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 THE RENEWAL OF A NATIONAL AUTHORISATION

Product identifier in R4BP	RAVIOX L
Product type(s):	14 (Rodenticide)
Active ingredient(s):	DIFENACOUM
Case No. in R4BP	BC-CW000083-40 (NA-RNL) BC-NW030712-18 (NA-ADC)
Asset No. in R4BP	ES-0000165-0000
Evaluating Competent Authority	SPAIN
Internal registration/file no	ES/APP(NA)-2018-14-00100
Date	April 2018

Table of content

1 Conclusion

The assessment presented in this report has shown that the ready-to-use product, RAVIOX L, with the active substance difenacoum, at a level of 0.005% w/w, may be authorised for use as a rodenticide (product-type 14) since the conclusions of initial evaluation remain valid.

However, the biocidal product RAVIOX L contains 0.005 %w/w difenacoum and the Commission Regulation (EU) 2016/1179 of 19 July 2016 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures has been applied.

Due to national legislation in relation to categories of users which three categories of users are established (general public, professional and trained professional user) based on the qualification obtained, therefore the professional is extrapolated to the general public (under this national regulation the professional user is not bounded to use PPE when they apply the product). For that, the biocidal product rodenticides containing 0.005 %w/w difenacoum only can be authorised by trained professional user because of the toxicological classification the use of PPE are mandatory. Given that, this legislation is national and in other Member States legislation could be different, each Competent Authority should consider that in order to grant the authorisation.

RAVIOX L is identical to RATONEX LIQUIDO. The applicant is the same and the data and the criteria in the evaluation of RATONEX LIQUIDO has been used in the evaluation of this biocidal product.

Physical, chemical and technical properties remain valid to the initial evaluation other than the low temperature stability test. This test has been submitted and the results fulfil the Guidance criteria.

The conclusions about physical hazards and methods for detection and identification remain valid to the initial evaluation and no new information has been submitted.

The conclusion from the former assessment regarding efficacy against target organisms remains valid.

According to Commission Regulation (EU) 2016/1179 the product RAVIOX L, with the active substance difenacoum, at a level of 0.005% w/w is classified as REPRODUCTIVE TOXICITY CATEGORY 1B ; H360D and SPECIFIC TARGET ORGAN TOXICITY AFTER REPEATED EXPOSURE. CATEGORY 2 (STOT RE 2); H373 May cause damage to organs (blood) through prolonged or repeated exposure.

Concerning dermal absorption, no study was submitted at renewal of this product. In the initial evaluation for authorisation of RAVIOX L concluded, a default value of 10% was appropriate. But, an in vitro study has been submitted for RATONEX LIQUIDO, according to OECD TG 428. The study has been conducted as a multisite study where the analysis of biological samples generated in the absorption study phase has been delegated to an external GLP Certified Laboratory by LC-MSMS with the internally GLP validated analytical method. ES CA accepts a read across because it is an identical formulation.

The difenacoum content was quantified in the receptor fluid after 2h, 4h, 6h and 24h, in the residual quantity of product on skin surface, in the Stratum Corneum, and in the dermal homogenates and epidermal homogenates. Based on the analytical data the total mass balance was calculated. The values of difenacoum total mass balance on 3 skin explants calculated meet the reference acceptance criteria of ENV/JM/MONO (2011)36 which contains the same recommendations of OECD TG 428 with a caveat that for test substances unlabelled a range of 80-120% is acceptable.
In conclusion, the results of the study lead to an absorbed dose of 0.04%, an absorbable dose of 53.95% and a tape stripping content of 2.56%. This gives a total dermal absorption of 56.55%

The conclusion for the first risk assessment for the environment remains valid.

Therefore, RAVIOX L can be authorised as a rodenticide product against house mice (*Mus musculus*) and brown rats (*Rattus norvegicus*). It is to be used indoors, outdoors around buildings and outdoor in open areas and waste dumps. The users can be trained professional. The product must be supplied in non-refillable bottles with a safety childproof cap.

