation of AS (%) | - | -4.1% | 0.0% |   Quantification of AS has been done by HPLC UV detection with the method evaluated in the PAR.  Conclusion: The storage stability studies during 24 months at rt allow to consider that the product is stable in the claimed packaging (PE film bag) under tested conditions.  The product being a solid, if it is compatible with one type of packaging, it is considered compatible with every types of packaging. The product is thus compatible with bag several paper layers + PE film. | DEMANGEL, B. (2013), Study No. 10-920010-017 |
| Particle size distribution, content of dust/fines, attrition, friability | CIPAC 94.6  CIPAC MT171 | NYNA D + AVOINE  (0.005% w/w of difenacoum)  Batch No. 12/13 | Particle size distribution (by dry sieving):   |  |  | | --- | --- | | Test sieves | % of residues | | 4.0 | <0.1 | | 2.8 | 6.4 | | 2.0 | 87.0 | | 1.4 | 6.4 | | Pan | 0.2 |   Dust content:   |  |  | | --- | --- | | Test sieves | % of residues | | 250 µm | 99.9 | | 125 µm | 0.1 | | Pan | <0.1 |   Conclusion: The majority of the particles (87.0%) of the test item were between 2.0 mm and 2.8 mm. The dust content of the test item represents less than 0.1%. When the product is supplied in bulk, eCA recommends wearing protecting gloves and a respiratory protection equipment during decanting. Thus no friability test will be needed. | DEMANGEL, B. (2013), Study No. 13-920010-003 |

|  |
| --- |
| **General conclusion on the physical, chemical and technical properties of the product for renewal of national authorisation applications - 2017** |
| The product NYNA D + AVOINE is a ready to use bait formulation. All studies have been performed in accordance with the current requirements and the results are deemed to be acceptable. It is not explosive and has no oxidising properties. The product is not flammable.  The product is an heterogeneous blue-green oat grain.  Storage stability study results are acceptable. The biocidal product is stable 2 weeks at 54°C and 2 years at ambient temperature with a PE film bag packaging. Considering the product is a solid and it is compatible with PE film bag, compatibility with other claimed packagings is considered acceptable.  eCA recommends to store away from light due to the sensitivity of the active substance to light.  Its technical characteristics are acceptable for a ready to use bait formulation. |

### Analytical methods – PAR 2012

Data on the active substance difenacoum were required at the product authorization stage as stated in the AR of the active substance and were provided by Activa:

- Analytical data to prove the isomeric composition and impurity profile of the active substance,

- A validated method for the analysis of difenacoum in animal and human tissues,

- Validation data for the determination of residues of difenacoum in meat and oil-seed rape (food/feeding stuffs),

- Validation data for the determination of difenacoum in sediment.

Results of the assessment of the analytical methods provided by Activa on the active substance as required in the CAR:

- Analytical data to prove the isomeric composition and impurity profile of the active substance,

Results of the assessment:

→ The method provided doesn’t allow to identify and quantify separately the two diastereoisomers. Nevertheless FR CA considers that the provided data allow the determination of the isomeric composition.

→ The submitted data allow to determine the impurity profile.

See table below and the confidential appendix “Technical equivalence Difenacoum Activa” for detailed information.

- A validated method for the analysis of difenacoum in animal and human tissues

Results of the assessment: The method is validated and is acceptable.

- Validation data for the analytical method for determination of residues of difenacoum in meat and oil-seed rape (food/feeding stuffs)

Results of the assessment: The data provided were not validation data based on the analysis method already provided in the dossier, as requested. The submitted study report provided a new method with validation data. This new method is validated and is acceptable.

- Validation data for analytical method for determination of difenacoum in sediment (based on the analysis method for difenacoum in soil)

Results of the assessment: The data provided were not validation data based on the analysis method for difenacoum in soil, as requested. The submitted study report provided a new method with validation data. This new method is validated and is acceptable.

|  |  |
| --- | --- |
|  | Principle of method |
| Technical active substance as manufactured: | HPLC-UV |
| Impurities in technical active substance: | - |
| Active substance in the formulation: | HPLC-UV |

**Technical active substance as manufactured:**

The determination of the active substance was performed by HPLC using an internal standard and UV detector at 275nm. The quantification of difenacoum is achieved by comparing the ratio of the analytical standard peak area versus 1,3,5-triphenylbenzene internal standard (IS) peak area and the same ratio determined for a sample containing a known amount of internal standard (I.S). The analytical method is considered to be acceptable.

**Impurities in technical active substance:**

No methods required since there are no impurities higher than 0.1% w/w.

**Active substance in the formulation:**

Difenacoum is analyzed after extraction from the formulation and quantified by liquid chromatography using a reverse phase column and an UV detector. Two validated analytical methods have been provided. An analytical method validation was performed on another difenacoum-based formulation, NYNA D+ BLOC SP, by definition of the specificity, the linearity, the precision and the accuracy of the method. This is acceptable for NYNA D+ AVOINE. A complementary analytical method for the determination of difenacoum in NYNA D+ AVOINE was performed by definition of the specificity and the accuracy of the method.

* **Assessment of new uses’ addition (2013)**

**Analytical method for toxicological part**

**Report:** ACTIPELLET-DIFE: *In vitro* dermal delivery with human skin, JAGER, M. 2013

**Study GLP N°:** 1503302

**Test facility:** Harlan Cytotest Cell Research GmbH,

In den Leppsteinswiesen 19

64380 Rossdorf

Germany

Principle of the method:

Skin samples were minced and mixed then extracted with MeOH as extraction solution. PBS buffer/EtOH (80:20, v/v) was used as receptor solution. The samples from the skin dermal delivery assay are then analyzed by LC-MS/MS (Column: C18 reversed phase)(ESI transition m/z=445 -> 257) for the quantification of Difenacoum. Positive or Negative ionization is not specified in the report.

The validation of this method was considered in compliance with SANCO 3029/99.

Validation data:

|  |  |
| --- | --- |
| Specificity | Chromatograms are not legible on the document provided by the applicant. However, the recovery rates obtained are acceptable and could confirm that there is no interference. Moreover, regarding the detector used (MS/MS) the method should be sufficiently specific. |
| Linearity | Linearity was studied by carrying out 10 tests with concentrations between 0.2 and 100 ng.mL-1 for Difenacoum in receptor solution (n=3) and extraction solution (n=3).  Calibration curve has been provided with a R2 higher than 0.99. |
| Accuracy | Accuracy was determined by analyzing four different concentrations of Difenacoum in receptor solution (n=6) and in extraction solution (n=3). The accuracy results are expressed as the recovery rate.  Receptor solution:   |  |  |  |  | | --- | --- | --- | --- | | Fortification level  (ng.mL-1) | Recovery rate (%) | Mean recovery rate  (%) | RSD (%) | | 80.0 | 89.9, 96.4, 92.0, 101.8, 104.4, 100.8 | 97.5 | 6.0 | | 10.0 | 107.0, 99.2, 109.0, 129.0, 111.0, 106.0 | 106.4 | 4.0 | | 0.8 | 111.5, 88.4, 94.5, 86.8, 99.4, 95.6 | 96.0 | 9.7 | | 0.2 | 100.0, 99.5, 93.0, 88.5, 81.5, 88.0 | 93.8 | 6.7 |   Extraction solution:   |  |  |  |  | | --- | --- | --- | --- | | Fortification level  (ng.mL-1) | Recovery rate (%) | Mean recovery rate  (%) | RSD (%) | | 80.0 | 94.1, 99.3, 100.4 | 97.9 | 3.5 | | 10.0 | 97.7, 100.0, 107.0 | 101.6 | 4.7 | | 0.8 | 92.6, 90.4, 77.1 | 91.5 | 1.9 | | 0.2 | 96.5, 88.0, 13.1\* | 92.3 | 7.0 |   \*outlier |
| Precision | See results above.  There are 4 levels and more than 8 samples for the extraction solution. FR considers that the precision is acceptable according to guidance SANCO 3029/99.  The limit of quantitation (LOQ) was determined in receptor and in extraction solution as follows: Lower Limit of Quantitation: 0.20 ng/mL for Difenacoum. |

|  |
| --- |
| **Conclusion on the method for detection and identification of Difenacoum** |
| ACTIPELLET-DIFE report for the determination of Difenacoum in the skin dermal delivery assay is available and acceptable. The limit of quantification (LOQ) is 0.20 ng/mL for Difenacoum. |

## Risk assessment for Physico-chemical properties

NYNA D+ AVOINE is a ready-to-use rodenticide. It is cereal grains, not highly flammable, not auto-flammable (up to 400°C), not explosive and not oxidizing.

The accelerate storage 14 days at 54°C shows that NYNA D+ AVOINE is stable. Other data are missing (shelf life and reactivity toward container material) and are required in post registration.

* **Renewal application (2017)**

NYNA D+ AVOINE is not highly flammable, not auto-flammable (up to 387°C), not explosive and does not have oxidizing properties according to GHS guideline. FR considers these conclusions are still valid and do not impact the CLP classification. No formulant is expected to be classified for physico-chemical CLP properties.

## Effectiveness against target organisms

### Function

MG 03: Pest Control

Product Type 14: Rodenticide

### Organism(s) to be controlled and products, organisms or objects to be protected.

According to the uses claimed by Triplan, NYNA D+ AVOINE is intended to be used to control rodents inside buildings (private and public including farm buildings). . The target organisms to be controlled are brown rat *(Rattus norvegicus),* roof rat or house rat (*Rattus rattus)* and wild and house mouse *(Mus musculus).*

The products, organisms or objects to be protected are public health, domestic animal heath and material protection (i.e. historical buildings, technical objects).

* **Assessment of minor change (2015)**

The product is also intended to be used around the buildings and in open areas in landfills and waste dumps.

### Effects on Target organisms

Anticoagulants rodenticides disrupt the blood-cutting mechanisms. Signs of poisoning in rodents are those associated with an increased tendency to bleed, leading ultimately to profuse haemorrhage. After feeding on bait containing the active substance for 2-3 days the animal becomes lethargic and slow moving. Signs of bleeding are often noticeable and blood may be seen around the nose and anus. As symptoms develop, the animal will lose its appetite and will remain in its burrow or nest for increasingly long periods of time. As the active substance has a long acting action, death will usually occur within 4-10 days of ingesting a lethal dose and animals often die out of sight in their nest or burrow.

The application rates recommended by the applicant are the following:

Rats: (*Rattus norvegicus and Rattus rattus)*

180-200 g grains/secured bait point separated by 5-10 m.

Mice: (*Mus musculus*)

30-40 g grains/secured bait point separated by 1-2 m.

The product is intended to be applied in secured bait stations by professional and non-professional users in infested areas with obvious tracking of feces, and smears next to holes and harbourages. Distances between each bait station, so as the number and timings of application and the amount of product depend on several factors: the treatment site, the size and severity of the infestation.

The applicant submitted following studies:

Laboratory studies on albino house mice

Two laboratory studies are conducted with the old formulation of NYNA D+ BLE

* Efficacy laboratory study of cereal rodenticide containing 0.005% difenacoum with albino house mice *(Mus musculus).*

This combined study (efficacy and consumption) was done with the aim to limit the number of trials and animal suffering.

The mortality rate obtained after only 3 days of bait consumption was 100% which corresponds to the accepted and known lethal dose (LD50) of difenacoum and the efficacy of anticoagulants generally noticed.

The laboratory tests with albino house mice had shown from 84 to 91 % of bait acceptance and 100% of mortality.

* Acceptance comparison with albino house mice (*Mus musculus)* for wheat versus a blend of 3 cereals.

In this study, the objective was to demonstrate that the wheat is as well accepted as the 3-cereals blend and it could be exchanged without decreasing the rodents’ acceptance.

So as the efficacy trials are performed with another difenacoum-based formulation,NYNA D+ BLE (containing only wheat), results can be taken into account in order to support the product authorization of NYNA D+ AVOINE.

Field trial on Brown rat wild strain (*Rattus norvegicus*)

A field study with a brown rats population within cereals storage warehouse has been conducted with NYNA D+ BLE and the test system was respected. However, the operator has made two experimental deviations (and pointed out by the applicant):

* Early stop of pre-baiting after 9 days although pre-baiting plateau has not been reached.
* Early stop of poisoning after 3 days instead of the expected 5 days, whereas the consumption was regularly increasing, which was in favour of a poisoning level superior to 90% over a period of five days of poisoning.

Despite these deviations, an efficacy rate of 78 % has been demonstrated. It can be sure that a strict protocol application would lead to more than 90% mortality. Moreover, the preliminary laboratory tests with albino house mice had shown an excellent efficacy.

**Although this field study contains experimental flaws, it has been conducted according to the standard, the acceptability and efficacy on *Rattus norvegicus* in field were sufficient. Thus, FR CA accepts this field study to support the efficacy of the product NYNA D+ AVOINE.**

All efficacy studies are presented in annex 3a.

* **Renewal application (2017)**

For the renewal of the authorisation of the product NYNA D+ AVOINE (0.005 % w/w difenacoum), no change in the composition has been declared and new efficacy field data from the product NYNA CEREALES A 25 (0.0025 % w/w difenacoum) aged formulation after a storage period of 3 years, have been submitted to complete the dossier.

As the product NYNA CEREALES A 25 (0.0025 % w/w difenacoum) differs only from the product NYNA D+ AVOINE for the content of the active substance difenacoum. (0.0025 % w/w instead of 0.005% w/w), read-across is acceptable.

All efficacy studies conducted with the product NYNA CEREALES A 25 are presented in annex 3b.

Regarding the claimed uses, submitted efficacy data are compliant with the requirements of the TNsG PT14 (2009) and the results of these tests are respecting the criteria of the TNsG PT14 (2009).

Consequently, the product NYNA D+ AVOINE (0.005 % w/w difenacoum), aged up to 36 months has shown a sufficient efficacy and can be used for the control of rats (*Rattus norvegicus* and *Rattus rattus*) and house mice (*Mus musculus*) in and outdoor environments (open areas, waste dumps and landfills) at doses claimed.

Uses and doses validated for NYNA D+ AVOINE are the following:

|  |  |  |  |
| --- | --- | --- | --- |
| **Produit** | **Targets organism** | **Application rate and intervals** | **Use area** |
| NYNA D+ AVOINE  Bait (cereals) containing 0.005% w/w of difenacoum. | Rats (*Rattus norvegicus* and *Rattus rattus)* | 200 g / bait point separated by 5 to 10 meters | in and around buildings, and outdoor environments (open areas, waste dumps and landfills) |
| Mice (*Mus musculus*) | 40 g / bait point separated by 1 to 2 meters | in and around buildings, and outdoor environments (open areas, waste dumps and landfills) |

### Occurrence of resistance

The use of massive anticoagulants in the management of rodents since the 1970's has been at the origin of the first batches of resistance (genetic and not behavioral) to the first generation of anticoagulants (coumafene in particular).

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 populations to coumafene.

Only an exhaustive study carried out at the French and European levels could enable pointed-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”).

Indeed, we cannot sustain that resistance to difenacoum in all geographical areas where it could be used cannot occur and the occurrence of resistance has an impact on the dosages and efficacy of rodenticides used in a more consequent way. Thus, it compels users to take into account the following precautions to reduce the possibility of rodents developing a resistance to difenacoum:

* Products have always to be used in accordance with the label.
* Efficacy level has to be monitored (periodic check), and the case of reduced efficacy has to be investigated for possible evidence of resistance.
* Treatment has to be alternated with active substances having different mode of action.
* Integrated pest management (combination of chemical control, physical and hygienic measures) has to be taken into account.
* Difenacoum must not be used in an area where resistance to this active substance is suspected or established.
* If signs of resistance begin to appear, then, every effort has to be made to eradicate the population. The measures necessary for eradication will vary in different situations; they may involve a number of procedures using both chemical and non-chemical ways.

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

* **Renewal application (2017)**

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%.

The enzyme vitamin K 2, 3 epoxide reductase (VKOR) is the target for anticoagulants. Modifications in the protein structure due to polymorphisms on the gene coding the VKOR may induce anticoagulant resistance. Most resistant strains are characterised by one single nucleotide polymorphism (SNP). These SNPs cause the exchange of one amino acid in the VKOR enzyme. The biochemical mechanism of anticoagulant resistance has been studied in several geographic strains/VKORC1-variants of the Norway rat. Amino acid substitutions in the VKOR seem to alter its structure and function, resulting in decreased sensitivity to anticoagulant inhibition, depending on strain characteristics.

For house mice, a dominant autosomal warfarin-resistance gene was determined on chromosome 7 in house mice. Three VKORC1 sequence variants mediating resistance to anticoagulants seem to be widely distributed. House Mice carrying the homozygous of one of these variants (Y139C) were found highly resistant to warfarin and bromadiolone.

For roof rats, experiments on warfarin resistant rats indicated considerable instability in the resistance and suggested a multifactorial basis for resistance.

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]](#footnote-6); Lund, 1984[[7]](#footnote-7); Pelz et al. 1995[[8]](#footnote-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]](#footnote-9)). The study 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]](#footnote-10)).

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 populations to coumafene. Moreover, a 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 bromadiolone (Grandemange et al., 2009). 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.

House mice carrying the homozygous Y139C sequence variant were found to be highly resistant to warfarin and bromadiolone.

So, resistance to second generation anticoagulant rodenticides should not be minimized.

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”).

The document CropLife International (RRAC 2015) provides guidance to advisors, national authorities, professionals, practitioners and others on the nature of anticoagulant resistance in rodents, the identification of anticoagulant resistance, strategies for rodenticide application that will avoid the development of resistance and the management of resistance where it occurs.

The following are the essential elements of an effective program: survey, use of physical and chemical control techniques, environmental management, record keeping, monitoring and review.

The authorization holder should report any observed resistance incidents to the Competent Authorities or other appointed bodies involved in resistance management at the renewal of the product.

To ensure a satisfactory level of efficacy and avoid the development of resistance, the recommendations proposed in the SPC have to be implemented.

### Evaluation of the Label Claims

The authority in charge of the risk assessment assessed that the product NYNA D+ AVOINE has shown a sufficient efficacy for the control of mice and rats for an indoor use in domestic, public and private including in farm buildings. Moreover, difenacoum efficacy on a cereal has anyway been successfully experimented and used for more than 30 years corroborating the present recommendation of the product.

The application rates validated are the following:

Rats: (*Rattus norvegicus and Rattus rattus)*

- 200 g grains/secured bait point separated by 5-10 m (instead of 5- 6 m presented in the label). These intervals between bait points have to be corrected in the product label in accordance with those validated.

Mice: (*Mus musculus*)

- 40 g grains/secured bait point separated by 1-2 m.

According to the product label submitted for NYNA D+ AVOINE in sachet (minimum packaging of 25 g), users have to apply 8 sachets/bait point for rats and 2 sachets/bait points for mice. However, for mice, the final dose per bait point is higher (50 g) than the efficient rate validated (40 g).Therefore, the applicant has to adapt the amount per sachet and bait boxes to the efficient doses and the amount of bait per bait station must not exceed the validated application rates.

The label claim reflects the efficacy data of the product. Nevertheless because of cross-resistances occurrence to second-generation anticoagulants, the product label has to contain information on resistance management for rodenticides:

* Products have always to be used in accordance with the label.
* Efficacy level has to be monitored (periodic check), and the case of reduced efficacy has to be investigated for possible evidence of resistance.
* Treatment has to be alternated with active substances having different mode of action.
* Integrated pest management (combination of chemical control, physical and hygienic measures) has to be taken into account.
* Difenacoum must not be used in an area where resistance to this substance is suspected or established.
* Users should report straightforward to the registration holder any alarming signals which could be assumed to be resistance development.
* **Assessment of frame formulation establishment (2012)**

**Efficacy comparison with the frame formulation product**

Within the framework of the establishment of the frame formulation requested by the applicant, the differences between compositions of the reference product NYNA D+ AVOINE and the frame formulation are slight.

The proposed variation of the composition of the frame formulation can be considered as minor and the efficacy of all the products in this frame formulation will be similar to the reference product NYNA D+AVOINE.

**Conclusion**

Based on the detailled composition of the frame formulation required, the proposed variation of the composition of this frame formulation can be considered as minor and the efficacy of all the products in this frame formulation will be similar to the reference product NYNA D+AVOINE.

Therefore, uses and doses validated for all of frame formulation products depending of the product NYNA D+AVOINE are the following:

|  |  |  |  |
| --- | --- | --- | --- |
| **Produit** | **Targets organism** | **Application rate and intervals** | **Use area** |
| **NYNA D+ AVOINE**  Bait (cereals) containing 0.005% p/p of difenacoum. | Rats (*Rattus norvegicus and Rattus rattus*) | 200 grammes/bait point separated by 5 to 10 meters | Indoor in secured bait by professionnal user |
| Mice (*Mus musculus*) | 40 grammes/bait point separated by 1 to 2 meters | Indoor in secured bait by professionnal user |

* **Renewal application (2017)**

French competent authorities (FR CA) assessed that the product NYNA D+ AVOINE has shown a sufficient efficacy for the control of mice (*M. musculus*) and rats (*R. norvegicus* and *R. rattus*) by professional users: in and around buildings, and outdoor environments (open areas, waste dumps and landfills).

Submitted data allow to conclude that the product

The application rates validated are the following:

Rats: (*Rattus norvegicus and Rattus rattus)*

- 200 g grains/secured bait point separated by 5-10 m

Mice: (*Mus musculus*)

- 40 g grains/secured bait point separated by 1-2 m.

To ensure a satisfactory level of efficacy and avoid the development of resistance, the recommendations proposed in the SPC have to be implemented.

## Exposure assessment

### Description of the intended use(s) – PAR 2012

The doses and uses validated are the following:

|  |  |  |  |
| --- | --- | --- | --- |
| Product | Field of use envisaged | User | Likely concentration at which active substance will be used |
| Main group 03;  PT 14  NYNA D+ AVOINE  Cereal baits containing 0.005% p/p of difenacoum. | In buildings for control of rats (brown and black rats). | Professionals | 200 g grains /secured bait point separated by 5-10 m. |
| In buildings for control of mice. | Professionals | 40 g grains /secured bait point separated by 1-2 m. |
| In buildings for control of rats (brown and black rats). | Non  professionals | 200 g grains /secured bait point separated by 5-10 m. |
| In buildings for control of mice. | Non  professionals | 40 g grains /secured bait point separated by 1-2 m. |

According to Triplan, NYNA D+ AVOINE is intended to be used inside building (public, private and farms buildings) for control of house mice (*Mus musculus*), brown rats (*Rattus norvegicus*) and black rats (*Rattus rattus*).

The control of mice and rats is based on the principle of applying baits on infested areas with obvious tracking of feces, and smears next to holes and harbourages.

The product is ready-to-use cereal grains with no dilution and or other substances added for application. It is supplied in sachets for professional and non-professional users or in bulk for professional users only and manually applied in secured bait boxes or bait stations. If the baits are supplied in bulk, NYNA D+ AVOINE was loaded in bait boxes with a shovel.

Over a period of 28 days for application, cleaning, refilling (4 times over 28 days period) and collect of dead rodents.

Professionals:

According to Triplan, a professional applies 180-200 g baits per secured point for the control of rats and 30-40 g baits per secured points for the control of mice. The validated doses are 200g for the control of rats and 40g for the control of mice. According to Triplan the worst case is 30 bait points treated per day plus remains of 30 bait points collected. However, in the *HEEG opinion on harmonizing the number of manipulations in the assessment of rodenticides (anticoagulants)* agreed at the European Technical Meeting TM III 2010, 63 loadings and 16 cleanings bait stations per day are considered for professional using loose grain, pellets and granules.

Non-professionals:

According to Triplan, a non-professional applies 180-200 g baits per secured point for the control of rats and 30-40 g baits per secured points for the control of mice. The validated doses are 200g for the control of rats and 40g for the control of mice. According to Triplan, the worst case is 4 bait points treated per day plus remains of 4 bait points collected. However, in the *HEEG opinion on harmonizing the number of manipulations in the assessment of rodenticides (anticoagulants)* agreed at TM III 2010, 5 loadings and 5 cleanings bait stations per day are considered for non-professional using loose grain, pellets and granules.

The professional or non-professional users are exposed to ready-to-use cereal grains containing 0.005% (w/w) difenacoum.

* **Renewal application (2017)**

The intended uses are only for professionals.

### Assessment of exposure to humans and the environment – PAR 2012

**Assessment of human exposure**

No new human exposure studies have been submitted. 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 “*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 (Finland) of the active substance in the Assessment report on difenacoum. This study examined the inhalation and dermal exposures associated with all activities involved in using a grain bait (decanting material from a large container to a pail, filling and placing bait points, and clean-up and disposal of bait points). The used grain bait containing coumatetralyl was selected as a worst case representative product of all cereal-based 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 NYNA D+ AVOINE.

For non professional users, the same CEFIC study and assumptions were used for the estimation of human exposure since the values available in the TNsG and User Guidance (Human exposure to biocidal products – TNsG June 2002 – version 1) are considered as unrealistic (see argumentation in the Assessment report on difenacoum).

Additionally, the Human Exposure Expert Group (HEEG) opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant), agreed at TMIII2010 and the HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants) agreed at TMII2011 were taken into account for the estimation of exposure for professionals and non professionals.

* **Renewal application (2017)**

The intended uses claimed for NYNA D+ AVOINE authorisation’s renewal are only for professional users.

**Assessment of environmental exposure**

It is important to notice that the applicant did not provide ecotoxicological data about the biocidal product NYNA D+ AVOINE. So all the environment risk assessment is based on data extrapolated from the active substance, difenacoum. The environmental risk assessment is summarized in section 2.8 of this document.

* **Assessment of minor change (2015)**

The product is also intended to be used around the buildings and in open areas in landfills and waste dumps.

## Risk assessment for human health

### Hazard potential – PAR 2012, updated 2017

#### Toxicology of the active substance

The toxicology of the active substance was examined extensively according to standard requirements of Directive 98/8/EC. The results of this toxicological assessment can be found in the CAR. The threshold limits and labelling regarding human health risks listed in Annex 4 of this report “Toxicology and metabolism” must be taken into consideration.

#### 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*”, NYNA D+ AVOINE does not contain any substance of concern.

* **Renewal application (2017)**

Considering the definition of a substance of concern set in the Guidance on the BPR Volume III Human Health – Part B Risk Assessment NYNA D+ AVOINE does not contain any substance of concern.

#### Toxicology of the biocidal product

The toxicology of the biocidal product was examined appropriately according to standard requirements. The product was not 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 of this report “Toxicology – biocidal product”.

New data:

Acute oral and dermal toxicity, skin and eye irritation and skin sensitisation studies have been provided on the old formulation of another difenacoum-based product, NYNA D+ BLE. Since it is not expected that the differences of composition between these two formulations impact the toxicity, the extrapolation of study results from the old formulation of NYNA D+ BLE to NYNA D+ AVOINE was accepted.

A dermal penetration study was submitted with NYNA D+ CEREALES. Since it is not expected that the differences of composition between these two formulations impact the result, the extrapolation to NYNA D+ AVOINE was accepted.

* Dermal absorption

A non-radioactive *in vitro* dermal absorption study in rat’s skin performed with another difenacoum-based formulation, NYNA D+ CEREALES was submitted and showed a very low dermal absorption of difenacoum (< LOQ). Due to several deviations from the OECD guideline 428 (exact composition of the receptor fluid and solubility of NYNA D+ CEREALES in the receptor fluid not available, no detailed information on the skin membrane (site, thickness...), no justification about the choice of the unique dose applied, scarce information in order to validate the analytical method), this study was not accepted. However, despite these deficiencies, this study supports a low dermal absorption of difenacoum grain formulation.

Furthermore, in the Assessment report on difenacoum, a dermal absorption of 3% was used for pellet and grains (Sorex study). However, since Triplan has no letter of access to the Sorex data, the FR CA cannot use this value for NYNA D+ AVOINE.

Therefore, based on the physico-chemical properties of difenacoum, on the low dermal absorption values observed with different formulations containing 0.005 % of difenacoum and on the dermal absorption of other similar second generation anticoagulants, a default value of 10% was considered for the risk assessment of NYNA D+ AVOINE (see table below).

|  |  |  |  |
| --- | --- | --- | --- |
| Compound | Molecular mass | Log Pow | Dermal absorption  (from the assessment reports of active substances) |
| Difethialone | 539 g/mol | 6.29 | 4% (*in vitro* and *in vivo* data) |
| Bromadiolone | 527 g/mol | > 3 | 10 % (default value) and 1.6 % (*in vitro* studies on products) |
| Brodifacoum | 523 g/mol | 6.12 | 5 % (*in vitro* study, worst case) |
| Flocoumafene | 542 g/mol | 6.12 | 10 % (default value) and 4 % (based on the dermal absorption of other second generation anticoagulants) |
| Difenacoum | 444.5 g/mol | 7.6 | 0.047 % (*in vitro* study on wax block and paste) and 3 % (*in vitro* study on grain) |

* **Assessment of new uses’ addition (2013)**

***Percutaneous absorption***

The dermal absorption of difenacoum formulated as pellet bait (containing 0.005% difenacoum) was investigated *in vitro* using human skin. The measured samples were below the limit of detection or quantification, but as a worst case, the corresponding validated LOQ value was used for the calculations of dermal absorption. The percentage of absorbed difenacoum was 0.647% (receptor fluid + epidermis + dermis + stratum corneum). The total recovery of difenacoum was 97.3% when skin discs were exposed to 5 mg/cm2 of the product (equivalent to 250 ng a.s./cm2) for 24 hours.

* **Renewal application (2017)**

The dermal absorption was already assessed according to the EFSA guidance. Consequently, dermal absorption value is still valid.

* Acute oral and dermal toxicity

No mortality, systemic or local effects were observed in these studies. Based on the results, no classification is required for NYNA D+ AVOINE.

* Irritation and corrosivity

Based on the results of the irritation assays on rabbit’s skin and eye, no classification is required for NYNA D+ AVOINE.

* Sensitisation

A non-radioactive LLNA using cell counting was submitted. This method is not currently validated. Furthermore, according to Basketter *et al[[11]](#footnote-11)*, the “*proposed non-RI LLNA uses cell number as a correlate of cell proliferation, but, as other modifications to the standard LLNA were also made, the method constitutes a major change*.” Therefore this test was considered as unacceptable by the FR CA.

Based on the composition of NYNA D+ AVOINE, no ingredients were listed as skin sensitisers. Therefore, it is expected that this product is not a skin sensitiser.

Justification for non submission:

* Acute inhalation toxicity:

As the product is a solid bait, the generation of inhalable particle is not expected as negligible in particular when NYNA D+ AVOINE is supplied in sachet. Additionally, the vapor pressure of difenacoum is very low (< 5x10-5 Pa at 45°C based on an Activa/Pelgar estimation). Therefore, an acute toxicity test by inhalation is not required.

The current harmonised classification of the active substance is the following:

|  |
| --- |
| **Classification under regulation (EC) 1272/2008** |
| Acute Tox. 2 H300  STOT Rep. 1 H372  Aquatic. Acute 1 H400  Aquatic Chronic 1 H410  No specific concentration limit |

Based on the results of the studies, the concentration of the active substance and of other components contained in the product and according to the above classification, NYNA D+ AVOINE is not classified.

* **Renewal application (2017)**

|  |
| --- |
| **Classification under regulation (EC) 1272/2008** |
| Acute Tox 1 – H300 ; H310 ; H330  STOT RE 1 – H372 (blood)  Repr. 1B – H360D  Repr. 1B; H360D: C ≥ 0,003 % STOT RE 2; H373: 0,002 % ≤ C < 0,02 % STOT RE 1; H372: C ≥ 0,02 % |

Based on the results of the studies, the concentration of the active substance and of other components contained in the product and according to the above classification, the following classification is required for NYNA D+ AVOINE:

* Repr. 1B - H360D: May damage the unborn child
* STOT RE 2 - H373: May cause damage to organs through prolonged or repeated exposure
* Other studies

The product is not used with other biocidal products. Therefore, no additional study was conducted.

The product is a solid bait only used in buildings in secured bait points. Collecting unconsumed baits and dead rodents must be done every week during the treatment so in these recommended conditions, no contamination is expected for feeding stuffs. Finally, according to the Assessment report on difenacoum, “*difenacoum baits should not be placed where food, feedingstuffs or drinking water could be contaminated*”. Therefore, no data on residue was submitted.

* **Assessment of frame formulation establishment (2012)**

**Toxicological properties comparison**

The differences between the reference product and the frame formulation are considered as minor and without any impact on the toxicity.

Toxicological studies (acute oral and dermal toxicity studies, eye and skin irritation studies) were not performed on NYNA D+ AVOINE but on another formulation, NYNA D+ BLE. A comparison of composition of the tested product and the frame formulation has been done to ensure that the read-across is still acceptable. Based on the concentration and classification of the active substance and of formulants, the toxicological properties of the tested product and the frame formulation can be considered as similar.

**Determination of the toxicological classification of biocidal product**

**Classification of active susbtance:**

The current harmonised classification of the active substance is the following:

|  |  |
| --- | --- |
| Classification under directive 67/548/EEC | Classification under regulation (EC) 1272/2008 |
| T+ R28  T R48/25  N, R50/53  No specific concentration limit | Acute Tox. 2 H300  STOT Rep. 1 H372  Aquatic. Acute 1 H400  Aquatic Chronic 1 H410  No specific concentration limit |

**Classification of biocidal product:**

None

**Conclusion**

Based on available data on active substance and information submitted on the frame formulation, the toxicological classification for the frame formulation is unchanged:

None.

Based on the concentration and classification of the active substance and of formulants, the toxicological properties initially assessed for the reference product NYNA D+ AVOINE can be considered as valid for the frame formulation.

No new exposure assessment was done since the modification of composition has been considered as minor.

### Exposure – PAR 2012, updated 2013

NYNA D+ AVOINE (PT14) is a ready-to-use rodenticide containing 0.005% of difenacoum (pure: 960 g/kg). Baits are packaged in sachets for professional and non-professional users or in bulk for professional users.The baits are placed in bait stations (bait boxes or secured bait stations) out of reach of children and domestic animals.

#### Exposure of professional users

**Primary exposure**

*Dermal exposure*

Based on the CEFIC study and taking into account the *HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants)* agreed at TMII2011, the amount of product on fingers/hands **during the decanting** was 93 mg per 3 kg of decanted product, when considering 1 to 4 decanting times per day and 52.3 mg per 3 kg of decanted product when considering more than 4 decanting times per day.

Since for the control of mice, the quantity of decanted product is 1.9 kg, 93 mg of product was considered. In contrast, for the control of rats, the quantity of decanted product is 12.6 kg corresponding to more than 4 decanting times, leading therefore to consider 52.3 mg of product on fingers/hands.

The following parameters were taken into account:

* Active substance in product: 0.005%,
* Quantity of decanted product: 12.6 kg for rat (200 g of grains per bait boxes; 63 loading of bait boxes[[12]](#footnote-12)) and 1.9 kg for mouse (40 g of grains per bait boxes; 63 loading of bait boxes),
* Frequency: one manipulation per day,
* Dermal absorption: 10%,
* Body weight: 60 kg.

The quantities of 200 g for the control of rats and 40g for the control of mice correspond to the validated efficient doses.

Therefore, the systemic dose of difenacoum on fingers/hands during decanting is

* For the control of rats: 1.83x10-5 mg/kg bw/day,
* For the control of mice: 6.51x10-6 mg/kg bw/day.

Based on the CEFIC study and taking into account the *HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants)* agreed at TMII2011, the amount of product on fingers/hands **during the loading** was 2.04 mg for the assessment of more than 4 manipulations per day (the agreed number is 63 manipulations in professional use based on the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant) agreed at TMIII2010). Therefore, considering 63 manipulations per day, the systemic dose of difenacoum on fingers/hands during loading is 1.07x10-5 mg/kg bw/day for the control of rats and mice because the amount of disposed bait is not taken into account during loading.

Based on the CEFIC study and taking into account the *HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants)* agreed at TMII2011, the amount of product on fingers/hands **during the cleaning** was 3.79 mg/manipulation for the assessment of more than 4 manipulations per day (the agreed number is 16 cleanings in professional use based on the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant) agreed at TMIII2010). Therefore, considering 16 cleanings per day, the systemic dose of difenacoum on fingers/hands during loading is 5.05x10-6 mg/kg bw/day for the control of both 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 3.41x10-5 mg/kg bw/day and 2.23x10-5 mg/kg bw/day without PPE for the control of rats and mice, respectively. When gloves are worn (10% gloves penetration factor), the exposure is reduced by a factor of 10 down to 3.41x10-6 mg/kg bw/day and 2.23x10-6 mg/kg bw/day for the control of rats and mice, respectively. According to the HEEG opinion agreed at TMI10 (default protection factors for protective clothing and gloves), a further refinement is possible with considering a glove penetration factor of 5% for solids. In this case, the total systemic dermal exposure is 1.70x10-6 mg/kg bw/day and 1.11x10-6 mg/kg bw/day for the control of rats and mice, respectively.

*Inhalation exposure*

Exposure by inhalation route is relevant **during the decanting** of the product. Based on the CEFIC study and taking into account the HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants) agreed at TMII2011, the air concentration is 9.62 mg product/m3.

The following parameters were considered:

* Duration of manipulation: 15 minutes per day for rats (3 minutes per decanting; 12.6 kg decanted in 3 kg buckets per day) and 3 minutes per day for mice (3 minutes per decanting; 1 decanting per day)
* Inhalation rate: 1.25 m3/hour
* Inhalation absorption: 100%
* Active substance in product: 0.005%
* Body weight: 60 kg

Based on these assumptions, the systemic concentration of difenacoum is 2.51x10-6 mg/kg bw/day for the control of rats and 5.01x10-7 mg/kg bw/day for the control of mice.

*Total exposure*

The total systemic exposure resulting from inhalation and dermal contacts with the product is 3.66x10-5 mg a.s/kg bw/day and 2.28x10-5 mg a.s/kg bw/day without gloves for the control of rats and mice, respectively. The systemic exposure is reduced to 5.91x10-6 mg a.s/kg bw/day and 2.73x10-6 mg a.s/kg bw/day for the control of rats and mice, respectively, with gloves, considering a 10% penetration factor or 4.21x10-6 mg a.s/kg bw/day and 1.61x10-6 mg a.s/kg bw/day for the control of rats and mice with gloves, considering a 5% penetration factor.

The estimations above are representative for exposure to NYNA D+ AVOINE in bulk but they represent a very worst case when the product is supplied and applied in sachets. In this case, it can be assumed that there is no decanting phase and no exposure is expected during loading in bait points as the sachet prevents dermal contacts and exposure by inhalation. Therefore, only exposure during cleaning can be considered: 5.05x10-6 mg a.s/kg bw/day without gloves and 5.05x10-7 mg a.s/kg bw/day with gloves (10 % penetration factor) for the control of both rats and mice because the amount of disposed bait is not taken into account during cleaning.

**Secondary exposure**

Secondary exposure of users could result in the handling of dead rodents. However, this scenario is excluded due to unrealistic assumptions (very low amount of difenacoum is expected on the fur because NYNA D+ AVOINE is an oral bait and toxicokinetics data showed that urine is a minor route of excretion for difenacoum).

In Annex 6 “Safety for professional operators”, results of the exposure calculations for the active substance for the professional user are laid out.

#### Exposure of non-professional users and the general public

**Primary exposure**

Since NYNA D+ AVOINE is only supplied and applied in sachets for non-professional users, it can be assumed that there is no decanting phase and no exposure is expected during loading in bait points as the sachets prevent inhalation and dermal contacts. Therefore, only exposure during cleaning can be considered.

Based on the CEFIC study and taking into account the *HEEG opinion on an harmonised approach for the assessment of rodenticides (anticoagulants)* agreed at TMII2011, the amount of product on fingers/hands **during the cleaning** was 4.52 mg/manipulation for the assessment of 1 to 4 cleanings per day and 3.79 mg/manipulation for the assessment of 1 to 4 cleanings per day. According to the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant) agreed at TMIII2010, 5 cleanings per day is considered for non-professional use. However, since the CEFIC study was designed for professional users and that the agreed number of cleanings for non-professionals is closed to 4, the amount of 4.52 mg/manipulation was used for exposure assessment. Therefore, the systemic exposure is 1.88x10-6 mg a.s/kg bw/day for the control of both rats and mice because the amount of disposed bait is not taken into account during cleaning.

**Secondary exposure**

Exposure of non users could result from the handling of dead rodents or ingesting poison baits. The “*handling of dead rodents*” scenario is excluded due to unrealistic assumptions (very low amount of difenacoum is expected on the fur because NYNA D+ AVOINE is an oral bait and toxicokinetics data showed that urine is a minor route of excretion for difenacoum).

For the scenario “ *oral exposure by ingesting bait*”, a reverse scenario was calculated. Based on the AEL of 1.1x10-6 mg a.s/kg bw/day, a body weight of 10 kg and an oral absorption of 68% (as stated in the Assessment report of difenacoum [Activa/Pelgar Study]), ingestion of more than 0.3 mg of product per day by an infant is needed to exceed the AEL.

In Annex 7 “Safety for non-professional operators and the general public”, the results of the exposure calculations for the active substance for the non-professional user and the general public are laid out.

#### Exposure to residues in food

Based on the intended uses, no residue assessment was performed (Annex 8 “Residue behaviour”).

* **Assessment of new uses’ addition (2013)**

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Exposure path** | **Industrial use** | **Professional use** | **General public** | ***via* the environment** |
| Inhalation | Not relevant | Yes | Yes | Negligible |
| Dermal | Not relevant | Yes | Yes | Negligible |
| Oral | Not relevant | No | Yes | Negligible |

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

The biocidal products are ready-to-use rodenticides containing 0.005 % of difenacoum. Baits are packaged in plastic sachets for professional and non-professional users or in bulk for professional users. In the case of plastic sachet, it can be assumed that there is no decanting phase and no exposure is expected during loading in bait points.

**Exposure of professional users**

As a worst case, exposure has been assessed considering the products supplied as loose grains at the maximum recommended dose of 200 g for the control of rats. This approach covers the packaging in sachets. This also covers human exposure during the control of mice, where the recommended doses are lower.

Exposure by inhalation route is relevant during the decanting of loose grains. 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 indicative air concentration is 9.62 mg product/m3.

The following parameters were considered:

- Duration of manipulation: 15 minutes per day (3 minutes per 3 kg decanting; 12.6 kg decanted per day)

- Inhalation rate: 1.25 m3/hour

- Inhalation absorption: 100 %

- Active substance in product: 0.005 %

- Body weight: 60 kg

Based on these assumptions, the systemic concentration of difenacoum is 2.5 x 10-6 mg/kg bw/day without respiratory protection and 2.5 x 10-7 mg/kg bw/day when professional wear a respiratory equipement during decanting (protection factor 90%).

*Dermal exposure*

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 indicative amount of product on fingers/hands during the decanting was 93 mg per 3 kg of decanted product, when considering 1 to 4 decanting times per day and 52.3 mg per 3 kg of decanted product when considering more than 4 decanting times per day. Since the quantity of decanted product is 12.6kg (200 g per bait point; 63 loadings), 52.3 mg of product was considered.

The following parameters were taken into account:

- Active substance in product: 0.005%,

- Quantity of decanted product: 12.6 kg for rat (200 g of grains per bait boxes; 63 loading of bait boxes )

- Frequency: one manipulation per day,

- Dermal absorption: 0.647%,

- Body weight: 60 kg.

Therefore, the systemic dose of difenacoum on fingers/hands during decanting is 1.2 x 10-6 mg/kg bw/day.

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 was 2.04 mg for the assessment of more than 4 manipulations per day (the agreed number is 63 manipulations for professional use based on the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant) agreed at TMIII 2010). Therefore, considering 63 manipulations per day, the systemic dose of difenacoum on fingers/hands during loading is 6.9 x 10-7 mg/kg bw/day.

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 was 3.79 mg/manipulation for the assessment of more than 4 manipulations per day (the agreed number is 16 cleanings for professional use based on the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant) agreed at TMIII 2010). Therefore, considering 16 cleanings per day, the systemic dose of difenacoum on fingers/hands during cleaning is 3.3 x10-7 mg/kg bw/day.

In conclusion, the total systemic dermal exposure is set at 2.2 x 10-6 mg/kg bw/day without individual protective equipment and 2.2 x 10-6 mg/kg bw/day with gloves.

*Total exposure*

The total systemic exposure resulting from inhalation and dermal contacts with the product is 4.7 x 10-6 mg/kg bw/day without any individual protective equipment. Considering the protection of respiratory equipment during decanting and the protection of gloves during all tasks, the total systemic exposure is 4.7 x 10-7 mg/kg bw/day.

The estimations above represent a very worst case when the products are supplied in plastic sachets. In this case, it can be assumed that there is no decanting phase and no exposure is expected during loading in bait points. Therefore, only exposure during cleaning can be considered: 3.3 x 10-7 mg a.s/kg bw/day without gloves.

*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.*

| **Tier** | **Inhalation exposure** | **Dermal exposure** | **Total exposure** |
| --- | --- | --- | --- |
| PPE | Systemic dose | Systemic dose | Systemic dose |
|  | mg a.i. / kg bw /day | mg a.i. / kg bw /day | mg a.i. / kg bw /day |
| **Task – time frame:** | **Scenario ( population) – frequency** | | |
| Bulk | | | |
| Tier 1:  Without PPE | 2.5 x 10-6 | 2.2 x 10-6 | 4.7 x 10-6 |
| Tier 2:  With respiratory protection + gloves | 2.5 x 10-7 | 2.2 x 10-7 | 4.7 x 10-7 |
| Sachet | | | |
| Tier 1:  Without PPE | na | 3.3 x 10-7 | 3.3 x 10-7 |

* **Renewal application (2017)**

| **Tier** | **Inhalation exposure** | **Dermal exposure** | **Total exposure** |
| --- | --- | --- | --- |
| PPE | Systemic dose | Systemic dose | Systemic dose |
|  | mg a.i. / kg bw /day | mg a.i. / kg bw /day | mg a.i. / kg bw /day |
| **Task – time frame:** | **Scenario ( population) – frequency** | | |
| Professional exposure : Bulk formulation (exposure during decanting, loading and cleaning phases) | | | |
| Tier 1:  Without PPE | 2.5 x 10-6 | 2.2 x 10-6 | 4.7 x 10-6 |
| Tier 2:  With respiratory protection + gloves | 2.5 x 10-7 | 2.2 x 10-7 | 4.7 x 10-7 |
| Professional exposure\* : Bulk formulation (loading and cleaning phases) packaging < 10kg without decanting | | | |
| Tier 1:  Without PPE | - | 1.2 x 10-6 | 1.2 x 10-6 |
| Professional exposure : Sachet formulation (exposure during cleaning phase) | | | |
| Tier 1:  Without PPE | na | 3.3 x 10-7 | 3.3 x 10-7 |

\* For packaging below 10 kg, a decanting phase could be not necessary as its weight allows the worker to handle it from a bait point to another.