The specific intended uses of the product are in section 2.4. of this assessment report.

Please, note that this assessment report includes all the uses requested by the applicant and assessed by ES CA, only as information for the concerned Member States.

Spanish CA only grants the use of RAVIOX L according to the Decision about liquid rodenticide (2016/1174) in this assessment report.

2 Summary of the product assessment

2.1 Administrative information

2.1.1 Identifier in R4BP

RAVIOX L

2.1.2 Manufacturer(s) of the product

Name of manufacturer	WILL KILL, S.A.
Address of manufacturer	C/4 de Noviembre, 6
Location of manufacturing sites	07011 – Palma de Mallorca, España

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

Active substance	DIFENACOUM
Name of manufacturer	ACTIVA S.r.l. / Dr. TEZZA S.r.l.
Address of manufacturer	ACTIVA S.r.l. Via Feltre, 32 20132 – Milano - ITALY
Location of manufacturing sites	Dr. TEZZA S.r.l. Via Tre Ponti, 22 37050 – S. Maria di Zevio (VR) ITALY

2.2 Composition and formulation

2.2.1. Qualitative and quantitative information on the composition

Table 1

Common name	IUPAC name	Function	CAS number	EC number	Content (%)

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
-	-	Non-active substance	-	-	-

- The product contains a bittering agent and a dye.

Information on the full composition is provided in the confidential annex

- According to the information provided the product contains no nanomaterial as defined in Article 3 paragraph 1 (z) of Regulation No. 528/2012

2.2.1 Information on the substance(s) of concern

No substance of concern was identified upon initial assessment (the application for authorisation was submitted and the assessment took place before the Biocidal Products Regulation 528/2012 entered into force).

2.2.2 Candidate(s) for substitution

No candidate for substitution was identified upon initial assessment (the application for authorisation was submitted and the assessment took place before the Biocidal Products Regulation 528/2012 entered into force).

Now that the Biocidal Products Regulation 528/2012 entered into force, the following substance(s) was/were identified as candidate(s) for substitution upon this renewal:

Difenacoum does meet the exclusion criteria according to Article 5(1) BPR. Because the following exclusion criteria are met:

- toxic for reproduction category 1B
- persistent and very persistent, bioaccumulative and toxic

And therefore, difenacoum does meet the conditions laid down in Article 10 BPR, and is consequently a candidate for substitution.

2.2.3 Type of formulation

Ready-to-use bait: Liquid

2.3 Classification and Labelling according to the Regulation (EC) No 1272/2008

Table 2

Classification **Hazard classes, Hazard categories**	**Hazard statements**
Reproductive toxicity; Repr. 1B	H360D May damage the unborn child
Specific target organ toxicity after repeated exposure. Category 2	H373 May causes damage to organs (blood) through prolonged or repeated exposure

Table 3

Labelling	**Code**	**Pictogram / Wording**
Pictograms	GHS08	
Signal word	-	Danger
Hazard statements	H360D	May damage the unborn child
	H373	May causes damage to organs (blood) through prolonged or repeated exposure
Supplemental hazard information	-	-
Supplemental label elements	-	
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 vapours.
	P280	Wear protective gloves/ protective clothing/eye protection/face protection
	P314	Get medical advice/attention if you feel unwell.
	P405	Store locked up.
	P501	Dispose of contents and/ or container as a hazardous waste to a registered establishment or undertaking, in accordance with current regulations.
Note	-	

2.4 Use(s) appropriate for <u>further</u> authorisation

In order to make proper use of the standard sentences for SPCs for rodenticides it is considered necessary to split the uses currently evaluated in Spain further down:

Table 4

Use(s) considered appropriate for authorisation after former assessment (uses currently <u>evaluated in SPAIN</u>		**Use(s) appropriate for further authorisation**	
1	House mice and/or brown rats – trained professionals – indoor, outdoor around buildings, outdoor open areas & waste dumps	1	House mice and/or brown rats – trained professionals - indoor
		2	House mice and/or brown rats – trained professionals – outdoor around buildings
		3	Brown Rats – trained professionals – outdoor open areas & waste dumps