**Exposure of non-professional users**

For non-professional users, considering the available packaging (only in plastic sachet), it can be assumed that there is no decanting phase and no exposure is expected during loading in bait points.

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 was 3.79 mg for the assessment of more than 4 manipulations per day and 4.52 mg for the assessment of up to 4 manipulations per day (the agreed number is 5 cleanings for non-professional use based on the HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant) agreed at TMIII 2010). As a worst-case, considering 5 manipulations per day, the amount of product of 4.52 mg is used and therefore, the systemic dose of difenacoum on fingers/hands during cleaning is 1.2 x 10-7 mg/kg bw/day.

In conclusion, the total systemic dermal exposure is set at 1.2 x 10-7 mg/kg bw/day.

*In Annex 7 “Safety for non-professional operators and the general public”, the results of the exposure calculations for the active substance and the substance of concern for the non-professional user and the general public are laid out.*

| **Tier** | **Inhalation exposure** | **Dermal exposure** | **Total exposure** |
| --- | --- | --- | --- |
| PPE | Systemic dose | Systemic dose | Systemic dose |
|  | mg a.i. / kg bw /day | mg a.i. / kg bw /day | mg a.i. / kg bw /day |
| **Task – time frame:** | **Scenario ( population) – frequency** | | |
| Sachet | | | |
| Without PPE | na | 1.2 x 10-7 | 1.2 x 10-7 |

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

Exposure of non users, especially infants, could result from the handling of dead rodents or ingesting poison baits.

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

Secondary exposure of users and non users could result in the handling of dead rodents. However, this scenario is excluded because it is considered of low relevance due to unrealistic assumptions (TNsG on human exposure (2007)). Exposure due to this senario is considered negligible.

***Oral exposure by ingesting bait (infant) – acute scenario***

A reverse scenario was calculated. Based on the short-term AEL of 1.1x10-6 mg a.s/kg bw/day, a body weight of 10 kg and an oral absorption of 68%, ingestion of more than 0.3 mg of product per day is needed to exceed the AEL.

**Combined exposure**

Not relevant

* **Renewal application (2017)**

Non professional uses are no longer claimed for the renewal of authorisation.

Exposure of general public (secondary exposure) is still relevant and unchanged.

### Risk characterisation – PAR 2012, updated 2013

#### Risk for professional users

The estimated exposures for the professional users are compared to the systemic AEL of difenacoum set in the Assessment report (1.1x10-6 mg/kg bw/day for short, medium and long-term exposures).

**Primary exposure**

Based on the risk assessment of the active substance, the risk for professional users resulting from the intended use is unacceptable when NYNA D+ AVOINE is supplied in bulk, even if gloves are worn (%AEL at 382% and 147% for the control of rats and mice, respectively, with a gloves penetration factor of 5%).

For NYNA D+ AVOINE supplied and applied in sachet, the risk resulting from the intended use is acceptable when professionals are wearing gloves with a penetration factor of 10% (%AEL at 46% for the control of rats and 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.

**Secondary exposure**

No relevant secondary exposure is expected for professional users, thus no unacceptable risk has been identified.

* **Assessment of new uses’ addition (2013)**

**Risk for direct exposure**

*Based on the risk assessment of the active substance, a risk for professional users resulting from the intended use is unlikely. Regarding occupational safety, there are no objections against the intended use.*

**Professional users**

The estimated exposures for the professional users are compared to the systemic AEL of difenacoum set in the assessment report (1.1x10-6 mg/kg bw/day for short, medium and long-term exposures).

Based on the risk assessment of the active substance, the risk for professional users resulting from the intended use is acceptable only with respiratory protection during decanting and with gloves during all tasks for the products packaged as loose grains (%AEL is set at 42.8%). The risk is acceptable without any protection equipment for the products in sachet (%AEL is set at 29.7%).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scénario** | **AEL (mg/kg bw/d)** | **Exposure (mg/kg bw/d)** | **%AEL** | **Risk** |
| **Bulk formulation (exposure during decanting, loading and cleaning phases)** | | | | |
| Professional  (without PPE) | 1.1x10-6 | 4.7 x 10-6 | 428 | Unacceptable |
| Professional  (with respiratory protection during decanting and gloves during all tasks) | 1.1x10-6 | 4.7 x 10-7 | 42.8 | Acceptable |
| **Sachet formulation (exposure during cleaning phase)** | | | | |
| Professional  (without PPE) | 1.1x10-6 | 3.3 x 10-7 | 29.7 | Acceptable |

* **Renewal application (2017)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scénario** | **AEL (mg/kg bw/d)** | **Exposure (mg/kg bw/d)** | **%AEL** | **Risk** |
| **Bulk formulation (exposure during decanting, loading and cleaning phases)** | | | | |
| Professional  (without PPE) | 1.1x10-6 | 4.7 x 10-6 | 428 | Unacceptable |
| Professional  (with respiratory protection during decanting and gloves during all tasks) | 1.1x10-6 | 4.7 x 10-7 | 42.8 | Acceptable |
| **Bulk formulation (loading and cleaning phases) packaging < 10kg without decanting** | | | | |
| Professional  (without PPE) | 1.1x10-6 | 1.2 x 10-6 | 93 | Acceptable |
| **Sachet formulation (exposure during cleaning phase)** | | | | |
| Professional  (without PPE) | 1.1x10-6 | 3.3 x 10-7 | 29.7 | Acceptable |

Based on the risk assessment of the active substance, the risk for professional users resulting from the intended use is acceptable only with respiratory protection during decanting for NYNA D+ AVOINE as loose grains (%AEL is set at 42.8%) and without any protection equipment for NYNA D+ AVOINE in sachet (%AEL is set at 29.7%).

Considering packaging below 10 kg, for which a decanting phase is not expected, the risk is acceptable without PPE.

Therefore, a restriction of packaging to 10kg is proposed to prevent the inhalation exposure and to reduce the use of PPE. Moreover, the following mitigation measure is necessary: *Decanting is to be avoided. In case decanting cannot be avoided, an RPE of APF 10 has to be used.*

#### Risk for non-professional users and the general public

The estimated exposure for the non-professional users is compared to the systemic AEL of difenacoum set in the Assessment report (1.1x10-6 mg/kg bw/day for short, medium and long-term exposures).

**Primary exposure**

Based on the risk assessment of the active substance, the risk for non-professional users resulting from the intended use is unacceptable (% AEL at 171% for the control of rats and mice).

**Secondary exposure**

Based on a reverse scenario, more than 0.3 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 NYNA D+ AVOINE contains a bittering agent which reduces the likelihood of ingestion, the baits should be placed in areas which do not allow access to children and in secured bait boxes. Product label (“do not open the sachet”) and good practice advise users to prevent access to bait by children and infants.

* **Assessment of new uses’ addition (2013)**

**Non-professional users**

The estimated exposure for the non-professional users is compared to the systemic AEL of difenacoum set in the assessment report, such as for professional users (1.1x10-6 mg/kg bw/day for short, medium and long-term exposures).

Based on the risk assessment of the active substance, the risk for non-professional users resulting from the intended use is acceptable without gloves for the products in sachet (%AEL is set at 11.1%).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scénario** | **AEL (mg/kg bw/d)** | **Exposure (mg/kg bw/d)** | **%AEL** | **Risk** |
| **Sachet formulation (exposure during cleaning phase)** | | | | |
| Non-professional  (without PPE) | 1.1x10-6 | 1.2 x 10-7 | 11.1 | Acceptable |

**Risk for indirect exposure**

Based on a reverse scenario, more than 0.3 mg of product per day should be ingested by infant to exceed the AEL. This indicates that infants are at significant risk of poisoning. Therefore, even if the products contain a bittering agent which reduces the likelihood of ingestion, the baits must be unattainable which do not allow access to children.

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

**Risk for combined exposure**

Not relevant.

* **Renewal application (2017)**

Non professional uses are no longer claimed for the renewal of authorisation.

Conclusion remains unchanged and risk is acceptable only with RMMs proposed in SPC to prevent access to the bait from children.

#### Risk for consumers via residues

Since no contamination is expected for feeding stuffs, the risk for consumers via residues was not assessed.

**Summary of risk characterisation**

**Table 2.7.3-1: Summary of risk characterisation for professionals and non professionals for the control of rats**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scénario** | **AEL (mg/kg bw/d)** | **Exposure (mg/kg bw/d)** | **%AEL** | **Risk** |
| **Bulk formulation (exposure during decanting, loading and cleaning phases)** | | | | |
| Professional (without gloves) | 1,1x10-6 | 3.7x10-5 | 3324 | Unacceptable |
| Professionnal (with gloves ; penetration factor of 10 %) | 1,1x10-6 | 5.9x10-6 | 537 | Unacceptable |
| Professionnal (with gloves ; penetration factor of 5 %) | 1,1x10-6 | 4.2x10-6 | 382 | Unacceptable |
| **Sachet formulation (exposure during cleaning phase)** | | | | |
| Professionnal (without gloves) | 1,1x10-6 | 5.1x10-6 | 459 | Unacceptable |
| Professionnal (with gloves ; penetration factor of 10 %) | 1,1x10-6 | 5.1x10-7 | 46 | **Acceptable** |
| Non-professional (without gloves) | 1,1x10-6 | 1.9x10-6 | 171 | Unacceptable |

**Table 2.7.3-2: Summary of risk characterisation for professionals and non-professionals for the control of mice**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scénario** | **AEL (mg/kg bw/d)** | **Exposure (mg/kg bw/d)** | **%AEL** | **Risk** |
| **Bulk formulation (exposure during decanting, loading and cleaning phases)** | | | | |
| Professional (without gloves) | 1,1x10-6 | 2.3x10-5 | 2070 | Unacceptable |
| Professionnal (with gloves ; penetration factor of 10 %) | 1,1x10-6 | 2.7x10-6 | 248 | Unacceptable |
| Professionnal (with gloves ; penetration factor of 5 %) | 1,1x10-6 | 1.6x10-6 | 147 | Unacceptable |
| **Sachet formulation (exposure during cleaning phase)** | | | | |
| Professionnal (without gloves) | 1,1x10-6 | 5,1x10-6 | 459 | Unacceptable |
| Professionnal (with gloves ; penetration factor of 10 %) | 1,1x10-6 | 5,1x10-7 | 46 | **Acceptable** |
| Non-professional (without gloves) | 1,1x10-6 | 1,9x10-6 | 171 | Unacceptable |

* **Assessment of new uses’ addition (2013)**

**Summary of risks characterisation of the product for human health**

Based on the new study submitted for this application, the risk for operators resulting from the intended uses is acceptable :

* when the product is supplied in bulk : when professionals are wearing protecting gloves and a respiratory protection equipment during decanting of grains ;
* when the product is supplied in sachet : whithout gloves for professional and non professional users.

Finally, there is a significant risk of poisoning for infants, thus, the baits should be unattainable for children.

**Specific use restriction and issues accounted for product labelling**

* For professionals : wear protective gloves when handling the product and dead rodents.
* For professionals : wear respiratory protection equipment during decanting of grains in bulk.
* 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.
* Tamper-resistant bait boxes should be clearly marked to show that they contain rodenticides and that they should not contain other products than rodenticides.
* 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 on surfaces in contact with food, feed or drinks and beverages.
* Collect uneaten bait, bait fragments dragged away from the tamper-resistant bait boxes and dead rodents, during and after treatment.
* Remove all bait points after the end of treatment.
* **Assessment of minor change (2015)**

Reminder : the risk for operators resulting from the intended uses is acceptable :

* when the product is supplied in bulk : when professionals are wearing protecting gloves and a respiratory protection equipment during decanting of grains ;
* when the product is supplied in sachet : whithout gloves for professional and non-professional users.

Finally, there is a significant risk of poisoning for infants, thus, the baits should be unattainable for children.

* **Renewal application (2017)**

The conclusions of the risk assessment remain unchanged for professional users considering the RMMs required by the risk assessment and described in the summary of product characteristics (SPC). The use of NYNA D+ AVOINE by general public is no longer claimed for the renewal of authorisation.

## Risk assessment for the environment

|  |
| --- |
| * **Renewal application (2017)**   New information was submitted at the renewal stage of the approval of difenacoum :   * A bioaccumulation tests in fish lead to a new BCF of 1100 L//kg which was lower than the predicted BCF of 9010 L/kg and 35645 L/kg. It was assumed in the original risk assessment that secondary poisoning via the aquatic food chain would not be significant due to low water solubility and high adsorption tendency of difenacoum. Even though risk is identified in the terrestrial food chain for birds, the risk via poisoned rodents is considered significantly higher compared to risk via earthworms or other invertebrates. Thus, conclusion from the original assessment is not changed. * An earthworm reproduction test: this test permits to revise the PNECsoil which could have an impact only for open area uses (not intended for this dossier). Therefore, this new PNECsoil has no impact on the previous conclusion for NYNA D+ AVOINE.   Regarding this new information, the conclusion of the environmental risk assessment performed for the first authorization (PAR 2012) remains unchanged.  The intended uses “around buildings, open areas, landfills and waste dump” have been added in the frame of a minor change (2015). The risk assessment linked to these new uses is presented in the renewal section of the PAR, using the new data presented above. |

### Fate and distribution of the active substance, difenacoum, in the environment – PAR 2012, updated 2017

The summary of information about the active substance difenacoum is carried out with the data from the CAR of difenacoum owned by the Activa/Pelgar Difenacoum & Brodifacoum Task Force. No new ecotoxicological information on the active substance difenacoum has been submitted in the product dossier.

#### Biodegradation of difenacoum

According to the OECD tests 301B and 302D, difenacoum is not readily or inherently biodegradable. No studies on degradation in soil is available, but using the calculated value of Kp of 1.34 and considering the absence of biodegradation of difenacoum, it can be assumed that half life in soil is over 300 days. It was stated during technical meeting (TMII-04) that no further degradation studies are needed for intended uses in building.

So the risk assessment is based on the assumption that difenacoum is not readily biodegradable and a half life in soil is over 300 days.

#### Hydrolysis as a function of pH

According to the test OECD 111, the half-life (DT50) of difenacoum is over 1 year at pH 4, 7 and 9 at 25°C. The active substance is hydrolytically stable.

#### Photolysis in water

The active substance undergoes rapid photodegradation. Half-life varied from 0.6 hours to 3.8 hours. Greater than 80% photolysis was noted to have occurred by around five hours. Two breakdown products above 10% of the initial difenacoum concentration were detected and the proposal for the identification of structures was made. The photodegradation is regarded as a minor removal process for difenacoum and the exposure to water is low, therefore it was stated that no further characterisation of metabolites was requested.

#### Photodegradation in air

Photodegradation characteristics of the active substance have been estimated using the EPIWIN v. 3.12 programme in the CAR of the Task Force Difenacoum dossier. Difenacoum has an estimated half-life of approximately 2 hours, therefore it is predicted to have a negligible effect on stratospheric ozone. It is predicted not to be a potential greenhouse gas. Finally, difenacoum has a low volatility (Henry’s law constant< 0.046 Pa.m3.mol-1) and emissions to the air compartment are expected to be low.

#### Distribution

##### Adsorption/desorption

The experimentally derived Koc values are not supported by the physical and chemical properties of difenacoum. Difenacoum is a large aromatic molecule with two polar groups which can potentially ionised at environmental relevant pH. Difenacoum has also a low water solubility and a high log Kow.

According to the Technical Guidance Document (TGD) Part 3, Table 4, the QSAR equation used to calculate log Koc from log Kow (7.62, a QSAR estimation) is:

**log Koc = 0.81 log Kow + 0.1** (chemical class: Predominantly hydrophobics)

The properties of difenacoum may hamper the estimation of log Kow that is why it should be considered with some caution. The calculated log Koc is 6.27 and Koc = 1 871 544.

In the difenacoum dossier it has been stated that, according to its behaviour, the active substance would not be mobile and would be expected to absorb irreversibly to soil particles. Significant leaching could be expected to occur only in recently contaminated soil under alkaline conditions. Under other conditions, binding to the inorganic component of soil would be largely irreversible. The rate of binding is likely to be limited by steric hindrance of reaction in forming the cation bridge from the organic material.

##### Accumulation

The aquatic BCF has been estimated with calculation method because the fish bioconcentration test was invalid. In the absence of valid measured log Kow, the estimated value of log Kow used is 7.6. This value allows to calculate an estimated BCF for fish : 9010 (according to EPIWIN v 3.12) and 35 645 (Equation 75, TGD).

This log Kow is also entered the equation 82d of the TGD to get a BCFearthworm equal to 477 729.

The calculations show that difenacoum has a considerable bioaccumulation potential in aquatic and terrestrial organisms.

* **Assessment of frame formulation establishment (2012)**

**Ecotoxicological properties comparison**

No new ecotoxicological study was submitted for the establishment of this frame formulation. The differences between the reference product and the frame formulation are considered as minor and without any impact on the ecotoxicity.

**Determination of the environmental classification of biocidal product**

**Classification of active substance**

The current harmonised classification of the active substance is the following:

|  |  |
| --- | --- |
| Classification under directive 67/548/EEC | Classification under regulation (EC) 1272/2008 |
| T+ R28  T R48/25  N, R50/53  No specific concentration limit | Acute Tox. 2 H300  STOT Rep. 1 H372  Aquatic. Acute 1 H400  Aquatic Chronic 1 H410  No specific concentration limit |

**Classification of biocidal product:**

None (based on calculation according to the regulation 1272/2008/EC including the directive 2006/8/EC modifiyng the directive 1999/45/EC)

**Conclusion**

Based on the detailed compositions and the classification of each formulant, the difference between the reference product NYNA D+ AVOINE and the frame formulation are considered as minor and without impact on the ecotoxicity. The initial risk assessment carried out for the reference product NYNA D+ AVOINE can be considered applicable for the frame formulation.

* **Renewal application (2017)**

Based on calculation according to the regulation 1272/2008/EC, no classification is required for the product NYNA D+ AVOINE.

### Effects of the active substance on environmental organisms – PAR 2012

#### Aquatic compartment (including water, sediment and STP)

Difenacoum is very toxic to aquatic organisms. Difenacoum was equally toxic to fish (LC50= 0.33 mg a.s/L, OECD 203), daphnia (EC50= 0.91 mg a.s/L, OECD 202) and algae (EbC50 =0.14 mg a.s/L, OECD 201). Nevertheless, a lower fish test result (LC50=0.064 mg/L) is available in the difenacoum dossier of Sorex Limited. Therefore, it is used for the derivation of PNECwater in the Difenacoum Task force dossier as recommended in the CAR.

In the absence of any ecotoxicological data for sediment-dwelling organisms, the PNECsediment was calculated using the equilibrium partitioning method.

Difenacoum has shown to degrade photolytically in water under laboratory conditions and it may form degradation products exceeding 10% of the parent compound. The metabolites are not considered to have ecotoxicological significance, because photolysis is considered to be a minor transformation path for difenacoum and the exposure to water via the STP is expected to be low.

Difenacoum did not cause any effects on the activated sludge respiration inhibition up to the nominal concentration of 999.7 mg/L (OECD 209). Because all test concentrations exceeded the water solubility of difenacoum, the water solubility of 0.48 mg/L will be used as PNECSTP.

#### Atmosphere

No data are available on the biotic effects in the atmosphere. Difenacoum is not expected to contribute to global warming, ozone depletion in the stratosphere, or acidification on the basis of its physical or chemical properties.

#### Terrestrial compartment

Difenacoum caused no toxic effects on earthworms up to the nominal concentration of 994 mg/kg dry weight (OECD 207). Difenacoum may not be bioavailable to earthworms in soil which would explain the low toxicity. No studies on soil microorganisms or plants were submitted.

The photolysis degradation products are not considered ecotoxicologically relevant because the direct exposure of difenacoum to soil is expected to be low.

Toxicity of difenacoum in birds increased with exposure time. Difenacoum was considered as moderately toxic in acute oral exposure (LD50= 153 mg/kg bw), toxic in 5-day dietary test (LC50=1.4 mg/kg feed) and very toxic in the reproduction test (NOEC= 0.31 mg/kg water, exposure via drinking water). Several dose related effects were detected in the reproduction test: increased adult mortality, increased mortality of 14-day old hatchlings, increased liver and spleen weights in adult females, a declining trend in number of eggs laid/hen/day, declining trend in viability of eggs. Due to methodological deficiencies the reproduction test is not considered to represent the worst case, and therefore the PNECoral of birds was derived from the dietary test. Difenacoum is very toxic to mammals, and rats seem to be particularly susceptible. The PNECoral for birds and mammals has been used for the risk characterization of primary and secondary poisoning.

#### PBT assessment

Due to the properties of persistence, accumulation and toxicity of difenacoum, this substance fulfills the PBT criteria.

#### Non compartment specific effects relevant to the food chain

As already stated in the previous sections, difenacoum is concern for bioaccumulation with a calculated log Kow of 7.62, a high predicted aquatic BCF of 9 010 (US EPA EPIWIN) or 35 645 (TGD) and a high predicted terrestrial BCF of 477 729 (TGD).The active substance is not readily biodegradable and is of low solubilty (0.5 mg/L pH7). Therefore, difenacoum has a considerable bioaccumulation potential in aquatic and terrestrial organisms.

The primary concern is from predators eating the rodent carcasses and earthworms which have ingested the active substance absorbed to soil. In guidance document for PT14, the active substance is considered to be placed in protected bait point. Therefore, a risk should be taken into account for primary poisoning mainly for birds and mammals of equal or smaller size than the target rodents. Also when target animals carry bait away from e.g. bait stations, non-target animals may be exposed. For the risk characterization of primary poisoning, the PNECoral described in section 2.8.2.7 will be used.

Also requiring consideration are predators eating fish or earthworms which have accumulated difenacoum from water and soil. The secondary exposure should be taken in consideration.The participant has submitted, in the CAR, one acceptable study report where effects of difenacoum are studied in Barn Owls which have been exposed to poisoned mice. However, the PNECoral for birds and mammals are derived from a bird 5-day dietary test and a 90-day subchronic test in rat provided in the Activa/Pelgar difenacoum Task Force dossier as described below (section 2.8.2.6)

#### Effects assessment of metabolites formed in target organisms

A metabolism study presented in the Activa/Pelgar Difenacoum Task Force Annex I inclusion dossier (doc IIIA-6.4 of the CAR of difenacoum) shows that total excreted radioactivity in rat faeces and urine (7 days after single dosing, low and high dose) was 41-71% of the dose administered. Two major faecal metabolites F7 and F8 (max 11.3% and 7.3%, respectively) were identified as isomers of hydroxylated difenacoum. Two other major metabolites, F5 and F6 (max 12.2% and 8.0 %, respectively) were characterised as isomers of difenacoum-based structure which formed glucuronide conjugates. Unchanged difenacoum was present at maximum at 2.9 %. The excretion and retention of radioactivity was also investigated after the final dose following administration of seven consecutive daily oral doses, no substantial differences in excretion patterns between single and repeated level oral doses was observed.

No information on toxicity of these four major metabolites is available. Considering that the metabolites could be potent as anticoagulants, the sum of these four metabolites and unchanged difenacoum in faeces will be taken into account in PEC calculation with assumption that the toxicity of metabolites is comparable to parent (data from the validated CAR of the Activa/Pelgar Difenacoum Task Force Annex I inclusion dossier). Therefore in the environmental exposure calculations, it is assumed that 40% of excreted amount in urine and faeces is metabolised and that 40 % of administered total amount is unchanged difenacoum in faeces (data from the validated CAR of the Activa/Pelgar Difenacoum Task Force dossier). These assumptions represent a worst case for release.

#### Summary of PNEC

##### PNEC for aquatic organisms:

The PNECwater is derived from the lowest available LC50 value 0.064 mg/L (fish test) with an assessment factor of 1000 as only data on acute toxicity is available. Therefore,

**PNECwater = 0.06 μg/L**

##### PNEC for sediment-dwelling organisms:

In the absence of data on sediment-dwelling organisms, the PNECsediment is derived from the equilibrium partitioning method.

**PNECsediment = 2.51 mg/kg wet weight.**

##### PNEC for STP micro-organisms:

As described in section 2.8.2.1, the water solubility of 0.48 mg/L will be used as the PNECSTP.

**PNECSTP = 0.48 mg/L**

##### PNEC for terrestrial organisms:

The PNECsoil is derived from the experimental data. An assessment factor of 1000 was applied to the LC50 > 994 mg/kg issued from an earthworms study to derived the PNECsoil.

PNECsoil = 0.994 mg/kg dry weight (0.877 mg/kg wet weight)

Nevertheless, as only one experimental test result is available, the PNECsoil derived with the equilibrium partitioning method (EPM) from the aquatic PNEC has also be taken into account :

PNECsoil = 2.04 mg/kg wet weight

Because the PNECsoil derived from the earthworms test is lower, it will be used for the risk characterization. So,

**PNECsoil = 0.994 mg/kg dry weight (0.877 mg/kg wet weight)**

##### PNEC for birds and mammals

PNECoral for birds is derived from the LC50 of 1.4 mg/kg food origin from the 5-day dietary test. The appropriate assessment factor according to the TGD is 3000. In order to transform the LC50 to LD50, LC50 is multiplied with average food consumption (13.5 g) and divided by average body weight 71.3 g. The food consumption and body weight are averaged for all treatment groups and over the 5-day exposure period. The resulting LD50 is 0.3 mg/kg bw/d. The PNECoral value kept for the risk assessment is:

**PNECoral for birds = 0.5 μg/kg food** equivalent to

**PNECoral for birds = 0.1 μg/kg bw/d**

PNECoral for mammals is derived from the NOAEL of 0.03 mg/kg bw/d origin from the 90-day subchronic test in rat (Doc IIIA6.4.1 in the CAR of difenacoum). The NOAEL is transformed to NOEC (concentration in food) by multiplying with the conversion factor of 20 (TGD, Table 22). The appropriate assessment factor according to the TGD is 90. The PNECoral value kept for the risk assessment is:

**PNECoral for mammals = 7 μg/kg food** equivalent to

**PNECoral for mammals = 0.3 μg/kg bw/d**

The PNECoral for birds and mammals have been used for the risk characterization of primary and secondary poisoning.

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| Table 2.8.2.7‑1 : summary of the difenacoum PNECs | | | | |
| **Compartment** | | **Test Value** | **AF** | **PNEC Unit** |
| Aquatic | PNECwater | LC50 =0.064 mg/L | 1000 | 0.064 µg/L |
| PNECsediment | PNECwater in eq. 70 (TGD) | | 2.51 mg/kg wet weight |
| PNECSTP | Water solubility= 0.48 mg/l | | 0.48 mg/L |
| Terrestre | PNECsoil | LC50 >994 mg/kg | 1000 | 0.994 mg/kg dry weight (0.877 mg/kg wet weight) |
| PNECoral for birds | LC50 =1.4 mg/kg food  LD50= 0.3 mg/kg bw/d | 3000 | 0.5 μg/kg food eq. to  0.1 μg/kg bw/d |
| PNECoral for mammals | NOEC= 0.6 mg/kg food  NOAEL=0.03 mg/kg bw/d | 90 | 7 μg/kg food eq.to  0.3 μg/kg bw/d |

### Effects on environmental organisms for biocidal product NYNA D+ AVOINE – PAR 2012

It is important to notice that the applicant did not provide ecotoxicological data about the biocidal product NYNA D+ AVOINE. So all the environment risk assessment of NYNA D+ AVOINE is based on data obtained from the active substance, difenacoum.

#### Aquatic compartment (including water, sediment and STP)

Product NYNA D+ AVOINE is a ready-to-use impregnated grains based product provided in a loose form or enclosed in a paper sachet which is not removed, that contains difenacoum as active substance and denatonium benzoate as an aversive compound. Since difenacoum is the only substance of concern, the ecotoxicological effects can be derived from the effect studies conducted with the active substance.

#### Terrestrial compartment

According to the TNsG on data requirements (Chapter 2.5, Part B) additional data are required from rodenticidal products if they are used outside buildings in the form of baits, granulates and powder. Nevertheless, the intended uses proposed by the applicant are only indoor application. Therefore, no further study is needed for the terrestrial compartment.

#### Non compartment specific effects relevant to the food chain (secondary poisoning)

In the NYNA D+ AVOINE product no substance of concern has been identified, and hence the secondary poisoning is caused entirely by the active substance difenacoum. Secondary poisoning studies have been reviewed in this document, section 2.8.4.4.2.

#### Summary of PNECs

In NYNA D+ AVOINE, no substance of concern has been identified. So all the environment risk assessment is based on data obtained from the active substance, difenacoum and is presented in section 2.8.2.7.

### Environmental exposure assessment – PAR 2012, updated 2017

Exposure scenarios are defined as a set of conditions about sources, pathways and use patterns that quantify the release of the substance from processing, use and disposal into soil, water, air and waste. To describe the possible release of rodenticides from its use and disposal, the exposure scenarios for PT14 introduced in EUBEES ESD (2003), with an addendum endorsed at the 23rd CA meeting Nov. 2006 are used.

In accordance with EUBEES ESD (2003) and TGD for Risk Assessment (2003), a quantitative approach is used in the risk assessment for NYNA D+ AVOINE biocidal product. Quantitative PEC estimations are performed for the relevant environmental compartments for difenacoum. The different PEC values are derived from model calculations, but available measured data (e.g. difenacoum metabolism in rat) are also taken into consideration.

The product NYNA D+ AVOINE is a ready-to-use impregnated grains based product with 0.005% of difenacoum, the active substance. These impregnated grains, in sachet or in bulk, are placed in secured bait stations. According to the applicant, the product is intended to be used in bait boxes inside industrial, commercial and residential buildings. Bait points are inspected and replenished once a week when grains take is observed.

The available data about the treatment campaign are extracted from the applicant’s dossier:

* Duration of a treatment campaign: 28 d,
* Rat application rates: 200 g of product / bait point separated by 5-10 meters,
* Mouse application rates: 40 g of product / bait point separated by 1-2 meters,
* The NYNA D+ AVOINE grains are placed only in bait stations,
* The product is used inside buildings only,
* Number of bait stations: 20 inside, 5 meters apart for rats, 1 meter for mice,
* Day 1: Treatment with 200 g product per box for rat, 40g per box for mouse,
* Day 7, 14 and 21: bait refilling.

As the product is applied indoor only, no environmental compartment is exposed to NYNA D+ AVOINE. 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 3 to 11 days before dying. Therefore, they have the time to escape outside buildings and to be eaten by predators.

Primary and secondary poisoning calculations are carried out considering the ‘in and around buildings’ scenario from the EUBEES ESD PT14 as a worst case scenario in view of the fact that the product is applied inside buildings only.

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| * **Renewal application (2017)**   The product NYNA D+ AVOINE is a ready-to-use impregnated extruded cereal block product with 0.005% of difenacoum, the active substance. The product is used in paper sachet or in bulk. The product is placed in secured bait stations. According to the applicant, the rodenticidal product is intended to be used in bait boxes in and around buildings, in open areas, in landfills and in waste dump area for professional users. Bait points are inspected and replenished once a week when bait taken is observed.  The available data about the treatment campaign are extracted from the applicant’s dossier:   * Duration of a treatment campaign: 28 d, * Rat application rates: up to 200 g of product / bait point separated by 5-10 meters, * Mouse application rates: up to 40 g of product / bait point separated by 1-2 meters, * The NYNA D+ AVOINE grains are placed only in bait stations, * The product is used in and around building and in waste dump area, * Number of bait stations: 20 inside, 5 meters apart for rats, 1 meter for mice, * Day 1: Treatment with 200 g product per box for rat, 40 g per box for mouse, * Day 7, 14 and 21: bait refilling.   According to the mode of application and the intended uses, the environmental exposure assessment is done with the scenarios “in and around building” and “waste dump”. If areas in and around buildings and waste dump are treated, the NYNA D+ AVOINE baits must be placed in bait stations to increase, if they are robust enough, the safety of rodenticides and reduce the primary poisoning hazards of non-target animals. Besides spills, exposure of the environment by difenacoum is also expected from urine, faeces and carcasses of the target animals (EUBEES ESD, 2003).  From the intended uses, the terrestrial compartment is the only relevant compartment to consider release of difenacoum. However, the risks are also calculated for groundwater, primary and secondary poisoning. |

#### PEC in surface water and sediment

Exposure of surface water and sediment after the treatment with rodenticides is only relevant for indoor application of liquid poisons, residues from mixing and cleaning (ESD PT14) when a release is foreseen via the STP. As NYNA D+ AVOINE is a solid form and is intended to be used in and around building, no indirect or direct exposure to surface water and sediment is expected.

#### PEC in air

Difenacoum is not expected to partition to the atmosphere to any significant extent due to low vapour pressure and Henry's Law constant. Difenacoum has a potential for rapid photo-oxidative degradation in the air (half-life about two hours). The exposure of air is therefore considered negligible for the application of NYNA D+ AVOINE biocidal product.

#### PEC in soil and groundwater

As NYNA D+ AVOINE is intended to be used indoor only, no exposure to soil and groundwater is expected.

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| * **Renewal application (2017)**   2.8.4.3.1 In and around buildings  2.8.4.3.1.1 Scenario 1 : control of rats  ***Tier 1 (realistic worst case)***  The realistic worst case assessment (Tier 1) considers all the default parameters from the EUBEES ESD (2003):   * the fraction of release directly to soil (0.01), * the fraction of unmetabolised active ingredient released indirectly to soil (0.9), * the number of refilling times *Nrefil* = 5 (100 % of product was eaten completely 4 times during the campaign) * and the amount of product used in control operation for each bait box (Qprod= 250 g instead of 200 g as intended by the applicant)   ***Tier 2 (Normal case scenario)***  In Tier 2, the default parameters from the ESD have been refined according to the normal intended use of the product as described in the label.  The scenario in EUBEES ESD (2003) is primarily based on grains and wax blocks. The formulation NYNA D+ AVOINE is a formulation/delivery type which does not strictly fit any of the product types for which emissions scenarios have been detailed in EUBEES ESD 2003. In fact, NYNA D+ AVOINE is never handled in a loose form during application; it is enclosed in a paper sachet which is not removed. Due to the special formulation of this product, an estimated direct release during application and use is estimated to be at least 10 times lower compared to the 1% stated in EUBEES ESD (2003). Therefore the estimated direct release (*Frelease-D-soil*)during application and use is set to 0.1% (this refinement was agreed during TMI06).  Moreover, according to metabolism and toxicokinetics study, it is assumed, cf. section **Erreur ! Source du renvoi introuvable.**, that 40% of administered dose is unchanged difenacoum in faeces and urine, which represents a worst case for release. Therefore, an estimated fraction of unmetabolised active ingredient released indirectly to soil during application and use (*Frelease-ID-soil*) is set to 0.4.  Finally, according to ESD (Larsen, 2003) and the applicant’s usage, the normal campaign baiting is:   * Day 1: Treatment with one normal bait per box , * Day 7: 100 % replenishment, * Day 14: 25-50 % replenishment, * Day 21: 10 % replenishment, * Day 28: 0% replenishment   The normal campaign baiting is roughly equivalent to 1.5 replenishments corresponding to a total direct release over 28 days.  All the results are summarized in **Erreur ! Source du renvoi introuvable.**. Only the calculations for the normal case scenario are detailed below.  According to EUBEES ESD (2003) the main exposure of environment is expected to be the soil. The following equation is introduced in EUBEES ESD (2003, Equation 2) to characterize the local direct release in the realistic worst case farm scenario based on bait in boxes:  ***Elocalsoil-D-campaign =Qprod x Fcprod x Nsites x Nrefil x Frelease-D-soil* (ESD eq. 2)**  With:  *Qprod*  = 0.2 kg; amount of product used at each refilling for each box,  *Fcprod* = 0.05 g a.i./kg; fraction of active substance in product,  *Nsites* = 10; number of outside application sites,  *Nrefil* = 1.5; number of refilling times  *Frelease-D-,soil* = 0.001 ; fraction released directly to soil.  ***Elocalsoil-D-campaign* = 1.50E-04 g a.i./campaign**  The concentration of active substance around each bait box after direct release can be estimated by equation 3 of the EUBEES ESD (2003):  ***Clocalsoil-D = (Elocalsoil-D-campaign x 1000) /(AREAexposed-D x DEPTHsoil x RHOsoil x Nsites)* (ESD eq. 3)**  with :  *Elocalsoil-D-campaign* = 1.50E-04 g a.i./campaign; local emission to soil from a campaign,  *AREAexposed-D* = 0.09 m² (directly exposed area 10 cm around bait boxes, default value); area directly exposed to rodenticide (around the bait box),  *DEPTHsoil* = 0.1 m (default value); depth of exposed soil, *RHOsoil* = density of exposed soil,  *Nsites* = 10; number of application sites,  *RHOsoil* = 1700 kg/m³ soil (default value)  ***Clocalsoil-D* = 9.80 E-04 mg a.i/kgwwt soil**  The calculated local concentration due to direct release after a treatment campaign of **9.80E-04 mg a.i/kgwwt soil** is a realistic worst case assumption. This concentration is relevant only for the “hot spot” areas directly around the bait boxes (10 cm around). This calculation cannot be corrected with the half-life criteria: the persistence half-life of difenacoum in soil exceeds 300 days (refer to section **Erreur ! Source du renvoi introuvable.**).  According to EUBEES ESD (2003), to the direct release should be added the contribution from disperse release of rodenticide via urine and faeces. Therefore the concentration of active substance around each bait box after indirect release can be estimated by equation 4 of EUBEES ESD (2003):  ***Clocalsoil-ID = (Qprod x Fcprod x Nsites x Nrefil x 103 x Frelease-ID,soil x (1-Frelease-D,soil))***  ***(AREAexposed-ID x DEPTHsoil x RHOsoil)***  With:  *Qprod* = 0.2 kg; amount of product used at each refilling for each box,  *Fcprod* = 0.05 g a.i./kg; fraction of active substance in product,  *Nsites* = 10; number of outside application sites,  *Nrefil* = 1.5; number of refilling times with a normal use  *Frelease-D-,soil* = 0.001; fraction released directly to soil  *Frelease-ID-,soil* = 0.4; fraction released indirectly to soil  *AREAexposed-ID* = 550 m² assuming that 10 bait stations are located with their back against a building at 5 meters intervals and that a 10-meter zone is the most frequented zone for the rodents (in scenario 2, *AREAexposed-ID*=110 m² because the interval is 1 meter, worst case)  *DEPTHsoil* = 0.1m (default value)  *RHOsoil =* 1700 kg/m³ (default value)  ***Clocalsoil-ID =* 6.41E-04 mg a.i./kgwwt soil**  Finally the total concentration of difenacoum in soil around the bait box takes into account both direct and indirect releases calculated in accordance with EUBEES ESD (2003, Equation 5).  ***Clocalsoil = Clocalsoil-D + Clocalsoil-ID* (ESD eq. 5)**  **Normal case scenario for difenacoum:**  *Clocalsoil*  = 9.80E-04mg a.i./kg soil + 6.41E-04mg a.i./kg soil  ***Clocalsoil* = 1.62E-03mg a.i/kgwwt soil**  A mean concentration in soil (*Clocalsoil mean concentration*) is also calculated in order to derive a more realistic concentration in pore water:  ***Clocalsoil mean concentration =***  ***((Elocalsoil-D-campaign + Elocalsoil-ID-campaign) x 1000) / (AREAexposed-ID x DEPTHsoil x RHOsoil)***  ***Clocalsoil mean concentration* = 6.43E-04 mg/ kgwwt**  The predicted environmental concentrations of difenacoum in groundwater are calculated in order to assess indirect exposure of biocides to humans *via* drinking water. In accordance with the guidance presented in the TGD, the concentration in pore water of soil has been calculated to provide an indication for potential groundwater contamination as a worst case. The Clocalporewater is calculated according to the equation 67 of the TGD from *Clocalsoil* and *Clocalsoil* mean concentration, considering a Koc value of 1 871 544 L/kg leading to a Ksoil-water value of 56 146   |  |  |  |  | | --- | --- | --- | --- | | Table 2.8.4.3‑1 : Difenacoum - In and around buildings - Rat control campaign - Realistic worst case and normal case scenarios | | | | | Symbol | Variable/parameter | Realistic worst case scenario  (default values) | Normal case scenario  (=block in a plastic film sachet, normal use replenishment and refined metabolism1) | | **Inputs** | | | | | ***Qprod*** | Amount of product used in control operation for each bait box | 0.250 kg | 0.200 kg | | ***Fcprod*** | Fraction of active substance in product | 0.05 g a.i./kg | 0.05 g a.i./kg | | ***Nsites*** | Number of application sites | 10 | 10 | | ***Nrefil*** | Number of refilling times | 5 | 1.5 | | ***Frelease-D-soil*** | Fraction of product released directly to soil | 0.01 | 0.001 | | ***Frelease-ID-soil*** | Fraction of unmetabolised active ingredient released indirectly to soil | 0.9 | 0.4 | | **Outputs** | | | | | ***Elocalsoil-D-campaign*** | Local direct emission of active sub-stance to soil from a campaign | 6.25E-03 g/camp. | 1.50E-04 g/camp. | | ***Elocalsoil-ID-campaign*** | Local indirect emission of active substance to soil from a campaign | 5.57E-01 g/camp. | 5.99E-02 g/camp. | |  | | | | | ***Clocalsoil-D*** | Local concentration in soil due to direct release after a campaign | 4.08E-02 mg/kgwwt | 9.80E-04 mg/kgwwt | | ***Clocalsoil-ID*** | Concentration in soil due to indirect release after a campaign | 5.96E-03 mg/kgwwt | 6.41E-04 mg/kgwwt | | ***Clocalsoil= Clocalsoil-D + Clocalsoil-ID*** | Total concentration in soil | 4.68E-02 mg/kgwwt | 1.62E-03 mg/kgwwt | | ***PEClocal soil, porew (acc. to TGD, eq.67)*** | Concentration in groundwater resulting from total concentration in soil | 1.42E-06 mg/L | 4.91E-08 mg/L | | ***Clocalsoil mean concentration*** | Total concentration in soil in 550m² – mean value for groundwater calculation | 6.02E-03 mg/kgwwt | 6.43E-04 mg/kgwwt | | ***PEClocal soil, porew (acc. to TGD, eq.67) - refined value*** | Concentration in groundwater resulting from total concentration in soil (mg/L) | 1.82E-07 mg/L | 1.95E-08 mg/L |   As a worst case assumption 40 % of ingested active substance is released via urine and faeces as unchanged difenacoum and difenacoum-based metabolites. The normal campaign baiting is roughly equivalent to 1.5 replenishments corresponding to a total direct release over 28 days.  2.8.4.3.1.2 Scenario 2 : control of mice  The available data about the treatment campaign for mouse control are extracted from the applicant’s dossier:   * Duration of a treatment campaign: 28 d, * Number of bait stations: 30 (20 inside and 10 outside, 1 meter apart) * Treatment with 40g per box for mouse * *Nrefil* = 1.5; number of refilling times with a normal use * NYNA D+ AVOINE is enclosed in a paper sachet which is not removed. Due to the special formulation of this product, an estimated direct release during application and use is set to 0.1%.   As for the rat scenario, a Tier 1 (***Frelease-D-soil*** = 0.01 and***Frelease-ID-soil*** = 0.9) and a Tier 2 (***Frelease-D-soil*** = 0.001 and***Frelease-ID-soil*** = 0.4) have been calculated.  According to EUBEES ESD (2003), the main exposure compartment is expected to be the soil. The following results (**Erreur ! Source du renvoi introuvable.**) have been obtained with the calculations described above in part **Erreur ! Source du renvoi introuvable.** to calculate a difenacoum PEClocal in a mice control campaign:   |  |  |  |  | | --- | --- | --- | --- | | Table 2.8.4.3‑2 : Difenacoum - In and around buildings - Mouse control campaign - Realistic worst case and normal case scenarios | | | | | Symbol | Variable/parameter | Realistic worst case scenario  (default values) | normal case scenario  (=block in a plastic film sachet, normal use replenishment and refined metabolism1) | | **Inputs** | | | | | ***Qprod*** | Amount of product used in control operation for each bait box | 0.25 kg | 0.040 kg | | ***Fcprod*** | Fraction of active substance in product | 0.05 g a.i./kg | 0.05 g a.i./kg | | ***Nsites*** | Number of application sites | 10 | 10 | | ***Nrefil*** | Number of refilling times | 5 | 1.5 | | ***Frelease-D-soil*** | Fraction of product released directly to soil | 0.01 | 0.001 | | ***Frelease-ID-soil*** | Fraction of unmetabolised active ingredient released indirectly to soil | 0.9 | 0.4 | | **Output** | | | | | ***Elocalsoil-D-campaign*** | Local direct emission of active sub-stance to soil from a campaign | 6.25E-03 g/camp. | 3.00E-05 g/camp. | | ***Elocalsoil-ID-campaign*** | Local indirect emission of active substance to soil from a campaign | 5.57E-01 g/camp. | 1.20E-02 g/camp. | |  | | | | | ***Clocalsoil-D*** | Local concentration in soil due to direct release after a campaign | 4.08E-02 mg/ kgwwt | 1.96E-04 mg/kgwwt | | ***Clocalsoil-ID*** | Concentration in soil due to indirect release after a campaign | 2.98E-02 mg/ kgwwt | 6.41E-04 mg/kgwwt | | ***Clocalsoil= Clocalsoil-D + Clocalsoil-ID*** | Total concentration in soil | 7.06E-02 mg/ kgwwt | 8.37E-04 mg/kgwwt | | ***PEClocal soil, porew (acc. to TGD, eq.67)*** | Concentration in groundwater resulting from total concentration in soil | 2.14E-06 mg/L | 2.53E-08 mg/L | | ***Clocalsoil mean concentration*** | Total concentration in soil – mean value for refined groundwater calculation | 3.01E-02 mg/kgwwt | 6.43E-04 mg/kgwwt | | ***PEClocal soil, porew refined (acc. to TGD, eq.67) - refined value*** | Concentration in groundwater resulting from mean concentration in soil | 9.12E-07 mg/L | 1.95E-08 mg/L |   As a worst case assumption 40 % of ingested active substance is released via urine and faeces as unchanged difenacoum and difenacoum-based metabolites.The normal campaign baiting is roughly equivalent to 1.5 replenishments corresponding to a total direct release over 28 days.  2.8.4.3.2 Waste dump  The default exposure scenario suggests in the event of an infestation outbreak a treatment with 40 kg of baits distributed over an area of 1 ha, with a total of seven applications per year. In this situation, soil exposure is assumed to arise through a combination of deposition via urine and faeces combined with rodenticide contained in the carcasses of poisoned target rodents. In general, ninety percent of the total amount of rodenticide consumed by the target rodents over the duration of each baiting campaign is assumed to enter soil over the 1 ha surface.  NYNA D+ AVOINE is intended to be used in secured bait boxes or bait stations containing 200 g of biocidal product (0.005%) with 5 m spacing for the rat treatment. So to predict the concentration of difenacoum in soil and groundwater for the uses in waste dump, the intended doses are calculated for the 1 ha surface as below:  **Q*prod*** = (length of the waste dump of 1ha/distance between bait) + 1) x (length of the waste dump of 1ha/distance between bait) x (amount of product per bait point  **Q*prod*** = ((100 m /5 m) + 1) x (100 m / 5 m) x 0.200 kgproduct  **Q*prod*** = 84 kg/ha  **Table 2.8.4.3‑3 PEC of difenacoum in soil and groundwater for uses in waste dump**   |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | | **Anticoagulant-Rat- ESD default values** | **Dose for rat intended by the applicant** | **Unit** | | **INPUTS** | | | | | | Q*prod* | Amount of product used in control operation / ha | 40 | 84 | [kg.ha-1] | | Fc*product* | Fraction of active substance in product | 0.05 | 0.05 | [g a.i.kg-1] | | N*app* | Number of applications | 7 | 7 | [-] | | F*release, soil* | Fraction of product released to soil | 0.9 | 0.9 | [-] | | AREA*exposed* | Area exposed to rodenticide | 10 000 | 10 000 | [m2] | | DEPTH*soil* | Depth of exposed soil | 0.1 | 0.1 | [m] | | RHO*soil* | Density of wet exposed soil | 1700 | 1700 | [kg.m-3] | | Koc | Organic carbon adsorption coefficient | 1 871 544 | 1 871 544 | [L.kg-1] | | **OUTPUTS** | | | | | | Elocal*soil-campaign* | *Local emission of active substance to soil from a campaign* | 1.26E+01 | 2.65E+01 | [g.camp-1] | | **Clocal*soil*** | ***Local concentration in soil after a campaign*** | **7.41E-03** | **1.56E-02** | **[mg.kg-1wwt]** | | Kpsoil | *Partition coefficient solid-water in soil* | 3.61E+04 | 3.61E+04 | [L.kg-1] | | Ksoil water | *Soil-water partitioning coefficient* | 5.41E+04 | 5.41E+04 | [m3.m-3] | | **PEClocal soil, porew** | ***Concentration in groundwater*** | **2.33E-07** | **4.89E-07** | **[mg.L-1]** | |

#### Non compartment specific exposure relevant to the food chain (primary and secondary poisoning)

##### Primary poisoning

The risk assessment for the primary poisoning presented below was extracted from the Annex I inclusion dossier for the active substance considering that difenacoum concentration is identical in the product NYNA D+ AVOINE and in the representative product presented for the Annex I inclusion. Primary poisoning calculations are carried out considering the ‘in and around buildings’ scenario from the EUBEES ESD PT14 as a worst case scenario in view of the fact that the product is applied inside buildings only.