2.4.1 Use 1 - House mice and/or brown rats – trained professionals – indoor

Product Type(s)	14
Where relevant, an exact description of the use	Not relevant for rodenticides
Target organism(s) (including development stage)	*Mus* musculus (house mice) *Rattus norvegicus* (brown rats)
Field(s) of use	Indoor
Application method(s)	The product must be supplied in non-refillable bottles with a safety childproof cap. The bottles will be opened by removing the stopper and, without breaking the membrane; the roll-on dispenser will be placed. Once inverted this device must always be placed in a tamper-resistant bait station correctly labelled.
Application rate(s) and frequency	**Rats:** bait station with a maximum of 250ml of product placed each 5-10m depending on the level of infestation. **Mice**: bait station with a maximum of 100ml of product placed each 2-5m, depending on the level of infestation.
Category(ies) of users	Trained professionals
Pack sizes and packaging material	Millilitres/Litres of bait per packed bag: Non-reusable set of 100ml or 250ml Packaging material: Bottles with a childproof cap and sealed with a membrane, roll-on dispenser with safety cap and a base. Material: HDPE

2.4.1.1 Use-specific instructions for use

- Remove the remaining product at the end of treatment period.

- Follow any additional instructions provided by the relevant code of best practice.

2.4.1.2 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

- 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.

- This product shall only be used indoors and in places that are not accessible to children or non-target animals.

2.4.1.3 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.

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

-See section 2.5.4.

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

-See section 2.5.5.

2.4.2 Use 2 – House mice and/or brown rats – trained professionals – outdoor around buildings

Product Type(s)	14
Where relevant, an exact description of the use	Not relevant for rodenticides
Target organism(s) (including development stage)	*Mus musculus* (house mice) *Rattus norvegicus* (brown rats)
Field(s) of use	Outdoor around buildings
Application method(s)	The product must be supplied in non-refillable bottles with a safety childproof cap. The bottles will be opened by removing the stopper and, without breaking the membrane; the roll-on dispenser will be placed. Once inverted this device must always be placed in a tamper-resistant bait station correctly labelled.
Application rate(s) and frequency	**Rats:** bait station with a maximum of 250ml of product placed each 5-10m depending on the level of infestation. **Mice**: bait station with a maximum of 100ml of product placed each 2-5m, depending on the level of infestation.
Category(ies) of users	Trained professionals
Pack sizes and packaging material	Millilitres/Litres of bait per packed bag: Non-reusable set of 100ml or 250ml Packaging material: Bottles with a childproof cap and sealed with a membrane, roll-on dispenser with safety cap and a base Material: HDPE

2.4.2.1 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.
- Follow any additional instructions provided by the relevant code of best practice.

2.4.2.2 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.
- 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.

2.4.2.3 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.

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

-See section 2.5.4

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

See section 2.5.5

2.4.3 Use 3 – Brown Rats – trained professionals – Outdoor open areas & waste dumps

Product Type(s)	14
Where relevant, an exact description of the use	Not relevant for rodenticides
Target organism(s) (including development stage)	*Rattus norvegicus* (brown rats)
Field(s) of use	Outdoor open areas Outdoor waste dumps
Application method(s)	The product must be supplied in non-refillable bottles with a safety childproof cap. The bottles will be opened by removing the stopper and, without breaking the membrane; the roll-on dispenser will be placed. Once inverted this device must always be placed in a tamper-resistant bait station correctly labelled.
Application rate(s) and frequency	**Rats:** bait station with a maximum of 250ml of product placed each 5-10m depending on the level of infestation.
Category(ies) of users	Trained professionals
Pack sizes and packaging material	Millilitres/Litres of bait per packed bag: Non-reusable set of 100ml or 250ml Packaging material: Bottles with a childproof cap and sealed with a membrane, roll-on dispenser with safety cap and a base

	Material: HDPE

2.4.3.1 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

-Follow any additional instructions provided by the relevant code of best practice.