According to ESD (Larsen, 2003), primary poisoning hazard to mammals and birds (both wild and domestic) can be considered small in the scenario “in and around buildings”. In use scenarios where difenacoum is placed in protected bait point, there is the risk for primary poisoning mainly for birds and mammals of equal size or smaller as the target rodents, which may be able to enter the bait stations. Also when target animals carry bait away from e.g. bait stations, non-target animals may be exposed.

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.

The Tier 1 assessment assumes that there is no bait avoidance by the non-target animals and that they obtain 100% of their diet in the treated area and has access to difenacoum product. **The worst case Tier 1 PECoral is 50 mg/kg** (difenacoum present at 0.005% w/w in NYNA D+ AVOINE) and is used in quantitative risk assessment for the long-term situation.

According to ESD (Larsen, 2003) a Tier 2 assessment can be done estimating daily uptake of a compound (ETE) by non-target animals according to the equation 19 of ESD:

ETE = (FIR/BW) \* C \* AV \* PT \* PD (mg/kg bw/day);

FIR: food intake rate of the indicator species,

BW: indicator species body weight,

C: concentration of the active substance in fresh diet,

AV: avoidance factor,

PT: fraction of diet obtained in treated area and

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) these AV and PT are refined to 0.9 and 0.8, respectively.

When elimination of active substance is taken into account the expected concentration of active substance (EC) in animal is calculated with equation **EC = ETE x (1-El),** where El is fraction of daily uptake eliminated (number between 0 and 1, default 0.3). According to the toxicokinetic study (section 2.8.2.6), the total daily elimination in rats taking into account excretion through faeces and metabolism of difenacoum in rat liver, is approximately 40% (elimination factor 0.4), which is used in calculations also for non-target animals as there is no other data available. Calculations for ETE and EC values for worst case and realistic worst case situations are presented in the table below. According to the guidance agreed at 23rd Comptetent Authority meeting, these values are used for qualitative risk assessment of primary poisoning in acute situation.

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| **Table 2.8.4.4‑1 : Expected concentrations of difenacoum in non-target animals in the worst case (Step 1) and realistic worst case (Step 2) for acute situations with and without elimination** |
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| Calculations of the expected concentrations (EC) for 5 days exposure considering elimination are calculated according to ESD equation 21 as a worst case i.e. AV, PT and PD are set to 1. According to the guidance agreed at 23rd CA meeting, EC5 values are used for quantitative risk assessment of primary poisoning in the long-term situation.  **Table 2.8.4.4‑2 : Expected concentrations of difenacoum (EC5) in non-target animals for the long-term situations (worst case).** |
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| Among the anticoagulant poisoning incidents, dogs are common victims. The intoxication of dogs are easily detected as they live together with man. Intoxication of incidents of wild animals may often remain unobserved. Small non-target rodents, such as voles, and small, granivorous birds can feed on rodenticidal baits because they can pass through the entrance hole of a bait station. Exposure may also arise if target animals carry bait away from the bait station. The domestic animals at risk are dog, pig and hen. Birds eating cereal and weed seeds like sparrows, pigeons and pheasants are possible wild species that may be at risk of primary poisoning. |

##### Secondary poisoning

***Secondary poisoning via the aquatic food chain***

As no exposure of the aquatic compartment is foreseen with the use of NYNA D+ AVOINE 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 NYNA D+ AVOINE inside buildings, no risk assessment for secondary poisoning through the terrestrial food chain is needed.

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| * **Renewal application (2017)**   According to the TGD, secondary poisoning through the terrestrial route is soil 🡪 terrestrial organisms (earthworm) 🡪 earthworm-eating mammal or bird. Since birds and mammals consume worms with their gut contents and the gut of earthworms can contain substantial amounts of soil, the exposure of the predators may be affected by the amount of substance that is in the soil. The PECoral,predator is calculated for rat application in normal case scenario as :  **PECoral, predator = Cearthworm (eq 80, TGD, 2003)**  **Cearthworm = (BCFearthworm\* *PEClocal soil, porew* + *Clocalsoil* \*Fgut\*CONVsoil)/ (1+Fgut kgdwt/kgwwt\*CONVsoil kgwwt/kgdwt) (eq 82c, TGD 2003).**  No measured BCF for earthworm is available and the calculated **BCF** of **477 729 L/kgwet earthworm** is used in calculations.  **Cearthworm** = (477729 L/kgwet earthworm x 4.89E-07 mg/L + 1.56E-02 mg/kgwwt x 0.1 kgdwt/kgwwt x 1.13 kgwwt/kgdwt) / (1+0.1 \*1.13) = **2.12**E-01 **mg/kgwetearthworm.**  According to the TGD (p. 131) the most appropriate scenario is that 50% of the diet comes from a local area and 50% comes from the regional area, thus when the PEClocal,soil is used in calculation, the **PECoral, predator** to be used in risk assessment is 2.12E-01 mg/kgwet earthwom x 0.5 = **1.06**E-01 **mg/kgwet earthworm.**  The primary poisoning for the scenario “in and around buildings” is cover by the primary poisoning for the scenario “waste dump” (see above). |

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

As secondary poisoning assessment according to the TGD part II considers the oral intake of a chemical only via fish or worms, another food chain rodenticide (bait) →rodent → rodent-eating mammal or rodent-eating bird is assessed in the EUBEES ESD PT14.

The risk assessment for the secondary poisoning presented below was extracted from the Annex I inclusion dossier for the active substance considering that difenacoum concentration is identical in the product NYNA D+ AVOINE and in the representative product presented for the Annex I inclusion. Secondary poisoning calculations are carried out considering the ‘in and around buildings’ scenario from the EUBEES ESD PT14 as a worst case scenario in view of the fact that the product is applied inside buildings only.

According to 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), also scavengers may search for food close to buildings and thus secondary poisoning through poisoned rats exists. 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.

For estimation of secondary poisoning risk through poisoned rats, tiered approach is presented in the ESD:

* The Tier 1 assessment of secondary poisoning is based on the concentration in the predators or scavenger's food i.e. poisoned rodents (concentration in food); the predator is assumed to catch the rodent after last meal on day 5 or day 14.
* The Tier 2 assessment of long-term secondary poisoning is based on the expected concentration in predators compared to PNECoral expressed as a daily dose; the predators accumulate difenacoum by feeding on poisoned target rodents during one day (rodents ate baits every day during 5 and 14 days).

Therefore, the amount of difenacoum in rats is estimated according to equations 19 and 21 in ESD:

**(ETE = (FIR/BW) \* C \* AV \* PT \* PD (mg/kg bw/day),**

In calculations AV and PT for rodent are set to 1 and PD values to 1 and 0.5 and 0.2. The daily elimination is assumed to be 40%, see details in section **Erreur ! Source du renvoi introuvable.**. Results are presented in the following table.

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| **Table 2.8.4.4‑3 : Estimated concentration (EC) of difenacoum in target rodents (rats) in mg a.s./kg bw at different times during a control operation** |
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Tier 1 PECoral for short term situation is calculated according to the equation 22 in ESD (Larsen, 2003):

**PEC oral, predator = (ECn +ETE) x Frodent**

using value 1 for Frodent (non-target animal consume 100% of their daily intake on poisoned rodents).

where:

Frodent; fraction of poisoned rodents in predator's diet

ECn: expected concentration of a.s. in the rodent on day 'n' before the last meal

n; the number of days the rodent is eating rodenticide until caught, default 5.

These values, presented in Table 2.8.4.4-4 below, are used for qualitative risk assessment of secondary poisoning in acute situation.

* Tier 1 PECoral for long term situation is calculated similar way, but the Frodent is set to 0.5, which means that it is assumed that non-target animal consume 50 % of their daily intake on poisoned rodents. These values, presented in Table 2.8.4.4-4 below, are used for Tier 1 quantitative risk assessment of secondary poisoning in the long-term situation.

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| **Table 2.8.4.4‑4 : Predicted environmental concentrations of difenacoum in food of predator (PECoral) for acute and long-term situations.** |
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* Tier 2 for long-term exposure: According to the CAR of difenacoum, the PECoral is the concentration in non-target animals after a single day of exposure (mg/kg bw) using values PD of 1 (100% bait consumption by rodent) and Frodent of 0.5. PECoral values presented in the table 2.8.4.4-5 below are used for Tier 2 quantitative risk assessment of secondary poisoning in the long-term situation.

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| **Table 2.8.4.4‑5 : Expected concentrations of difenacoum in non-target animals due to secondary poisoning after a single day exposure (concentration of difenacoum in rodenticide bait 0.005%); rodents caught by predators on day 5 and 14 (after feeding), PD 1, Frodent 0.5.** |
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### Risk characterisation for the environment – PAR 2012, updated 2017

Risk characterisation for the environment is done quantitatively by comparing predicted environmental concentrations (PEC) and the concentrations below which effects on organism will not occur (PNEC) according to the guidance in Technical guidance document (TGD, 2003) and 'Emission scenario document for biocides used as rodenticides' (Larsen, 2003, hereafter ESD).

The environmental risk characterization has been carried out for difenacoum.

#### Primary poisoning

Concentration of the bait is compared to the PNECoral expressed as the concentration in food.

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| **Table 2.8.5.1‑1 : Tier 1 risk characterisation of primary poisoning.** | | | |
|  | PEC mg/kg food | PNEC mg/kg food | PEC/PNEC |
| Birds | 50 | 0.0005 | 100 000 |
| Mammals | 50 | 0.007 | 7 143 |

With a Tier 1 Approach, the risk for primary poisoning in birds and mammals is not acceptable.

The expected concentrations (EC) in the non-target animals after five days exposure have been calculated with the Step 2 assumptions, i.e, PT=0.8 and AV=0.9. The PNECoral is expressed as the daily dose.

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| **Table 2.8.5.1‑2 : Tier 2 risk characterisation of primary poisoning.** |
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With a Tier 2 Approach, the risk for primary poisoning is not acceptable for the non-target animals.

The risk characterization indicates a very high risk to non-target mammals and birds from direct eating of grains. 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 grains are used 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 grains have to be accessible to target rodents, they may as well be accessible to non-target mammals and birds of equal or smaller size than the target rodents.

Nevertheless, as the product 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.

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| * **Renewal application (2017)**   **Assessment of oudoor uses**  2.8.5.1 Aquatic compartment  Exposure of surface water (including sediment and STP) arising from the use of NYNA D+ AVOINE bait in waste dumps is not expected to be significant. Therefore, estimates of difenacoum concentrations in the aquatic compartment have not been calculated. The risks to aquatic biota for this use are expected to be low.  2.8.5.2 Atmospheric compartment  Difenacoum is not expected to partition to the atmosphere to any significant extent due to low vapour pressure and Henry’s Law constant. Difenacoum has a potential for rapid photo-oxidative degradation in the air (half-life about two hours). The exposure of air is therefore considered negligible for the application of NYNA D+ AVOINE biocidal product.  2.8.5.3 Terrestrial compartment (including soil and groundwater)  2.8.5.3.1 In and around  Detailed PNEC and PEC calculations are presented in sections 2.8.2.7 and 2.8.4. Only local PECs are used since regional and continental releases are regarded to be negligible (ESD EUBEES 2003). No risk characterization for the manufacturing and formulation processes is conducted as the environmental exposure from these life-cycle steps is expected to be low. Realistic worst case predicted soil concentrations (PECs) for difenacoum have been calculated for the use scenario in and around buildings, for application in rat control campaign and mouse control campaign. The resulting PEC/PNEC ratios for the soil are summarized in Table 2.8.5-1.  Table 2.8.5-1: Difenacoum PEC/PNEC ratios – Terrestrial compartment – Realistic worst case and normal case scenarios.   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Exposure scenario | | PECsoil(mg/kgwwt) | | PNECsoil  (mg/kgwwt) | PECsoil/PNECsoil | | | Rat scenario | Mouse scenario | Rat scenario | Mouse scenario | | Difenacoum | | | | | | | | In and around buildings | Realistic worst case scenario (Tier 1) | 4.68E-02 | 7.06E-02 | 0.877 | 0.053 | 0.081 | | Normal case scenario  (Tier 2) | 1.62E-03 | 8.37E-04 | 0.877 | 1.85E-03 | 9.55E-04 |   The calculated PEC/PNEC values for difenacoum indicate that there is no unacceptable risk for the terrestrial compartment when the product NYNA D+ AVOINE is used in and around building against rats and mice.  Possible movement of the active substance from soil to groundwater is calculated according to the TGD (2003) by the equation 67, where concentration in pore water of agricultural soil is taken as an indication for potential groundwater levels. According to the TGD, this is a worst case assumption, neglecting transformation and dilution in deeper soil layers. Aerial deposition is negligible. According to the calculated groundwater concentration (Table 2.8.5-2) from the normal case scenario, in and around buildings, the maximum permissible concentration set for drinking water by the directive 80/778/EEC (amended by 98/83/EC) of 0.01 µg/L and also the threshold value for the toxicity in drinking water issued from the toxicological part are not exceeded.  Table 2.8.5-2 : Difenacoum – Risk assessment for groundwater – Realistic worst case and normal case scenarios   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Exposure scenario | | PECgroundwater (µg/L) | | Trigger value for drinking water  (µg/L) | Risk characterisation | | | Rat scenario | Mouse scenario | Rat scenario | Mouse scenario | | Difenacoum | | | | | | | | In and around buildings | Realistic worst case scenario (Tier 1) | 1.42E-06 | 2.14E-06 | 0.01\* | Acceptable | Acceptable | | Normal case scenario  (Tier 2) | 4.91E-08 | 2.53E-08 | 0.01\* | Acceptable | Acceptable |   \*0.01µg/L corresponds on the threshold value for the toxicity in drinking water from the toxicological part.  The PECgroundwater reported in the table 2.8.5-2 is the concentration in groundwater resulting from total concentration in soil (worst case). On the basis of difenacoum risk characterisation, there is no unacceptable risk for groundwater when the product NYNA D+ AVOINE is used in and around building against rats and mice.  2.8.5.3.2 Waste dump  Predicted soil concentration (PECs) have been calculated for the use scenario in waste dump. The resulting PEC/PNEC ratios for the soil are summarized in the table below:  Table 2.8.5-3: PECsoil/PNECsoil for soil organisms exposed to difenacoum following use of bait at waste dump.   |  |  |  |  | | --- | --- | --- | --- | | **Baiting scenario**  **(ESD PT14)** | **PECsoil**  **(mg difenacoum.kg wwt soil-1)** | **PNECsoil (mg difenacoum.kg wwt soil-1)** | **PEC/PNEC ratio** | | **Rat treatment**  **(40 kg.ha-1)** | 7.41E-03 | 8.77E-01 | 8.45E-03 | | **Rat treatment**  **(84 kg.ha-1)** | 1.56E-02 | 8.77E-01 | 1.77E-02 |   According to the ESD PT14 scenario, the amount of rodenticide normally used in waste dumps does not exceed **40kg/ha**. In this case, the risks are acceptable for soil. Taking into acount the application rate claimed by the applicant (*i.e.* 180g/5m), the ESD PT14 calculations lead also to acceptable risks for the terrestrial compartment.  Table 2.8.5-4: PEC groundwater due to use of NYNA D+ AVOINE in waste dump   |  |  |  |  | | --- | --- | --- | --- | | **Baiting scenario**  **(ESD PT14)** | **PECgroundwater**  **(µg difenacoum.kg wwt soil-1)** | **Threshold value in groundwater (µg.L-1)** | **Risk characterization** | | **Rat treatment**  **(40 kg.ha-1)** | 2.33E-07 | 0.01\* | Acceptable | | **Rat treatment**  **(84 kg.ha-1)** | 4.89E-07 | 0.01\* | Acceptable |   \*0.01µg/L corresponds on the threshold value for the toxicity in drinking water from the toxicological part.  The risks for groundwater are acceptable. |

#### 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.

***Rodent eating birds and mammals***

A qualitative assessment of the acute secondary poisoning is made by comparing the concentration in the rodents to LD50 values from acute oral studies. Rodents are assumed to eat entirely on bait containing difenacoum and the non-target animals are assumed to consume entirely poisoned rodents. The qualitative assessment indicates that birds are likely to survive and mammals are likely to die if they eat poisoned rats (Table 2.8.5.2-1). The species specific sensitivity differences or other aspects normally covered by the assessment factors are not taken into account in the qualitative assessment.

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| **Table 2.8.5.2‑2 : Qualitative assessment of acute secondary poisoning.** |
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###### ***Tier 1 assessment of secondary poisoning***

The Tier 1 assessment of secondary poisoning is based on the concentration in the predator's or scavenger's food, i.e. poisoned rodents. The rodents are assumed to consume entirely the grains (PD = 1), while half of the predator's or scavenger's daily food intake is poisoned rodents (Frodent = 0.5). The rodents are assumed to eat the grains in five or fourteen successive days, whereas the predator or the scavenger is assumed to eat the poisoned rodents during one day. The predator is assumed to catch the rodent after last meal on day 5 or day 14. Only resistant rodents are assumed to eat grains 14 day. The calculation of concentrations in rodents is explained in detail in Section 2.8.4.4.2. The PNECoral is based on the highest concentration causing no effects in the test with long-term exposure. The derivations of PNECs are explained in Section **Erreur ! Source du renvoi introuvable.**.

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| **Table 2.8.5.2‑3 : Tier 1 risk characterization of secondary poisoning.**  Expected concentration in target rodents is compared to the PNECoral expressed as concentration in food. Rodents are assumed to consume entirely bait (PD=1). Half of the predator's diet is poisoned rodents (Frodent=0.5). |
| The Tier 1 risk characterization shows that there is an unacceptable risk for secondary poisoning and birds are at higher risk due to lower PNECoral (Table 2.8.5.2-2).  Resistant rodents can feed on the poisoned baits longer and accumulate higher difenacoum residues than non-resistant rodents. Resistant rodents can continue to feed difenacoum up to two weeks, while the non-resistant rodents stop feeding after 5 days. Based on the calculations, the resistant rodents cause about 1.5 times higher risk for secondary poisoning of birds and mammals than non-resistant rodents. |

###### ***Tier 2 assessment of secondary poisoning***

In the Tier 2 assessment of long-term secondary poisoning the expected concentration in predators is compared to PNECoral expressed as a daily dose. The predators accumulate difenacoum by feeding on poisoned target rodents during one day. The rodents are assumed to eat entirely the bait (PD = 1), whereas half of the predator's or scavenger's daily food intake is poisoned rodents (Frodent = 0.5). The rodents are assumed to eat the baits in five or fourteen successive days. The susceptible rodents are assumed to stop feeding after 5 days, but resistant rodents are assumed to continue feeding until day 14. The calculation of expected concentrations is explained in detail in Section 2.8.4.4.2.

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| **Table 2.8.5.2‑4: Tier 2 risk characterization of secondary poisoning.**  The difenacoum expected concentrations in predatory birds and mammals are compared to the PNECoral expressed as daily dose. |
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The Tier 2 risk characterization shows a high risk for secondary poisoning (Table 2.8.5.2-3). The PNECoral expressed as a dose is approximately equal for birds and mammals, and the sensitivity of the species used in calculations is determined predominantly by the ratio of daily food consumption to body weight so that the higher ratio results in the higher risk. No data are available on the sensitivity of the example species (the species listed in Table 12 of the ESD) to difenacoum. Only one day exposure of predators is assumed in the ESD, but it is mentioned that predators could be exposed over several days. This would mean higher accumulation in predators, because daily elimination of difenacoum from the predators is assumed to be less than the ingested amount. On the other hand, it is unlikely that all worst case assumptions would materialize simultaneously in nature. It is likely that in the long-term exposure, the prey rodents do not eat only the bait and also the fraction of poisoned rodents in the predator's diet can be lower than 50%. The resistant rodents cause somewhat higher risk for predators than non-resistant rodents, but the difference is smaller than in the Tier 1 assessment.

The applicant has submitted two experimental studies on the secondary poisoning in Barn Owls. Tier 1 and Tier 2 risk characterization are recalculated for the Barn Owl on the basis of the measured concentrations in rats and mice with the experimental data provided in the Difenacoum Task Force Annex I inclusion dossier. The risks are significantly lower than with the ESD calculations however they are still considerably higher than 1 indicating an unacceptable risk for secondary poisoning of the Barn Owls.