2.4.3.2 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

- 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.

2.4.3.3 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.

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

See section 2.5.4

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

See section 2.5.5

2.5 General directions for use

2.5.1. Instructions for use

- 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 2.5.3 for the information to be shown on the label)*.

-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.

- 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.

- Fix the bait station to the ground.

- In case of accidental spillage of the liquid, dispose of the bait station as hazardous waste.

2.5.2 Risk mitigation measures:

- Where possible, prior to the treatment inform any possible bystanders about the rodent control campaign

- 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").

- 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

- 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]*.

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

- 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, always check for and remove contact lenses, 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.

2.5.4 Instructions for safe disposal of the product and its packaging

- At the end of the treatment, dispose 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*.
-Use for gloves is recommended

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

- 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: two years

2.5.6. Other information

- Because of their delayed mode of action, anticoagulant rodenticides take from 4 to 10 days to be effective after 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.

3 Assessment of the product

3.1 Use(s) considered appropriate for authorisation after former assessment (uses evaluated in Spain)

3.1.1 Use 1 – Brown rats and mice - Trained professional users – in and around (private, public and farm buildings), transports and outdoors (waste dumps/landfill sites and open areas)

Product Type(s)	14
Where relevant, an exact description of the use	Not relevant for rodenticides
Target organism(s) (including development stage)	*Mus musculus* (house mice) *Rattus norvegicus* (brown rats)
Field(s) of use	Trained professional use, indoors (inside private, public and farm buildings), in and around (private, public and farm buildings), transports and outdoors (waste dumps/landfill sites and open areas) into labelled tamper-resistant bait stations. Indoor use is considered inside industrial, commercial and residential buildings, parking lots and fixed or mobile closed installations. In and around use is considered, along the perimeter of buildings or installations, (not exceeding a maximum distance of 0.5 meters between the bait and the building/installation). Car parks that do not fall within the definition of interior or open areas, open bus or train stations, or port areas would also be included. Open areas use is considered that is carried out in areas such as parks, golf courses, open parking and the surrounding of crop fields, stations or port areas. Use in transports is considered that is carried out into the own transport (goods and/or people) and never outside of vehicles or in open vehicles.
Application method(s)	The sealed non-reusable bottles only will be opened when inserting the bottle into a roll-on dispenser within an additional small trough placed inside the bait station. This device must always be placed in a tamper-resistant bait station correctly labelled.
Application rate(s) and frequency	**Rats:** bait station with a maximum of 250ml of product placed each 5-10m depending on the level of infestation. **Mice**: bait station with a maximum of 100ml of product placed each 2-5m, depending on the level of infestation.
Category(ies) of users	Trained professionals
Pack sizes and packaging material	Millilitres/Litres of bait per packed bag: Non-reusable set of 100ml or 250ml Packaging material: Bottles with a childproof cap and sealed with a membrane, roll-on dispenser with safety cap and a base Material: HDPE

3.2 Physical, chemical and technical properties

Property	Guideline and Method	Purity of the test substance (% (w/w)	Results	Reference
Storage stability test – **low temperature**	CIPAC MT 39.3	0.0027	After being stored 7 days inside the refrigerator at 0°C±2°C, the sample remains unchanged, does not generate solid or oily material after storage	IUCLID 3.4

Apart from the properties mentioned above, neither new data was not provided nor had new guidance to be taken into account for re-assessment.
Accordingly, the conclusion from the former assessment regarding those physical, chemical and technical properties not provided remains valid.

3.3 Physical hazards and respective characteristics

Neither new data was not provided nor had new guidance to be taken into account for re-assessment.
Accordingly, the conclusion from the former assessment regarding physical hazards and respective characteristics remains valid.

3.4 Methods for detection and identification

Neither new data was not provided nor had new guidance to be taken into account for re-assessment.
Accordingly, the conclusion from the former assessment regarding methods for detection and identification remains valid.

3.5 Efficacy against target organisms

Neither new data was not provided nor had new guidance to be taken into account for re-assessment.
Accordingly, the conclusion from the former assessment regarding efficacy against target organisms remains valid.

3.6 Risk assessment for human health

3.6.1 Assessment of effects of the active substance on human health

Neither new data was not provided nor had new guidance to be taken into account for re-assessment. Accordingly, the conclusion from the former assessment regarding effects of the active substance on human health remains valid.

3.6.2 Assessment of effects of the product on human health

Neither new data was not provided nor had new guidance to be taken into account for re-assessment. Accordingly, the conclusion from the former assessment regarding effects of the product on human health remains valid.

Dermal absorption

Concerning dermal absorption, no study was submitted at renewal of RAVIOX L. In the initial evaluation for authorisation of RAVIOX L concluded, a default value of 10% was appropriate. But, an *in vitro* study has been submitted for RATONEX LIQUIDO, according to OECD TG 428. The study has been conducted as a multisite study where the analysis of biological samples generated in the absorption study phase has been delegated to an external GLP Certified Laboratory by LC-MSMS with the internally GLP validated analytical method. ES CA accepts a read across because it is an identical formulation.

The difenacoum content was quantified in the receptor fluid after 2h, 4h, 6h and 24h, in the residual quantity of product on skin surface, in the Stratum Corneum, and in the dermal homogenates and epidermal homogenates. Based on the analytical data the total mass balance was calculated. The values of difenacoum total mass balance on 3 skin explants calculated meet the reference acceptance criteria of ENV/JM/MONO (2011)36 which contains the same recommendations of OECD TG 428 with a caveat that for test substances unlabelled a range of 80-120% is acceptable.

In conclusion, the results of the study lead to an absorbed dose of 0.04%, an absorbable dose of 53.95% and a tape stripping content of 2.56%. This gives a total dermal absorption of **56.55%**

3.6.3 Exposure assessment

Regarding human exposure no studies have been submitted. However, special risk mitigation measures that could avoid any kind of exposure have been proposed. Firstly, rodenticide bait is placed inside a tamper-resistant bait station correctly labelled. Secondly, additional risk mitigation measures for liquid rodenticides, consisting on sealed bottles of 100ml and 250ml for trained professionals and that are

applied only when inserting the bottle into a roll-on dispenser within an additional small base placed inside the bait station. For additional detailed description of this device, please see the sections 2.4 (Uses appropriate for further authorisation) and 2.5 (General directions for use).. Trained professional users can use the product indoor, outdoor and around (maximum:- 0.5m) buildings and also outdoor open areas & waste dumps as described in Section 2.4.

With these risk mitigation measures the exposure is negligible, and thus there is no risk for human health, because the roll on device is an appropriate risk mitigation measure that does prevent from any spillage and any contact of humans and animals.

However, in terms of completeness of the assessment, we have estimated the human exposure for a hypothetical situation where there would be any accidental exposure to the liquid, due to a misuse of the product, for example, considering a worst case scenario where:

- Leaks from the roll-on could give splashes. According to the Technical Notes for Guidance (TNsG) on Human Exposure to Biocidal Products (2007), the US-EPQA has estimated the exposure from splashes during mixing and application to be about 6 ml/event to the bare hand. In order to better define the number of splashes, the applicant has carried out a simulation test in the presence of a notary who has stated the veracity of the result. This test intends to simulate the application of the product, and it has been shown that after 50 manipulations (25 loadings and 25 cleanings), 44 manipulations did not show any splash, and 3 manipulations produced 6 splashes. Thismeans 6 splashes / 50 manipulations = 0.12 splash / manipulation.

- The size of a splash is $33.5x10^{-3}$ ml, as a worse case, according to an experimental determination, provided by the applicant, Ref B0309-092 This gives an amount of exposure of:

0.12 splash/manipulation x $33.5x10^{-3}$ ml/splash = $4.02x10^{-3}$ ml/manipulation

- The dermal absorption of the product is 56.55%; according to the study submitted by the applicant.