A review of the available monitoring data was provided in the Difenacoum Task Force Annex I inclusion dossier to characterize the risk of secondary poisoning. Most of the incidents were due to misuse, abuse or unspecified use. Only few incidents resulted from approved use of difenacoum. However, like theoretical calculations and experimental results, the monitoring data clearly show that difenacoum poses an unacceptable risk for secondary poisoning. While all available information indicates risk, it does not tell the frequency of secondary poisoning incidents among wildlife.

However, considering the fact that NYNA D+ AVOINE 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 (section 3). The risk reduction measures are considered in the section 2.9.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| * **Renewal application (2017)**   **Assessment of oudoor uses**  2.8.5.1.1 Secondary poisoning via terrestrial food chains  ***Earthworms eating birds and mammals***  In the terrestrial environment birds and mammals may be at risk for difenacoum secondary poisoning if they feed on contaminated soil organisms. The calculation of PECoral, predator is presented in section 2.8.4.4.2. In the TGD it is assumed that 50% of earthworms eaten by birds and mammals are contaminated and the resting 50% is not. If NOEC for both birds and mammals are available, the lower value should be chosen for the risk characterization. However, here the risk characterization is done separately for birds and mammals to be consequent with the calculations done according to the ESD.  Table 2.8.5.2-1: Difenacoum secondary poisoning via terrestrial food chain.   |  |  |  |  | | --- | --- | --- | --- | |  | Terrestrial PECoral,predator (µg/kg wet earthworms) | PNECoral (µg/kg food) | Terrestrial PEC/PNEC | | Birds | 106 | 0.5 | 212 | | Mammals | 7 | 15.14 |   The PEC/PNEC ratio exceeds 1 for both earthworm eating birds and mammals. |

## Measures to protect man, animals and the environment – PAR 2012

The measures to protect man, animals and the environment are extracted from the Doc IIIB8 and updated according to the information submitted in the NYNA D+AVOINE dossier.

### Recommended methods and precautions concerning handling, use, storage, transport or fire

Bait stations are provided to avoid the possibility for children and domestic animals to be in contact with the biocidal product. Size of containers is appropriate to intended uses to be done.The product should be supplied in sachet for professionals only. Professional users have to be trained before using the biocidal product.

Handling and use

* The product should be applied with the sachet. Appropriate protective clothes and gloves are recommended for users during handling and cleaning. Placing the baits in secured bait station out of the reach of children and domestic animals is necessary. The bait station must be secured with no possibility for children and domestic animals to open the bait boxes or to access to the bait stations.

The bait station must not offer the possibility for rodents to take baits away in the nests. Collecting unconsumed baits and dead rodents must be done every week during the treatment.

Avoid exposure to high temperature and strong oxidising agents.

Storage

Keep out of the reach of children and domestic animals; store away from food, drink and animal feeding stuff. Keep container tightly closed in fresh and dry places and away from light.

Methods and precaution concerning transport

Not regulated.

Methods and precautions concerning fire

Suitable extinguishing media: foam and chemical powders. Water must not be used for environmental safety reasons.

Special protective equipment for fire-fighters: wear protective clothing and self-contained breathing apparatus.

Risk of toxic gases in fumes (carbon monoxide, carbon dioxide…)

### Emergency measures in case of an accident

Personal precautions

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.

Environmental precautions

In case of accidental contamination, avoid spreading in house drains, rainy waters and environment. In case of release had already occurred the competent authority has to be warned.

### Disposal considerations

Unconsumed products and packaging should be disposed according to national or local regulation.

Empty containers must not be reused.

The product is ready-to-use and applied directly in bait stations in buildings only. The baits which have not been consumed by rodents and dead rodents are kept away by operators.

It is not expected that any direct release to soil compartment would occur as a direct result of the indoor application of NYNA D+ AVOINE. However, if a spill occurs, baits must be collected with a shovel and stored in hermetic containers and eliminated according to national or local regulation.

# Proposal for the decision – minor change 2021

**Summary of product characteristics for a biocidal product**

## Administrative information

### Trade name(s) of the product

| **Trade name(s)** | NYNA D+ AVOINE |
| --- | --- |
|  | RODONCHOC  SOURICIDE DESIR  SANITOX  SUPP’ DIFE 50  DIFE RAT 50  DIFE RONGEUR 50  STOP DIFE 50 |

### Authorisation holder

|  |  |  |
| --- | --- | --- |
| **Name and address of the authorisation holder** | **Name** | TRIPLAN SA |
| **Address** | BP 258 LA POSTE FRANCAISE  AD500 ANDORRA LA VELLA  ANDORRE |
| **Authorisation number** |  | |
| **R4BP asset reference number** |  | |
| **Date of the authorisation** |  | |
| **Expiry date of the authorisation** |  | |

### Manufacturer(s) of the product

|  |  |
| --- | --- |
| **Name of manufacturer** | SOFAR France |
| **Address of manufacturer** | ZA DU DREVERS BP 02  29190 PLEYBEN  France |
| **Location of manufacturing sites** | ZA DU DREVERS BP 02  29190 PLEYBEN  France |

|  |  |
| --- | --- |
| **Name of manufacturer** | RATOUCY SAS |
| **Address of manufacturer** | 29 Rue de la forêt - LOOZE - BP145  89303 JOIGNY Cedex  France |
| **Location of manufacturing sites** | 29 Rue de la Forêt  89300 LOOZE  France |

|  |  |
| --- | --- |
| **Name of manufacturer** | IRIS |
| **Address of manufacturer** | 1126A Avenue Du Moulinas - Route De Saint Privat  30340 SALINDRES  France |
| **Location of manufacturing sites** | 1126A Avenue Du Moulinas - Route De Saint Privat  30340 SALINDRES  France |

|  |  |
| --- | --- |
| **Name of manufacturer** | NOXIMA |
| **Address of manufacturer** | Carrefour jean monnet - LACROIX SAINT OUEN  60201 COMPIEGNE  France |
| **Location of manufacturing sites** | Carrefour jean monnet - LACROIX SAINT OUEN  60201 COMPIEGNE  France |

|  |  |
| --- | --- |
| **Name of manufacturer** | INDUSTRIAL CHIMICA SRL |
| **Address of manufacturer** | VIA SORGAGLIA 40  35020 Arre (PD)  Italy |
| **Location of manufacturing sites** | VIA SORGAGLIA 40  35020 Arre (PD)  Italy |

|  |  |
| --- | --- |
| **Name of manufacturer** | FHS |
| **Address of manufacturer** | 2 RUE DE LA TETE A LOUP - ZAC DE GRANDCHAMP  77440 OCQUERRE  France |
| **Location of manufacturing sites** | 2 RUE DE LA TETE A LOUP - ZAC DE GRANDCHAMP  77440 OCQUERRE  France |

|  |  |
| --- | --- |
| **Name of manufacturer** | FARMAVIT OOD |
| **Address of manufacturer** | BUL. TSAR BORIS III, N°63, OFFICE 1  1612 SOFIA  Bulgaria |
| **Location of manufacturing sites** | INDUSTRIALNA 2 STR - PLEVEN DISTRICT  5960 GULIANTSI  Bulgaria |

|  |  |
| --- | --- |
| **Name of manufacturer** | HDA |
| **Address of manufacturer** | ZA LA CHARME MENETROL  63200 RIOM  France |
| **Location of manufacturing sites** | ZA LA CHARME MENETROL  63200 RIOM  France |

|  |  |
| --- | --- |
| **Name of manufacturer** | FARMA-CHEM |
| **Address of manufacturer** | Industrial Area of Sindos - P.O. BOX 1026 Block 53 Zone C,  57022 THESSALONIKI  Greece |
| **Location of manufacturing sites** | Industrial Area of Sindos - P.O. BOX 1026 Block 53 Zone C,  57022 THESSALONIKI  Greece |

|  |  |
| --- | --- |
| **Name of manufacturer** | AGGRESS |
| **Address of manufacturer** | EL. VENIZELOU 158 A,  16341 ATHENS  Greece |
| **Location of manufacturing sites** | ARMA THEBES,  32200 VOIOTIA  Greece |

|  |  |
| --- | --- |
| **Name of manufacturer** | AGROLOGY |
| **Address of manufacturer** | P.O. BOX 1089 - Industrial Area of Thessaloniki  57022 THESSALONIKI  Greece |
| **Location of manufacturing sites** | P.O. BOX 1089 - Industrial Area of Thessaloniki  57022 THESSALONIKI  Greece |

### Manufacturer(s) of the active substance(s)

|  |  |
| --- | --- |
| **Active substance** | Difenacoum |
| **Name of manufacturer** | ACTIVA S.r.l. |
| **Address of manufacturer** | Via Feltre, 32  20132 MILAN  Italy |
| **Location of manufacturing sites** | Dr. Tezza S.r.l - Via Tre Ponti 22  Santa Maria di Zevio (VR) 37050,  Italy |

## Product composition and formulation

### Qualitative and quantitative information on the composition of the product

| **Common name** | **IUPAC name** | **Function** | **CAS number** | **EC number** | **Content (%)** |
| --- | --- | --- | --- | --- | --- |
| Difenacoum | 3-(3-biphenyl-4-yl-1,2,3,4- tetrahydro-1-naphthyl)-4- hydroxycoumarin | Active substance | 56073-07-5 | 259-978-4 | 0.005 |

### Type of formulation

|  |
| --- |
| Ready-to-use bait: grain |

# 

## Hazard and precautionary statements according to Regulation (EC) 1272/2008

| **Classification** | |
| --- | --- |
| Hazard category | Repr. 1B  STOT RE 2 |
| Hazard statement | H360D: May damage the unborn child  H373: May cause damage to organs through prolonged or repeated exposure |
|  | |
| **Labelling** | |
| Signal words | Danger    GHS 08 |
| Hazard statements | H360D: May damage the unborn child  H373: May cause damage to organs through prolonged or repeated exposure |
| Precautionary statements | P201: Obtain special instructions before use.  P202: Do not handle until all safety precautions have been read and understood.  P260: Do not breathe dust/fumes/gas/mist/vapours/spray.  P280: Wear protective gloves/protective clothing/eye protection/face protection.  P308 + P313: If exposed or concerned: Get medical advice/attention.  P314: Get medical advice/attention if you feel unwell.  P405: Store locked up.  P501: Dispose of contents/container to … [*… in accordance with local/regional/national/international regulation]* |
|  | |
| Note | **-** |

## Authorised use(s)

### Use description

Table 4. Use # 1 – House mice and/or rats – trained professionals – indoor

|  |  |
| --- | --- |
| **Product Type** | 14 |
| **Where relevant, an exact description of the authorised use** | Not relevant for rodenticides |
| **Target organism(s) (including development stage)** | *Mus musculus* (house mice)  *Rattus norvegicus* (brown rat)  *Rattus rattus* (black or roof rat) |
| **Field(s) of use** | Indoor |
| **Application method(s)** | Bait formulations:  - Ready-to-use bait to be used in tamper-resistant bait stations[[13]](#footnote-13)  - *[Covered and protected baiting points]* |
| **Application rate(s) and frequency** | Bait products:  Rats: 200 g of bait per baiting point.  Mice: 40 g of bait per baiting point. |
| **Category(ies) of users** | Trained professionals |
| **Pack sizes and packaging material** | Minimum pack size of 3 kg*.*  *(****In France only*** *: minimum pack size of 5 kg)*  NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.  Sachets are packed in:   * Buckets (PE/PP) (5-10-15-18-20-25-30 kg) * Bags (paper/PE/PP) (5-10-15-20-25-30 kg) * Cardboards (carton) (5-10-12-15-20-25-30-50 kg) * Metal box (metal) (5-10-15-20-25 kg) * Bait box PET/PP/PE/PVC   The product is supplied in bulk in:   * Buckets (PE/PP) (5-10kg) * Bags (paper/PE/PP) (5-10 kg) * Cardboards (carton) (5-10 kg) * Metal box (metal) (5-10 kg) * Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg) |

#### Use-specific instructions for use

|  |
| --- |
| * Remove the remaining product at the end of treatment period. * *[When available]* Follow any additional instructions provided by the relevant code of best practice |

#### Use-specific risk mitigation measures

|  |
| --- |
| * Where possible, prior to the treatment inform any possible bystanders (e.g. users of the treated area and their surroundings) about the rodent control campaign *[in accordance with the applicable code of good practice, if any]*. * Consider preventive control measures (e.g. plug holes, remove potential food and drinking as far as possible) to improve product intake and reduce the likelihood of reinvasion. * To reduce risk of secondary poisoning, search for and remove dead rodents during treatment at frequent intervals, in line with the recommendations provided by the relevant code of best practice. * Do not use the product as permanent baits for the prevention of rodent infestation or monitoring of rodent activities. * Do not use the product in pulsed baiting treatments. |

#### Where specific to the use, the particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

|  |
| --- |
| * When placing bait points close to water drainage systems, ensure that bait contact with water is avoided. |

#### Where specific to the use, the instructions for safe disposal of the product and its packaging

|  |
| --- |
|  |

#### Where specific to the use, the conditions of storage and shelf-life of the product under normal conditions of storage

|  |
| --- |
|  |

### Use description 2

Table 2. Use # 2 Mice and/or rats – trained professionals – outdoor around buildings

|  |  |
| --- | --- |
| **Product Type** | 14 |
| **Where relevant, an exact description of the authorised use** | Not relevant for rodenticides |
| **Target organism(s) (including development stage)** | *Mus musculus* (house mice)  *Rattus norvegicus* (brown rat)  *Rattus rattus* (black or roof rat) |
| **Field(s) of use** | Outdoor around buildings |
| **Application method(s)** | Bait formulations:  - Ready-to-use bait to be used in tamper-resistant bait stations.  - *[Covered and protected baiting points]* |
| **Application rate(s) and frequency** | Bait products:  Rats: 200 g of bait per baiting point.  Mice: 40 g of bait per baiting point. |
| **Category(ies) of users** | Trained professionals |
| **Pack sizes and packaging material** | Minimum pack size of 3 kg*.*  *(****In France only*** *: minimum pack size of 5 kg)*  NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.  Sachets are packed in:   * Buckets (PE/PP) (5-10-15-18-20-25-30 kg) * Bags (paper/PE/PP) (5-10-15-20-25-30 kg) * Cardboards (carton) (5-10-12-15-20-25-30-50 kg) * Metal box (metal) (5-10-15-20-25 kg) * Bait box PET/PP/PE/PVC   The product is supplied in bulk in:   * Buckets (PE/PP) (5-10kg) * Bags (paper/PE/PP) (5-10 kg) * Cardboards (carton) (5-10 kg) * Metal box (metal) (5-10 kg) * Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg) |

#### Use-specific instructions for use

|  |
| --- |
| * Protect bait from the atmospheric conditions. Place the baiting points in areas not liable to flooding. * Replace any bait in baiting points in which bait has been damaged by water or contaminated by dirt. * Remove the remaining product at the end of treatment period. * *[When available]* Follow any additional instructions provided by the relevant code of best practice. * *[For outdoor use, baiting points must be covered and placed in strategic sites to minimise the exposure to non-target species].* |

#### Use-specific risk mitigation measures

|  |
| --- |
| * Where possible, prior to the treatment inform any possible bystanders (e.g. users of the treated area and their surroundings) about the rodent control campaign *[in accordance with the applicable code of good practice, if any]*. * Consider preventive control measures (plug holes, remove potential food and drinking as far as possible) to improve product intake and reduce the likelihood of reinvasion. * To reduce risk of secondary poisoning, search for and remove dead rodents during treatment at frequent intervals, in line with the recommendations provided by the relevant code of best practice. * Do not use this product as permanent baits for the prevention of rodent infestation or monitoring of rodent activities. * Do not use this product in pulsed baiting treatments. * Do not apply this product directly in the burrows. |

#### Where specific to the use, the particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

|  |
| --- |
| * When placing bait points close to surface waters (e.g. rivers, ponds, water channels, dykes, irrigation ditches) or water drainage systems, ensure that bait contact with water is avoided. |

#### Where specific to the use, the instructions for safe disposal of the product and its packaging

|  |
| --- |
|  |

#### Where specific to the use, the conditions of storage and shelf-life of the product under normal conditions of storage

|  |
| --- |
|  |

### Use description 3

Table 3. Use # 3 – Mice and/or rats – trained professionals – Outdoor open areas & waste dumps

|  |  |
| --- | --- |
| **Product Type** | 14 |
| **Where relevant, an exact description of the authorised use** | Not relevant for rodenticides |
| **Target organism(s) (including development stage)** | *Rattus norvegicus* (brown rat)  *Rattus rattus* (black or roof rat)  *Mus musculus* (house mice) |
| **Field(s) of use** | Outdoor open areas x  Outdoor waste dumps x |
| **Application method(s)** | - Ready-to-use bait to be used in tamper-resistant bait stations.  *- [Covered and protected baiting points]* |
| **Application rate(s) and frequency** | Bait products:  Rats: 200 g of bait per baiting point.  Mice: 40 g of bait per baiting point. |
| **Category(ies) of users** | Trained professionals only |
| **Pack sizes and packaging material** | Minimum pack size of 3 kg*.*  *(****In France only*** *: minimum pack size of 5 kg)*  NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.  Sachets are packed in:   * Buckets (PE/PP) (5-10-15-18-20-25-30 kg) * Bags (paper/PE/PP) (5-10-15-20-25-30 kg) * Cardboards (carton) (5-10-12-15-20-25-30-50 kg) * Metal box (metal) (5-10-15-20-25 kg) * Bait box PET/PP/PE/PVC   The product is supplied in bulk in:   * Buckets (PE/PP) (5-10kg) * Bags (paper/PE/PP) (5-10 kg) * Cardboards (carton) (5-10 kg) * Metal box (metal) (5-10 kg)   Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg) |

#### Use-specific instructions for use

|  |
| --- |
| * Protect bait from the atmospheric conditions. Place the bait stations in areas not liable to flooding. * Replace any bait in baiting points in which bait has been damaged by water or contaminated by dirt. * Remove the remaining product at the end of treatment period. * *[When available]* Follow any additional instructions provided by the relevant code of best practice. * *[For outdoor use, baiting points must be covered and placed in strategic sites to minimise the exposure to non-target species].* |

#### Use-specific risk mitigation measures

|  |
| --- |
| * Where possible, prior to the treatment inform any possible bystanders (e.g. users of the treated area and their surroundings) about the rodent control campaign *[in accordance with the applicable code of good practice, if any]*. * To reduce risk of secondary poisoning, search for and remove dead rodents during treatmentat frequent intervals*,* in line with the recommendations provided by the relevant code of best practice. * Do not apply this product directly in the burrows. |

#### Where specific to the use, the particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

|  |
| --- |
| * When placing bait points close to surface waters (e.g. rivers, ponds, water channels, dykes, irrigation ditches) or water drainage systems, ensure that bait contact with water is avoided. |

#### Where specific to the use, the instructions for safe disposal of the product and its packaging

|  |
| --- |
|  |

#### Where specific to the use, the conditions of storage and shelf-life of the product under normal conditions of storage

|  |
| --- |
|  |

### Use description 4

Table 4. Use # 4 *(not relevant in France)* – House mice – professionals – indoor

|  |  |
| --- | --- |
| **Product Type** | 14 |
| **Where relevant, an exact description of the authorised use** | Not relevant for rodenticides |
| **Target organism(s) (including development stage)** | *Mus musculus* (house mice) |
| **Field(s) of use** | Indoor |
| **Application method(s)** | Ready-to-use bait to be used in tamper-resistant bait stations[[14]](#footnote-14) |
| **Application rate(s) and frequency** | - 40 g of bait per bait station. If more than one bait station is needed, the minimum distance between bait stations should be of 1 meter. |
| **Category(ies) of users** | Professionals |
| **Pack sizes and packaging material** | Minimum pack size of 3 kg*.*  NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.  Sachets are packed in:   * Buckets (PE/PP) (5-10-15-18-20-25-30 kg) * Bags (paper/PE/PP) (5-10-15-20-25-30 kg) * Cardboards (carton) (5-10-12-15-20-25-30-50 kg) * Metal box (metal) (5-10-15-20-25 kg) * Bait box PET/PP/PE/PVC   The product is supplied in bulk in:   * Buckets (PE/PP) (5-10kg) * Bags (paper/PE/PP) (5-10 kg) * Cardboards (carton) (5-10 kg) * Metal box (metal) (5-10 kg) * Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg) |

#### Use-specific instructions for use

|  |
| --- |
| * The bait stations should be visited at least every 2 to 3 days at the beginning of the treatment and at least weekly afterwards, in order to check whether the bait is accepted, the bait stations are intact and to remove rodent bodies. Re-fill bait when necessary. * *[When available]* Follow any additional instructions provided by the relevant code of best practice. |

#### Use-specific risk mitigation measures

|  |
| --- |
|  |

#### Where specific to the use, the particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

|  |
| --- |
| * When placing bait stations close to water drainage systems, ensure that bait contact with water is avoided. |

#### Where specific to the use, the instructions for safe disposal of the product and its packaging

|  |
| --- |
|  |

#### Where specific to the use, the conditions of storage and shelf-life of the product under normal conditions of storage

|  |
| --- |
|  |

### Use description 5

Table 5. Use # 5 *(not relevant in France)* – Rats – professionals – indoor

|  |  |
| --- | --- |
| **Product Type** | 14 |
| **Where relevant, an exact description of the authorised use** | Not relevant for rodenticides |
| **Target organism(s) (including development stage)** | *Rattus norvegicus* (brown rat)  *Rattus rattus* (black or roof rat) |
| **Field(s) of use** | Indoor |
| **Application method(s)** | Ready-to-use bait to be used in tamper-resistant bait stations |
| **Application rate(s) and frequency** | - 200 g of bait per bait station. If more than one bait station is needed, the minimum distance between bait stations should be of 5 meters. |
| **Category(ies) of users** | Professionals |
| **Pack sizes and packaging material** | Minimum pack size of 3 kg*.*  NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.  Sachets are packed in:   * Buckets (PE/PP) (5-10-15-18-20-25-30 kg) * Bags (paper/PE/PP) (5-10-15-20-25-30 kg) * Cardboards (carton) (5-10-12-15-20-25-30-50 kg) * Metal box (metal) (5-10-15-20-25 kg) * Bait box PET/PP/PE/PVC   The product is supplied in bulk in:   * Buckets (PE/PP) (5-10kg) * Bags (paper/PE/PP) (5-10 kg) * Cardboards (carton) (5-10 kg) * Metal box (metal) (5-10 kg) * Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg) |

#### Use-specific instructions for use

|  |
| --- |
| * The bait stations should be visited only 5 to 7 days after the beginning of the treatment and at least weekly afterwards, in order to check whether the bait is accepted, the bait stations are intact and to remove rodent bodies. Re-fill bait when necessary. * *[When available]* Follow any additional instructions provided by the relevant code of best practice. |

#### Use-specific risk mitigation measures

|  |
| --- |
|  |

#### Where specific to the use, the particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

|  |
| --- |
| * When placing bait stations close to water drainage systems, ensure that bait contact with water is avoided. |