As the paper "HEEG opinion on a harmonised approach for the assessment of rodenticides (anticoagulants)" agreed at TMII 2011 and based on an operator exposure study conducted by CEFIC/EBPF Rodenticides Data Development Group (Chambers et al. (2004)) does not include information on liquid baits, the number of manipulations for this liquid rodenticide has been proposed by the applicant, according to information gathered from the market. After a survey among the applicators of this product, it was concluded that each operator applied two bottles a week at maximum. As a worse case, calculation will be done assuming 1 loading during application and 1 cleaning event during post application every day.

- The density of the product is the indicated by the applicant, 1.0161g/ml.

Identification of main paths of human exposure towards active substance(s) and substances of concern from its use in biocidal product

The most relevant routes of exposure are the following:

Summary table: relevant paths of human exposure			
Exposure path	**Primary (direct) exposure**	**Secondary (indirect) exposure**	
	Trained professional use	**Trained professional use**	**General public**
Inhalation	Not relevant	No	No
Dermal	Potentially significant	No	Potentially significant
Oral	Negligible	No	Relevant

The primary route of exposure to the active substance from formulation and use of the biocidal product will be the dermal route, confined to the hands only. Inhalation exposure to the active substance during manufacture and use in the biocidal product is unlikely due to the low vapour pressure of the active substance.

The secondary route of exposure will be potentially dermal and the oral route as the most relevant route.

List of scenarios

Summary table: scenarios			
Scenario number	**Scenario** (e.g. mixing/ loading)	**Primary or secondary exposure** **Description of scenario**	**Exposed group** (e.g. professionals, non-professionals, bystanders)
1.	Loading and placing bait boxes	Primary exposure. During use, professional operators will be exposed through the loading of bait stations with the RTU bottle and application of the bait. Exposure will be via the dermal route and to the hands only.	Trained professional users
2.	Cleaning	Primary exposure. During disposal, professional pest control operators will be exposed through the disposal of used bait and carcasses. Exposure will be via dermal route and to the hands only.	Trained professional users

Summary table: scenarios			
3.	Touching and mouthing unprotected bait	Secondary exposure: accidentaly touched of unprotected bait. Indirect exposure, especially of children may happen.	Bystanders (children, infants and adults)

Trained professional exposure

The following points have been taken into consideration for the assessment of the potential exposure of trained professional users to "RAVIOX L":

1. "RAVIOX L" is supplied in sealed bottles of 100 ml and 250 ml for use only by trained professional users.
2. As no human exposure studies have been submitted, the exposure assessment has been performed considering the exposure from splashes during application to be about 4.02 x 10^{-3} ml/manipulation to the hand.
3. The product is ready to use, then, there is no mixing and loading task. The number of contacts is considered critical rather than the size of the bait. Therefore, as a worse-case, the total daily exposure frequency is assumed to be 2 manipulations, for the placing of the equivalent to 200g bait (maximum dose for rats) on 1 sites and the cleaning of 1 bait sites.
4. Although it could be assumed that professional users wear protective gloves when handling the products, an exposure scenario without personal protective equipment is also included as a worst case. Gloves are assumed to reduce the exposure of hands by 90%.
5. It is assumed that 100% of inhalation exposure is absorbed. Concerning dermal absorption, a study is submitted for this RATONEX LIQUIDO, with a value of 56.55%.
6. Operator body weight is assumed to be 60 kg.

Trained professionals (Pest control operators)

Scenario [1] – Loading and placing bait boxes

Description of Scenario [1] - *Trained professional*		
During the process of loading the bait, the operator may be exposed by dermal contact to the bait. Trained professional users are bounded to use PPE during the development of the different tasks of their work. Total systemic exposure has been assessed without (Tier 1) and with PPE (Tier 2).		
	Parameters	Value

Description of Scenario [1] - *Trained professional*		
Tier 1	A.S. content of BP	0.005%
	Dermal absorption:	56,55%
	Operator body weight:	60 kg
	Amount of exposure to product during loading:	$4{,}02 \times 10^{-3}$ ml/manipulation
	Density:	1,0161 g/ml
	Number of manipulations during loading:	1
Tier 2	PPE (gloves)	10%

Calculations for Scenario [1]

Summary table: estimated exposure from trained professional uses					
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated oral uptake**	**Estimated total uptake**
Scenario [1]	Tier 1 / No PPE	-	1.92×10^{-6} mg/kg bw/day	-	1.92×10^{-6} mg/kg bw/day
Scenario [1]	Tier 2 / PPE(gloves)	-	1.92×10^{-7} mg/kg bw/day	-	1.92×10^{-7} mg/kg bw/day

Scenario [2] – Cleaning

Description of Scenario [2] - *Trained professional*		
During the process of cleaning the bait, the operator may be exposed by dermal contact to the bait. Trained professional users are bounded to use PPE during the development of the different tasks of his work. The total systemic exposure has been assessed without (Tier 1) and with PPE (Tier 2).		
	Parameters	Value
Tier 1	A.S. content of BP	0.005%
	Dermal absorption:	56,55%
	Operator body weight:	60 kg
	Amount of exposure to product during loading:	$4{,}02 \times 10^{-3}$ ml/manipulation
	Density:	1,0161 g/ml
	Number of manipulations during cleaning:	1
Tier 2	PPE (gloves)	10%

Calculations for Scenario [2]

Summary table: estimated exposure from trained professional uses					
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated oral uptake**	**Estimated total uptake**
Scenario [2]	Tier 1 / No PPE	-	1.92×10^{-6} mg/kg bw/day	-	1.92×10^{-6} mg/kg bw/day
Scenario [2]	Tier 2 / PPE (gloves)	-	1.92×10^{-7} mg/kg bw/day	-	1.92×10^{-7} mg/kg bw/day

Combined scenarios for professional users

Summary table: combined systemic exposure from Trained professional uses					
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated oral uptake**	**Estimated total uptake**
Scenarios [1+ 2]	Tier 1 / No PPE	-	3.85×10^{-6} mg/kg bw/day	-	3.85×10^{-6} mg/kg bw/day
Scenarios [1+ 2]	Tier 2 / PPE (gloves)	-	3.85×10^{-7} mg/kg bw/day	-	3.85×10^{-7} mg/kg bw/day

Exposure of the general public (indirect exposure)

Scenario [3]

In order to minimise the risk of ingestion of the bait by humans, the bait contains a bittering aversive agent. The bait stations have been manufactured to prevent incidental poisoning to both non-target animals and human, i.e. children. They are hard plastic and are either locked or sealed shut to prevent access to the bait. . However, indirect exposure, especially of children, may happen.

Description of Scenario [3]		
A reverse scenario calculation has been used to estimate the quantity of product that an infant should eat to reach the $AEL_{short\text{-}term}$. Based on this reverse scenario calculation, a child should be orally exposed to 2.17×10^{-4} ml to reach the $AEL_{short\text{-}term}$. Trained professional users should dispose unused or part-consumed products. Bait stations protect the product and should prevent access by infants (worse-case).		
	Parameters	Value
Tier 1	Infants Body weight	10 kg

Description of Scenario [3]		
	A.S. content of BP	0.005%
	Density	1.0161 g/ml

Calculations for Scenario [3]

Summary table: systemic exposure from general public					
Population	**Body weight (kg)**	**Oral absorption**	**AEL $_{short-term}$**	**A.S content of BP**	**Toxical amount of biocidal product (ml)**
Infant	10	100%	1.1×10^{-6} mg/kg bw/day	0.005%	2.17×10^{-4} ml

Further information and considerations on scenario [3]

These values assume ingestion of bait, however, the presence of denatonium benzoate as an aversive agent and the location of the bait in a sealed bait station and in an inaccessible area have always been considered enough to mitigate the risk. Since the bittering agent is not 100% efficient in protecting against ingestion in all children, it is therefore important that the bait stations are kept out of reach of children (and other non-target species, including pets and livestock) during storage and use.