#### Where specific to the use, the instructions for safe disposal of the product and its packaging

|  |
| --- |
|  |

#### Where specific to the use, the conditions of storage and shelf-life of the product under normal conditions of storage

|  |
| --- |
|  |

### Use description 6

Table 6. Use # 6 *(not relevant in France)* – House mice and/or rats – professionals – outdoor around buildings

|  |  |
| --- | --- |
| **Product Type** | 14 |
| **Where relevant, an exact description of the authorised use** | Not relevant for rodenticides |
| **Target organism(s) (including development stage)** | Mus musculus (house mice)  *Rattus norvegicus* (brown rat)  *Rattus rattus* (black or roof rat) |
| **Field(s) of use** | Outdoor around buildings |
| **Application method(s)** | Ready-to-use bait to be used in tamper-resistant bait stations |
| **Application rate(s) and frequency** | Rats  - 200 g of bait per bait station. If more than one bait station is needed, the minimum distance between bait stations should be of 5 meters.  Mice  - 40 g of bait per bait station. If more than one bait station is needed, the minimum distance between bait stations should be of 1 meter. |
| **Category(ies) of users** | Professionals |
| **Pack sizes and packaging material** | Minimum pack size of 3 kg*.*  NYNA D+ AVOINE is supplied in PE/PP sachets (10-20-25-30-40-50-60-90-100-200g) or in bulk.  Sachets are packed in:   * Buckets (PE/PP) (5-10-15-18-20-25-30 kg) * Bags (paper/PE/PP) (5-10-15-20-25-30 kg) * Cardboards (carton) (5-10-12-15-20-25-30-50 kg) * Metal box (metal) (5-10-15-20-25 kg) * Bait box PET/PP/PE/PVC   The product is supplied in bulk in:   * Buckets (PE/PP) (5-10kg) * Bags (paper/PE/PP) (5-10 kg) * Cardboards (carton) (5-10 kg) * Metal box (metal) (5-10 kg) * Sachets PE/PP (100-200-300-400-500-600-700-800-900-1000g) packed in carton box (5-10 kg) |

#### Use-specific instructions for use

|  |
| --- |
| * Protect bait from the atmospheric conditions (e.g. rain, snow, etc.). Place the bait stations in areas not liable to flooding. * The bait stations should be visited *[for mice -* at least every 2 to 3 days at*]* *[for rats -* only 5 to 7 days after*]* the beginning of the treatment and at least weekly afterwards, in order to check whether the bait is accepted, the bait stations are intact and to remove rodent bodies. Re-fill bait when necessary. * Replace any bait in a bait station in which bait has been damaged by water or contaminated by dirt. * *[When available]* Follow any additional instructions provided by the relevant code of best practice. |

#### Use-specific risk mitigation measures

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| * Do not apply this product directly in the burrows. |

#### Where specific to the use, the particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

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| --- |
| * When placing bait stations close to surface waters (e.g. rivers, ponds, water channels, dykes, irrigation ditches) or water drainage systems, ensure that bait contact with water is avoided. |

#### Where specific to the use, the instructions for safe disposal of the product and its packaging

|  |
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#### Where specific to the use, the conditions of storage and shelf-life of the product under normal conditions of storage

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## General directions for use

### Instructions for use

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| * Read and follow the product information as well as any information accompanying the product or provided at the point of sale before using it. * Carry out a pre-baiting survey of the infested area and an on-site assessment in order to identify the rodent species, their places of activity and determine the likely cause and the extent of the infestation. * Remove food which is readily attainable for rodents (e.g. spilled grain or food waste). Apart from this, do not clean up the infested area just before the treatment, as this only disturbs the rodent population and makes bait acceptance more difficult to achieve. * The product should only be used as part of an integrated pest management (IPM) system, including, amongst others, hygiene measures and, where possible, physical methods of control. * The product should be placed in the immediate vicinity of places where rodent activity has been previously explored (e.g. travel paths, nesting sites, feedlots, holes, burrows etc.). * Where possible, bait stations must be fixed to the ground or other structures. * Bait stations must be clearly labelled to show they contain rodenticides and that they must not be moved or opened *(see section 5.3 for the information to be shown on the label)*. * *[If national policy or legislation requires it]* When the product is being used in public areas, the areas treated should be marked during the treatment period and a notice explaining the risk of primary or secondary poisoning by the anticoagulant as well as indicating the first measures to be taken in case of poisoning must be made available alongside the baits. * Bait should be secured so that it cannot be dragged away from the bait station. * Place the product out of the reach of children, birds, pets and farm animals and other non-target animals. * Place the product away from food, drink and animal feeding stuffs, as well as from utensils or surfaces that have contact with these. * Wear protective chemical resistant gloves during product handling phase (glove material to be specified by the authorisation holder within the product information). * When using the product do not eat, drink or smoke. Wash hands and directly exposed skin after using the product. * ***FOR TRAINED PROFESSIONAL ONLY*** *- The* frequency of visits to the treated area should be at the discretion of the operator, in the light of the survey conducted at the outset of the treatment. That frequency should be consistent with the recommendations provided by the relevant code of best practice. * If bait uptake is low relative to the apparent size of the infestation, consider the replacement of bait points to further places and the possibility to change to another bait formulation. * If after a treatment period of 35 days baits are continued to be consumed and no decline in rodent activity can be observed, the likely cause has to be determined. Where other elements have been excluded, it is likely that there are resistant rodent so consider the use of a non-anticoagulant rodenticide, where available, or a more potent anticoagulant rodenticide. Also consider the use of traps as an alternative control measure. * ***FOR PROFESSIONNALS ONLY*** *-*Consider preventive *control* measures (e.g. plug holes, remove potential food and drinking as far as possible) to improve product intake and reduce the likelihood of reinvasion. * ***FOR PROFESSIONNALS ONLY*** *-*Remove the remaining bait or the bait stations at the end of the treatment period. * For non-emptiable sachets - Do not open the sachets containing the bait. * Loose pellets-granules, grains: Place the bait in the baiting point by using a dosage devise. Specify the methods to minimise dust (e.g. wet wiping). * Loose pellets-granules, grains: Decanting is to be avoided. In case decanting cannot be avoided, an RPE of APF 10 has to be used. |

### Risk mitigation measures

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| * Where possible, prior to the treatment inform any possible bystanders about the rodent control campaign *[in accordance with the applicable code of good practice, if any]*". * The product information (i.e. label and/or leaflet) shall clearly show that the product shall only be supplied to trained professional users holding certification demonstrating compliance with the applicable training requirements (e.g. "for trained professionals only"). * ***FOR TRAINED PROFESSIONAL ONLY*** - Do not use in areas where resistance to the active substance can be suspected. * Products shall not be used beyond 35 days without an evaluation of the state of the infestation and of the efficacy of the treatment. * ***FOR TRAINED PROFESSIONAL ONLY*** - Do not rotate the use of different anticoagulants with comparable or weaker potency for resistance management purposes. For rotational use, consider using a non-anticoagulant rodenticide, if available, or a more potent anticoagulant. * Do not wash the bait stations or utensils used in covered and protected bait points with water between applications. * Dispose dead rodents in accordance with local requirements *[The method of disposal shall be described specifically in the national SPC and be reflected on the product label]*. * ***FOR PROFESSIONAL ONLY*** - To reduce risk of secondary poisoning, search for and remove dead rodents at frequent intervals during treatment (e.g. at least twice a week). *[Where relevant, specify if more frequent or daily inspection is required].* * ***FOR PROFESSIONAL ONLY*** - Do not use baits containing anticoagulant active substances as permanent baits for the prevention of rodent infestation or monitoring of rodent activities. * ***FOR PROFESSIONAL ONLY - The product information (i.e. label and/or leaflet) shall clearly*** show that: * the product shall not be supplied to the general public (e.g. "for professionals only"). * the product shall be used in adequate tamper resistant bait stations (e.g. "use in tamper resistant bait stations only"). * users shall properly label bait stations with the information referred to in section 5.3 of the SPC (e.g. label bait stations according to the product recommendations"). * ***FOR PROFESSIONAL ONLY*** - Using this product should eliminate rodents within 35 days. The product information (i.e. label and/or leaflet) shall clearly recommend that in case of suspected lack of efficacy by the end of the treatment (i.e. rodent activity is still observed), the user should seek advice from the product supplier or call a pest control service. |

### Particulars of likely direct or indirect effects, first aid instructions and emergency measures to protect the environment

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| * This product contains an anticoagulant substance. If ingested, symptoms, which may be delayed, may include nosebleed and bleeding gums. In severe cases, there may be bruising and blood present in the faeces or urine. * Antidote: Vitamin K1 administered by medical/veterinary personnel only. * In case of:   + Dermal exposure, wash skin with water and then with water and soap.   + Eye exposure, rinse eyes with eyes-rinse liquid or water, keep eyes lids open at least 10 minutes.   + Oral exposure, rinse mouth carefully with water. Never give anything by mouth to unconscious person. Do not provoke vomiting. If swallowed, seek medical advice immediately and show the product's container or label *[insert* country specific information*]*. Contact a veterinary surgeon in case of ingestion by a pet *[insert* country specific information*]* * Bait stations must be labelled with the following information: "do not move or open"; "contains a rodenticide"; "product name or authorisation number"; "active substance(s)" and "in case of incident, call a poison centre [insert national phone number]" * Hazardous to wildlife. |

### Instructions for safe disposal of the product and its packaging

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| * At the end of the treatment, dispose the uneaten bait and the packaging in accordance with local requirements *[The method of disposal shall be described specifically in the national SPC and be reflected on the product label]*. |

### Conditions of storage and shelf-life of the product under normal conditions of storage

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| * Store in a dry, cool and well ventilated place. Keep the container closed and away from direct sunlight. * Store in places prevented from the access of children, birds, pets and farm animals. * Shelf life: 2 years * Store away from humidity. |

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## Other information

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| * **In France only**: The authorisation holder has to monitor the resistance phenomenon of rodent populations toward the active substance difenacoum. Results of the resistance monitoring must be submitted at the renewal of the product. * Because of their delayed mode of action, anticoagulant rodenticides may take from 4 to 10 days to be effective after effective consumption of the bait. * Rodents can be disease carriers. Do not touch dead rodents with bare hands, use gloves or use tools such as tongs when disposing them. * This product contains a bittering agent and a dye. |

Annex 1: List of studies reviewed

##### List of new data[[15]](#footnote-15) submitted in support of the evaluation of the active substance – PAR 2012

| **Section No** | **Reference No** | **Author** | **Year** | **Title** | **Owner of data** | **Letter of Access** | | **Data protection claimed** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | **Yes** | **No** | **Yes** | **No** |
| A2 | CH-299-2009 | Garofani S. | 2009 | Difenacoum technical: complete analysis of five batch samples | Activa |  |  |  |  |
| A2.7 | CH-297-2009 | Garofani S. | 2009 | Difenacoum technical: validation of the analytical method for the determination of the active ingredient content | Activa |  |  |  |  |
| A2.8 | CH-298-2009 | Garofani S. | 2009 | Difenacoum technical: validation of the analytical method for the determination of significant impurities content | Activa |  |  |  |  |
| A3.3 | CH – 082/2010 | Garofani S. | 2010 | Difenacoum technical: determination of the colour, odour and physical state | Activa |  |  |  |  |
| A4.2 (c) | CEMR-4470 | Marshall L. | 2009 | Validation of a method for the determination of Difenacoum residues in sediment | Activa / PelGar Brodifacoum and Difenacoum Task Force |  |  |  |  |
| A4.2 (c) | CEMR-4469 | Marshall L. | 2009 | Validation of a method for the determination of Difenacoum residues in animal Matrices (Liver and Muscle) and Crop matrix | Activa / PelGar Brodifacoum and Difenacoum Task Force |  |  |  |  |
| A4.2 (e) | CEMR-4469 | Marshall L. | 2009 | Validation of a method for the determination of Difenacoum residues in animal Matrices (Liver and Muscle) and Crop matrix | Activa / PelGar Brodifacoum and Difenacoum Task Force |  |  |  |  |

##### List of new data submitted in support of the evaluation of the biocidal product – PAR 2012, updated 2017

| **Section No** | **Reference No** | **Author** | **Year** | **Title** | **Owner of data** | **Letter of Access** | | **Data protection claimed** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | **Yes** | **No** | **Yes** | **No** |
| B3.1, 3.6 | 10-920010-015 | Demangel B. | 2010 | Physico chemical tests on NYNA D+ AVOINE | Triplan |  |  |  |  |
| B3.2, 3.4 | 09-920010-13 | Tieche A, Ferron N | 2010 | Physico chemical tests on NYNA D+ BLE | Triplan |  |  |  |  |
| B3.5, 3.7, 3.12 | 10-920010-016 | Demangel B. | 2010 | Physico-chemical tests before and after accelerated storage procedure for 14 days at 54 ± 2°C on on NYNA D+ AVOINE in compliance with CIPAC MT 46.3 (CIPAC Handbok J – 2000) | Triplan |  |  |  |  |
| B4.1.1 | 10-920010-008 | Ricau H | 2010 | Validation of an analytical method for the determination of difenacoum in NYNA D+ BLOC SP in compliance with CIPAC/3807R | Triplan |  |  |  |  |
| B4.1.2 | 10-920010-018 | Ricau H | 2010 | Validation of an analytical method for the determination of difenacoum in NYNA D+ AVOINE in compliance with CIPAC/3807R | Triplan |  |  |  |  |
| B5.10..2.1/01 | XXX | XXX | 2010 | Efficacy laboratory study of cereal rodenticide containing 0.005% difenacoum with albino house mice (*Mus musculus*). | Triplan |  |  |  |  |
| B5.10.2.1/02 | XXX | XXX | 2010 | Efficacy field study of cereal rodenticide containing 0.005% difenacoum with brown rats (*Rattus norvegicus*). | Triplan |  |  |  |  |
| B5.10.2.1/03 | XXX | XXX | 2010 | Acceptance comparison study between hulled oat and wheat with albino house mice (*Mus musculus*). | Triplan |  |  |  |  |
| B5.11 | Published data | Pelz HJ *et al* | 2005 | The genetic basis of resistance to anticoagulants in rodents. | Published data |  |  |  |  |
| B5.11 | Published data | Lasseur R et al | 2006 | Les rongeurs font de la résistance. Nuisibles et parasites | Published data |  |  |  |  |
| B5.11 | Published data | Myllymäki A | 1995 | Anticoagulant resistance in Europe: Appraisal of the data from the 1992 EPPO questionnaire | Published data |  |  |  |  |
| B5.11 | Published data | Kerins G M et al | 2001 | The interaction between the indirect Anticogulant Coumatetralyl and Calciferol (vitamin D3) in Warfarin-resistant rats (*Rattus norvegicus*) | Published data |  |  |  |  |
| B5.11 | Published data | Desideri D *et al* | 1978 | Note préliminaire sur la mise en évidence à Marseille d'une résistance au coumafène chez *Rattus rattus*. | published ata |  |  |  |  |
| B6.1.1 | XXX | XXX | 2010 | CÉREALES + 50 PPM DE DIFENACOUM acute oral toxicity in the rat – acute class method. | Triplan |  |  |  |  |
| B6.1.2 | XXX | XXX | 2010 | CÉREALES + 50 PPM DE DIFENACOUM acute dermal toxicity in the rat. | Triplan |  |  |  |  |
| B6.2.1 | XXX | XXX | 2010 | CÉREALES + 50 PPM DE DIFENACOUM skin irritation test in the rabbit. | Triplan |  |  |  |  |
| B6.2.2 | XXX | XXX | 2010 | CÉREALES + 50PPM DE DIFENACOUM eye irritation test in the rabbit. | Triplan |  |  |  |  |
| B6.3 | XXX | XXX | 2010 | CÉREALES + 50 PPM DE DIFENACOUM Local Lymph Node Assay in the mouse. | Triplan |  |  |  |  |
| B6.4 | XXX | XXX | 2010 | NYNA D+ CEREALES evaluation of skin absorption: in vitro method (non GLP study). | Triplan |  |  |  |  |

* **Renewal application (2017)**

| **Section No** | **Reference No** | **Author** | **Year** | **Title** | **Owner of data** | **Letter of Access** | | **Data protection claimed** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | **Yes** | **No** | **Yes** | **No** |
|  | XXX | XXX | 2016 | Efficacy evaluation of DB25V1 (difenacoum 0,0025% w/w a.i., blue wheat bait – aged formulation) against Norway rat (Rattus norvegicus Berk.) in Italy, XXX | Triplan |  | X | X |  |
|  | XXX | XXX | 2016 | Efficacy evaluation of DB25V1 (difenacoum 0,0025% w/w a.i., blue wheat bait – aged formulation) against Roof rat (Rattus rattus L.) in Italy, XXX | Triplan |  | X | X |  |
|  | XXX | XXX | 2016 | Efficacy evaluation of DB25V1 (difenacoum 0,0025% w/w a.i., blue wheat bait – aged formulation) against House mouse (Mus musculus L.) in Italy, XXX | Triplan |  | X | X |  |
|  | XXX | XXX | 2013 | Sieve test for granular materails and bulk density test on Nyna D+ Avoine, DEFITRACES, Report n° 13-920010-003, 27/08/17. | Triplan |  | X | X |  |
|  | 10-920010-017 | Demangel B | 2013 | Physico-Chemical test and chemical stability after a storage procedure for 2 years at 20 +/- 2°C on Nyna D+ Avoine, DEFITRACES, Report n° 10-920010-07, 18/01/13. | Triplan |  | X | X |  |
|  | 10-920010-016 | Demangel B | 2010 | Physico-Chemical tests before and after an accelerated storage procedure for 14 days at 54 +/- 2°C on Nyna D+ Avoine, DEFITRACES, Report n° 10-920010-016, 02/12/10 | Triplan |  | X | X |  |
|  | 10-920010-015 | Demangel B | 2010 | Physico Chemical tests on Nyna D+ Avoine, DEFITRACES Report n° 10-920010-015, 13/10/10. | Triplan |  | X | X |  |

Annex 2: Analytical methods residues – active substance - PAR 2012

**Difenacoum**

Date: 12/2011

**Matrix, action levels, relevant residue and reference**

|  |  |  |  |
| --- | --- | --- | --- |
| matrix | limit | relevant residue | reference or comment |
| plant products | LOQ= 0.01mg/kg | Difenacoum |  |
| food of animal origin | LOQ= 0.01mg/kg | Difenacoum |  |
| soil | LOQ= 0.0214 μg/g | Difenacoum |  |
| drinking water | LOQ = 0.05 μg/l | Difenacoum |  |
| surface water | LOQ = 0.05 μg/l | Difenacoum |  |
| air | Unnecessary due to the low vapour pressure of difenacoum | | |
| body fluids / tissues | LOQ= 0.01mg/kg | Difenacoum |  |

**Methods suitable for the determination of residues (monitoring methods)**

**Methods for products of plant origin**

| reference | matrix | LOQ (mg/kg) | principle | comment | owner |
| --- | --- | --- | --- | --- | --- |
| Marshall, L., 2009, Method Validation for the Determination of Difenacoum in Animal Matrices (Liver and Muscle) and Crop Matrix (Oilseed Rape), CEM Analytical Services Limited, Study CEMR-4469 | Oil-seed rape | LOQ= 0.01mg/kg | *LC-MS/MS* |  | Activa / PelGar Brodifacoum and Difenacoum Task Force |

**Methods for foodstuffs of animal origin**

| reference | matrix | LOQ (mg/kg) | principle | comment | owner |
| --- | --- | --- | --- | --- | --- |
| Marshall, L., 2009, Method Validation for the Determination of Difenacoum in Animal Matrices (Liver and Muscle) and Crop Matrix (Oilseed Rape), CEM Analytical Services Limited, Study CEMR-4469 | Meat | LOQ= 0.01mg/kg | *LC-MS/MS* |  | Activa / PelGar Brodifacoum and Difenacoum Task Force |

**Methods for soil**

| reference | LOQ (mg/kg) | principle | comment | owner |
| --- | --- | --- | --- | --- |
| Morlacchini, M., 2006, Residues determination of Brodifacoum, Difenacoum and Bromadiolone in soil, CERZOO (Italy), Study CZ/05/002/Activa/Soil | LOQ= 0.0214 μg/g | *HPLC – UV-VIS* |  | Activa / PelGar Brodifacoum and Difenacoum Task Force |

**Methods for sediment**

| reference | LOQ (mg/kg) | principle | comment | owner |
| --- | --- | --- | --- | --- |
| Marshall, L., 2009, Validation of a Method for the Determination of Difenacoum Residues in Sediment, CEM Analytical Services Limited, Study CEMR-4470 | LOQ= 0.01mg/kg | *LC-MS/MS* |  | Activa / PelGar Brodifacoum and Difenacoum Task Force |

**Methods for drinking water and surface water**

| reference | matrix | LOQ (µg/l) | principle | comment | owner |
| --- | --- | --- | --- | --- | --- |
| Martinez M.P. 2005. Difenacoum Technical: Validation of the Analytical Method for the Determination of the Residues in Drinking, Ground and Surface waters, Test Laboratory of ChemService S.r.l. ChemService Study No. CH-288/2005 | Water | LOQ = 0.05 μg/l | *HPLC – MS/MS* |  | Activa / PelGar Brodifacoum and Difenacoum Task Force |

**Methods for air**

| reference | LOQ (µg/m3) | principle | comment | owner |
| --- | --- | --- | --- | --- |
| Unnecessary due to the low vapour pressure of difenacoum | | | | |

**Methods for body fluids/tissue**

| reference | matrix | LOQ (mg/kg) | principle | comment | owner |
| --- | --- | --- | --- | --- | --- |
| Marshall, L., 2009, Method Validation for the Determination of Difenacoum in Animal Matrices (Liver and Muscle) and Crop Matrix (Oilseed Rape), CEM Analytical Services Limited, Study CEMR-4469 | Liver | LOQ= 0.01mg/kg | *LC-MS/MS* |  | Activa / PelGar Brodifacoum and Difenacoum Task Force |

Annex 3a: Efficacy of the Active Substance from its Use in the Product NYNA D+ AVOINE (note that this table has been summarized by the applicant and FR CA had assessed it) – PAR 2012.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Test substance** | **Test organism(s)** | **Test method**  **Test conditions** | **Test results: effects, mode of action, resistance** | **Reference** |
| NYNA D+ BLE  0.005% difenacoum  See composition in CI IIIB2.2 | Albino house mice  (*Mus musculus)*  5 males and 5 females per lot  (3 lots) | Laboratory: CEB n°1  Lot efficacy (no-choice food),  Lot acceptance (free-choice food)  Lot control animals.  Intoxication duration: 3 days with daily measurements of mortality and consumption.  Acclimation: 3 days in individual cage.  Room temperature was 22°C.  D0: food or bait biocidal product have been given:  - Control lot : 10 g per animal of usual food,  - Acceptance lot : 10 g per animal of usual food + 10 g of bait  - Efficacy lot: 10 g per animal of bait  During 3 consecutive days with daily consumption measurements.  Mortality was observed every 24 hours. | The overall average daily consumption within the free-choice food lot has been equal to the control animals’ lot and that the bait has been overwhelmingly preferred to usual food (84% to 90.9% of the overall consumption during 3 days).  This overall daily consumption for the bait alone has been a little bit lower for the lot efficacy than for the controls’ one with a quick induction of the toxic effect.  100% efficacy has been reached from 6 to 9 days (average of 6.9 days) within the lot appetence and from 5 to 9 days (average of 6.4 days) within the lot efficacy.  0% mortality in the control group.  No resistance is observed in this trial | Barbieux S, Grolleau G, 2010, report SB-2010-001  (IIIB5.10.2-01) |
| NYNA D+ BLE  0.005% difenacoum  See above. | Brown rat  (*Rattus norvegicus)* | Field study : CEB n° 2  The used method is relative and allows knowing the bait biocidal product efficacy on a rat population without knowing the precise population size.  After habituation of an isolated wild population of brown rats to their new environment, stations were loaded with 500 g grains (used for pre- and post-baiting phases) and with 500 g baits for poisoning phase.  The daily consumption was measured. | Despite the early stop of pre-baiting stage with not treated wheat by the operator causing a lower assessment of the consumption stage and a second mistake reducing the intoxication duration from 5 days to 3 days, the efficacy was good.   * Pre-baiting stage = 9.067 kg * Post-baiting stage = 2.031 kg * Assessed efficacy = 77.6%   It can be sure that 5 days of intoxication would lead to more than 90% mortality.  The assessed bait has been very well accepted by rats and effective and the results are coherent with laboratory ones.  Although this field study contains experimental flaws, it has been conducted according to the standard, the acceptability and efficacy on *Rattus norvegicus* in field were sufficient and the applicant has recognized his deviations. Thus, FR CA accepts this field study to support the efficacy of the product NYNA D+ AVOINE.  No resistance is observed in this trial | Barbieux S, Grolleau G, 2010, report SB-2010-002  **(**IIIB5.10.2)-02 |
| Wheat in comparison with a blend of 3 cereals (corresponding to the composition of NYNA D+ AVOINE) | Albino house mice  *(Mus musculus)* | Laboratory CEB n°1  Three lots (5 males and 5 females):  - lot control animals receiving usual food  - lot wheat-only  - lot 3-cereals blend  After 10 days of individual cages acclimation, mice have received a daily food quantity of ± 30 g  During 4 days with daily consumption measurement.  The mice have been weighed at D-3, D0 and D+4. | The objective of the study is to compare the acceptance rate of both ingredients by measuring daily food consumption in the 3 lots of animals.  We have seen that:  - Usual food was better consumed than cereals (from 1.5 to 6.5 g average per 100 g mice per days).  - Daily cereals consumptions have been skewed the 4th day (not the usual food), remaining well acceptable and they had no significant acceptance between wheat and hulled oat (despite D+1 where oat is preferred, what is well known).  We can conclude that hulled oat bait is at least equal to wheat one. | Barbieux S, Grolleau G, 2010, report SB-2010-009  (IIIB5.10.2-03) |

* **Renewal application (2017)**

**Annex 3b: Efficacy of the product** **NYNA CEREALES A 25 (0.0025 % w/w difenacoum)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Experimental data on the efficacy of the biocidal product against target organism(s)** | | | | | | | |
| **Function** | **Field of use envisaged** | **Test substance** | **Test organism(s)** | **Test method** | **Test system / concentrations applied / exposure time** | **Test results: effects** | **Reference** |
| Rodenticide | Indoor, outdoor | NYNA CEREALES A 25 (DAV25V1)  Difenacoum 0.0025%  aged formulation (3 years) | Brown rats  *Rattus norvegicus* | Field test  The trial was set up in an agricultural habitat in Piedmont Noth western Italy (breeding stables for chicken, fodder and equipment warehouses) in which rat infestation was signaled by the farmer.  - Method for recording / scoring effects: daily bait take and tracking score during the trial period  The percentage of efficacy of the test product against the rat population was calculated using the following formula:  % efficacy = 100 – [ Post-treatment rat population size index/Pre-treatment rat population size index x 100]  where:  Pre-treatment index: average weight of the bait amounts eaten on the last 4 days of the Pre-treatment census.  Post-treatment index: average weight of the bait amounts eaten on the last 4 days of the Post-treatment census.  - Intervals of examination: every day from 2015-12-27 to 2016-02-12 | Acclimatization: 15 days (200 g of wheat per station per day)  Treatment : 200 g of bait per day in each lockable bait station –total 8 bait stations) during 20 days  Post-baiting: 7 days  (200 g of wheat per station per day) | Estimated efficacy = 100 %.  Pre-baiting plateau = 1135.3 g/day  Post-baiting = 0 g  R.I= 1 | 2007.BCD.SAG16 |
| Rodenticide | Indoor, outdoor | NYNA CEREALES A 25 (DAV25V1)  Difenacoum 0.0025%  aged formulation (3 years) | Black rats  *Rattus rattus* | Field test  The trial was set up in an agricultural habitat in Piedmont North Western Italy (farm with hen stables, fodder and equipment warehouses) in which rats infestation was signaled by the farmer.  - Method for recording / scoring effects: daily bait take and tracking score during the trial period  The percentage of efficacy of the test product against the rat population was calculated using the following formula:  % efficacy = 100 – [ Post-treatment rat population size index/Pre-treatment rat population size index x 100]  where:  Pre-treatment index: average weight of the bait amounts eaten on the last 4 days of the Pre-treatment census.  Post-treatment index: average weight of the bait amounts eaten on the last 4 days of the Post-treatment census.  - Intervals of examination: every day from 2015-12-27 to 2016-02-08 | Acclimatization: 15 days (200 g of wheat per station per day)  Treatment : 200 g of bait per day in each lockable bait station –total 8 bait stations) during 16 days  Post-baiting: 7 days  (200 g of wheat per station per day) | Estimated efficacy = 100 %.  Pre-baiting plateau = 1053.5 g/day  Post-baiting = 0 g  R.I= 1 | 2008.BCD.SAG16 |
| Rodenticide | Indoor, outdoor | NYNA CEREALES A 25  (DAV25V1)  Difenacoum 0.0025%  aged formulation (3 years) | House mice  *Mus musculus* | Field test  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.  - Intervals of examination: every day from 2015-12-27 to 2016-02-10 | Acclimatization: 15 days (40 g of unpoisoned per station per day)  Treatment : 40 g of poisoned test bait in each lockable bait station (total 8 bait stations) during 18 days  Post-baiting: 3 days  (40 g of *census* per station per day) | Estimated efficacy = 100 %  Pre-baiting plateau = 198.8 g/day  Post-baiting = 0 g  R.I=1 | 2009.BCD.SAG16 |

Annex 4: Toxicology and metabolism –active substance – PAR 2012, updated 2017

**Difenacoum**

Threshold Limits and other Values for Human Health Risk Assessment

Date: 12/2011

| **Summary** | | | | | |
| --- | --- | --- | --- | --- | --- |
|  | Value | | Study | SF | |
| AEL long-term | 0.0000011 mg/kg bw/day | | Teratogenicity in rabbit | 600 | |
| AEL medium-term | 0.0000011 mg/kg bw/day | | Teratogenicity in rabbit | 600 | |
| AEL acute | 0.0000011 mg/kg bw/day | | Teratogenicity in rabbit | 600 | |
|  | | | | | |
| Inhalative absorption: 100% | | | | |  |
| Oral absorption: 68 % | | | | |  |
| Dermal absorption: 0.047 % for wax block bait (Activa Pelgar study) – 3 % for pellet and grain baits (Sorex study) | | | | |  |
| **Classification** | | | | | |
| with regard to toxicological data (according to the criteria in Dir. 67/548/EEC) | | Current classification: T+ ; R28, R48/25 - N; R50/53  Proposed classification by the RMS: T+; R26/27/28, Repr. Cat. 1, R61 - T; R48/23/24/25 - N ; R50/53 | | | |
| with regard to toxicological data (according to the criteria in Reg. 1272/2008) | | Current classification: Acute Tox 2, H300; STOT RE 1, H372 ; Aquatic Acute 1, H400; Acute chronic 1, H410 | | | |
|  | | Proposed classification by the RMS: Acute Tox 2, H330, H310, H300; Repr. 1A, H360D; STOT RE 1, H372; Aquatic Acute 1, H400; Acute chronic 1, H410 | | | |

* **Renewal application (2017)**

| **Classification** | |
| --- | --- |
| with regard to toxicological data (according to the criteria in Reg. 1272/2008) | Acute Tox 1 – H300 ; H310 ; H330  STOT RE 1 – H372 (blood)  Repr. 1B – H360D  Repr. 1B; H360D: C ≥ 0,003 % STOT RE 2; H373: 0,002 % ≤ C < 0,02 % STOT RE 1; H372: C ≥ 0,02 % |
|  |  |

Annex 5: Toxicology – biocidal product – PAR 2012, updated 2017

**NYNA D+ AVOINE**

Date: 12/2011

|  |  |
| --- | --- |
| **General information** | |
| Formulation Type: cereal grains |  |
| Active substance(s) (incl. content) : 0.005% difenacoum |  |

| **Acute toxicity, irritancy and skin sensitisation of the preparation (Annex IIIB, point 6.1, 6.2, 6.3)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| Rat LD50 oral (OECD 420) > 2000mg/kg bw | |  | |  |  | |  |
| Rat LD50 dermal (OECD 402) > 2000mg/kg bw | |  | |  |  | |  |
| Rat LC50 inhalation (OECD 403) no study submitted |  | |  |  |  | |
| Skin irritation (OECD 404) non irritant |  | |  |  |  | |
| Eye irritation (OECD 405) non irritant |  | |  |  |  | |
| Skin sensitisation (OECD 429; LLNA) Study submitted but not acceptable |  | |  |  |  | |

Acute toxicity tests:

| Route | Method Guideline | Species Strain Sex no/group | dose levels  duration of exposure | Value LD50/LC50 | Remarks | Reference |
| --- | --- | --- | --- | --- | --- | --- |
| Oral | OECD 423 | Sprague Dawley  6 Females | 2000mg/kg bw | > 2000mg/kg bw | No mortality  Material tested: NYNA D+ BLE old formulation | Richeux F. 2010 |
| Dermal | OECD 402 | Sprague Dawley  5/sex | 2000mg/kg bw | > 2000mg/kg bw | No mortality  Neither cutaneous nor systemic effects  Material tested: NYNA D+ BLE old formulation | Richeux F. 2010 |

Dermal irritation test:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Method | Average score 24, 48 and 72 h | | Reversibility yes/no | Result | Remarks | Reference |
| Erythema | Oedema |
| Albinos NZ rabbit  3 females | OECD 404  Semi-occlusive, 4h | 0 | 0 | na | Not irritant | Material tested: NYNA D+ BLE old formulation | Richeux F. 2010 |

Ocular irritation test:

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Method | Average Score (24h, 48h, 72h) | | | | Result | Reversibility yes/no | Remarks | Reference |
| Cornea | Iris | Redness  Conjunctiva | Chemosis |
| Albinos NZ rabbit  3 Males | OECD 405 | 0 | 0 | 1 | 0.7 | Not irritant | Redness reversible on day 4  Chemosis reversible on day 3 | Material tested: NYNA D+ BLE old formulation | Richeux F. 2010 |

Sensitisation test:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Species** | **Method** | **Result** | **Remark** | **Reference** |
| CBA/J mice  4 females/group | Non radioactive cell counting LLNA: 5, 10, 25% in ethanol/water (7:3) on Day 1, 2, 3. Sacrifice on Day 6 and determination of the proliferation of lymphocytes in the draining auricular lymph nodes by cell counting | SI < 1.4: not sensitiser | Material tested: NYNA D+ BLE old formulation  Not acceptable (method not currently validated) | Richeux F. 2010 |

Dermal penetration study:

| Route | Method Guideline | Species Strain Sex no/group | dose levels  duration of exposure | Result | Remarks | Reference |
| --- | --- | --- | --- | --- | --- | --- |
| Dermal | *In vitro* non-radioactive dermal penetration study (OECD 428) | Sprague Dawley rats  3 females | 0.35 mL of NYNA D+ CEREALES diluted at 50% in distilled water  24h-exposure | Concentration of difenacoum in the receptor fluid < LOQ at 4, 8 and 24 hours post-dose quantification.  Concentration of difenacoum in the skin discs < LOQ | Material tested: NYNA D+ CEREALES  Not acceptable (several deficiencies from OECD guideline) | Richeux F. 2010 |

| **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 |

* **Renewal application (2017)**

|  |  |
| --- | --- |
| **Classification and labelling proposed for the preparation with regard to toxicological properties (Annex IIIB, point 9)** | |
| Regulation 1272/2008/EC | Repr. 1B - H360D  STOT RE 2 - H373 |

Annex 6: Safety for professional operators – PAR 2012, updated 2013

**NYNA D+ AVOINE**

Date: 12/2011

**Exposure assessment**

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

Primary exposure of professionals – NYNA D+ AVOINE in bulk (exposure during decanting, loading and cleaning considered) – Control of rats

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Component** | **CAS** | **Potential Dermal Total**  **[mg/kg/d]** | **Actual Dermal Total**  **[mg/kg/d]** | **Inhalation Exposure**  **[mg/m³]** | **Model** |
| Tier 1 (without PPE) | Difenacoum | 56073-07-5 | 3.4x10-5 | 3.4x10-5 | 2.5x10-6 | Cefic study |
| Tier 2 a (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 3.4x10-5 | 3.4x10-6 | 2.5x10-6 | Cefic study |
| Tier 2 b (gloves penetration factor: 5%) | Difenacoum | 56073-07-5 | 3.4x10-5 | 1.7x10-6 | 2.5x10-6 | Cefic study |

Primary exposure of professionals – NYNA D+ BLE in bulk (exposure during decanting, loading and cleaning considered) – Control of mice

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Component** | **CAS** | **Potential Dermal Total**  **[mg/kg/d]** | **Actual Dermal Total**  **[mg/kg/d]** | **Inhalation Exposure**  **[mg/m³]** | **Model** |
| Tier 1 (without PPE) | Difenacoum | 56073-07-5 | 2.3x10-5 | 2.3x10-5 | 5.0x10-7 | Cefic study |
| Tier 2 a (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 2.3x10-5 | 2.3x10-6 | 5.0x10-7 | Cefic study |
| Tier 2 b (gloves penetration factor: 5%) | Difenacoum | 56073-07-5 | 2.3x10-5 | 1.1x10-6 | 5.0x10-7 | Cefic study |

Primary exposure of professionals – NYNA D+ BLE in sachet (exposure only during cleaning) – Control of rats and mice

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Component** | **CAS** | **Potential Dermal Total**  **[mg/kg/d]** | **Actual Dermal Total**  **[mg/kg/d]** | **Inhalation Exposure**  **[mg/m³]** | **Model** |
| Tier 1 (without PPE) | Difenacoum | 56073-07-5 | 5.1x10-6 | 5.1x10-6 | Not applicable | Cefic study |
| Tier 2 (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 5.1x10-6 | 5.1x10-7 | Not applicable | Cefic study |

Risk assessment – Control of rats

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **Component** | **CAS** | **AEL [mg/kg/d]** | **Absorption**  **[%]** | | **Total syst exposure**  **[mg/kg bw/d]** | | Risk |
|  |  |  |  | inh | derm | Expo | %AEL |  |
| NYNA D+ BLE in bulk | | | | | | | | |
| Professional  (without gloves) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 3.7x10-5 | 3324 | Unacceptable |
| Professional  (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 5.9x10-6 | 537 | Unacceptable |
| Professional  (gloves penetration factor: 5%) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 4.2x10-6 | 382 | Unacceptable |
| NYNA D+ BLE in sachet | | | | | | | | |
| Professional  (without gloves) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 5.1x10-6 | 459 | Unacceptable |
| Professional  (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 5.1x10-7 | 46 | Acceptable |

Risk assessment – Control of mice

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **Component** | **CAS** | **AEL [mg/kg/d]** | **Absorption**  **[%]** | | **Total syst exposure**  **[mg/kg bw/d]** | | Risk |
|  |  |  |  | inh | derm | Expo | %AEL |  |
| NYNA D+ BLE in bulk | | | | | | | | |
| Professional  (without gloves) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 2.3x10-5 | 2070 | Unacceptable |
| Professional  (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 2.7x10-6 | 248 | Unacceptable |
| Professional  (gloves penetration factor: 5%) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 1.6x10-6 | 147 | Unacceptable |
| NYNA D+ BLE in sachet | | | | | | | | |
| Professional  (without gloves) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 5.1x10-6 | 459 | Unacceptable |
| Professional  (gloves penetration factor: 10%) | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 5.1x10-7 | 46 | Acceptable |

* **Assessment of new uses’ addition (2013)**

NYNA D+ BLE / NYNA D+ AVOINE / NYNA D+ CEREALES

Date: 07.03.2013

Exposure assessment

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

Primary exposure of professionals

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Component | CAS | Actual Dermal Total  [mg/kg/d] | Inhalation Exposure  [mg/kg/d] | Model |
| Bulk | | | | | |
| Tier 1:  Without PPE | Difenacoum | 56073-07-5 | 2.2 x 10-6 | 2.5 x 10-6 | CEFIC study |
| Tier 2:  With respiratory protection and gloves | Difenacoum | 56073-07-5 | 2.2 x 10-7 | 2.5 x 10-7 | CEFIC study |
| Sachet | | | | | |
| Tier 1:  Without PPE | Difenacoum | 56073-07-5 | 3.3 x 10-7 | na | CEFIC study |

Risk assessment

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Component | CAS | AEL [mg/kg/d] | Absorption [%] | | Inhal  [mg/kg/d] | Derm  [mg/kg/d] | Total syst exposure  [mg/kg bw/d] | % AEL | Risk |
|  |  |  |  | inhalation | dermal |  |  |  |  |  |
| Bulk | | | | | | | | | | |
| Tier 1:  Without PPE | Difenacoum | 56073-07-5 | 1.1 x 10-6 | 100 | 0.647 | 2.5 x 10-6 | 2.2 x 10-6 | 4.7 x 10-6 | 428 | Unacceptable |
| Tier 2:  With respiratory protection and gloves | Difenacoum | 56073-07-5 | 1.1 x 10-6 | 100 | 0.647 | 2.5 x 10-7 | 2.2 x 10-7 | 4.7 x 10-7 | 42.8 | Acceptable |
| Sachet | | | | | | | | | | |
| Tier 1:  Without PPE | Difenacoum | 56073-07-5 | 1.1 x 10-6 | 100 | 0.647 | na | 3.3 x 10-7 | 3.3 x 10-7 | 29.7 | Acceptable |

* **Renewal application (2017)**

The conclusions of the risk assessment remain unchanged. The RMMs required by the risk assessment remain also unchanged.

Annex 7: Safety for non-professional operators and the general public – PAR 2012, updated 2013

**NYNA D+ AVOINE**

Date: 12/2011

| **General information** | |
| --- | --- |
| Formulation Type: Cereal grain |  |
| Active substance(s) (incl. content): Difenacoum (0.005%) |  |

| **Difenacoum** |
| --- |

| **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: non-professional use |  |
| Secondary exposure, acute: child ingesting bait |  |
| Secondary exposure, chronic: none |  |

Conclusion:

Exposure of non-professional users to the biocidal product containing difenacoum as active substance is considered unacceptable.

The accidental ingestion of baits poses a risk to infants since the AEL is exceeded when infant ingests more than 0.3 mg of product per day.

Details for the exposure estimates:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **Component** | **CAS** | **Potential Dermal Total**  **[mg/kg/d]** | **Actual Dermal Total**  **[mg/kg/d]** | **Inhalation Exposure**  **[mg/m³]** | **Model** |
| Control of rats and mice - Sachet considered (exposure only during cleaning) | | | | | | |
| Non professional | Difenacoum | 56073-07-5 | 1.9x10-6 | 1.9x10-6 | na | Cefic study |

Risk assessment

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **Component** | **CAS** | **AEL [mg/kg/d]** | **Absorption**  **[%]** | | **Total syst exposure**  **[mg/kg bw/d] [mg/m3]** | | **Risk** |
|  |  |  |  | inh | derm | Expo | %AEL |  |
| Control of rats and mice - Sachet considered (exposure only during cleaning) | | | | | | | | |
| Non-professional | Difenacoum | 56073-07-5 | 1.1x10-6 | 100 | 10 | 1.9x10-6 | 171 | Unacceptable |

* **Assessment of new uses’ addition (2013)**

NYNA D+ BLE / NYNA D+ AVOINE / NYNA D+ CEREALES

Date: 07.03.2013

| General information | |
| --- | --- |
| Formulation Type |  |
| Active substance(s) (incl. content) |  |
| Category |  |
| Authorisation number |  |

| <Difenacoum > |
| --- |

| 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 | Non professional use |
| Secondary exposure, acute | Infant ingesting bait |
| Secondary exposure, chronic | None |

Conclusion:

Exposure of non-professionals to the biocidal product containing difenacoum as active substance is considered acceptable, if the biocidal product is used as intended and all safety advices are followed.

The accidental ingestion of baits poses a risk to infants since the AEL is exceeded when infant ingests more than 0.3 mg of product per day.

Details for the exposure estimates:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Component | CAS | Actual Dermal Total  [mg/kg/d] | Inhalation Exposure  [mg/m³] | Model |
| Without PPE | Difenacoum | 56073-07-5 | 1.2 x 10-8 | na | CEFIC study |

Risk assessment

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Component | CAS | AEL [mg/kg/d] | Absorption [%] | | Total syst exposure  [mg/kg bw/d] | % AEL | Risk |
|  |  |  | inhalation | dermal |  |  |  |
| Difenacoum | 56073-07-5 | 1.1 x 10-6 | 100 | 0.647 | 1.2 x 10-8 | 11.1 | Acceptable |

* **Renewal application (2017)**

General public uses are no longer claimed for the renewal of authorisation.

Annex 8: Residue behaviour – PAR 2012

**Difenacoum**

Date: 12/2011

Intended Use (critical application): Control of mice and rats

Active substance(s): Difenacoum

Formulation of biocidal product: Cereal grains

Place of treatment: inside building (domestic industrial and farm)

The product is a solid bait only used inside buildings in secured bait points. Collecting unconsumed baits and dead rodents must be done every week during the treatment so in these recommended conditions, no contamination is expected for feeding stuffs. Finally, according to the Assessment report on difenacoum, “*difenacoum baits should not be placed where food, feedingstuffs or drinking water could be contaminated*”.

The intended use descriptions of the difenacoum-containing biocidal products for which authorisation is sought indicate that these uses are not relevant in terms of residues in food and feed. No further data are required concerning the residue behaviour.

1. Applies only to existing authorisations [↑](#footnote-ref-1)
2. Please insert additional columns as necessary [↑](#footnote-ref-2)
3. Please insert additional columns as necessary [↑](#footnote-ref-3)
4. Technical guidance document in support of the directive 98/8/ec concerning the placing of biocidal products on the market - Guidance on data requirements for active substances and biocidal products, October 2000. [↑](#footnote-ref-4)
5. Guidance on the Biocidal Products Regulation Volume III Human Health – Part B Risk Assessment, October 2015. [↑](#footnote-ref-5)
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. [↑](#footnote-ref-6)
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. [↑](#footnote-ref-7)
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 [↑](#footnote-ref-8)
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. [↑](#footnote-ref-9)
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 [↑](#footnote-ref-10)
11. An evaluation of performance standards and non-radioactive endpoints for the LLNA – The report and recommendations of ECVAM Workshop 65 (2008) [↑](#footnote-ref-11)
12. HEEG opinion on harmonising the number of manipulations in the assessment of rodenticides (anticoagulant), agreed at TMII2010 [↑](#footnote-ref-12)
13. See document CA-Nov16-Doc.4.x-Final on the concept of tamper-resistant bait stations. [↑](#footnote-ref-13)
14. See document CA-Nov16-Doc.4.x-Final on the concept of tamper-resistant bait stations. [↑](#footnote-ref-14)
15. Data which have not been already submitted for the purpose of the Annex I inclusion. [↑](#footnote-ref-15)