Monitoring data

The exposure assessment has been performed using the paper "HEEG opinion on a harmonised approach for the assessment of rodenticides (anticoagulants)" agreed at TMII 2011. This paper was based on an operator exposure study conducted by CEFIC/EBPF Rodenticides Data Development Group (Chambers *et al.* (2004)) and the number of manipulations has been proposed by the applicant.

Dietary exposure

Exposure to residues in food is not assessed because no contamination of food or feeding stuff is foreseen.

Aggregated exposure

No aggregated exposure is foreseeable since the product is not intended to be used under another biocidal product type.

Summary of exposure assessment

Scenarios and values to be used in risk assessment			
Scenario number	**Exposed group (e.g. professionals, non-professionals, bystanders)**	**Tier/PPE**	**Estimated total uptake**
1.	Trained-professional	Tier 2 / PPE	1.92×10^{-7} mg/kg bw/day
1.	Trained-professional	Tier 1/ no PPE (unrealistic)	1.92×10^{-6} mg/kg bw/day
2.	Trained-professional	Tier 2/ PPE	1.92×10^{-7} mg/kg bw/day
2.	Trained-professional	Tier 1/ no PPE (unrealistic)	1.92×10^{-6} mg/kg bw/day
3.	Bystander (infants)	Reverse scenario	2.17×10^{-4} ml
1 + 2	Trained-professional	Tier 1 (No PPE)	3.85×10^{-6} mg/kg bw/d
1 + 2	Trained-professional	Tier 2 (PPE)	3.85×10^{-7} mg/kg bw/d

3.6.4 Risk characterisation for human health

Reference values to be used in Risk Characterisation

Reference	Study	NOAEL (LOAEL) (mg/kg bw/day)	AF[1]	Correction for oral absorption	Value (mg/kgbw/day)
AEL_{acute}	-	0.00034	300 (+ factor 2 to extrapolation from LOAEL)	-	1.1×10^{-6}
$AEL_{medium\text{-}term}$	-	0.00034		-	1.1×10^{-6}
$AEL_{long\text{-}term}$	-	0.00034		-	1.1×10^{-6}
ARfD	Not applicable	-	Not applicable	-	Not applicable
ADI	Not applicable	-	Not applicable	-	Not applicable

[1]Assessment factor have been obtained from the Difenacoum's CAR.

The acceptable level of exposure for short, medium and long-term exposure (AEL) is established in the EU Endpoint List as 1.1×10^{-6} mg/kg bw/day, based on the endpoint from the teratogenicity test in rabbits (NOAEL: 0.00034 mg/kg bw/day) and a safety factor of 3. This is considered to be a suitable endpoint for all users applying rodenticide baits, and for indirect exposure.

Maximum residue limits or equivalent

Exposure to residues in food is not assessed because no contamination on food or feeding stuff is foreseen.

Risk for professional users

- ***Trained professional (Pest control operators)***

Systemic effects

Task/ Scenario	Tier	Systemic NOAEL mg/kg bw/d	AEL mg/kg bw/d	Estimated uptake mg/kg bw/d	Estimated uptake/ AEL (%)	Acceptable (yes/no)
Loading / Scenario [1]	Tier 1	0.00034	1.1×10^{-6}	1.92×10^{-6}	175	No
	Tier 2			1.92×10^{-7}	17.5	Yes
Cleaning / Scenario [2]	Tier 1			1.92×10^{-6}	175	No
	Tier 2			1.92×10^{-7}	17.5	Yes
Scenario (1+2)	Tier 1			3.85×10^{-6}	350	No
	Tier 2			3.85×10^{-7}	35	Yes

Local effects

There is no need to consider local effects separately.

Conclusion

No risk can be expected for trained professional users if PPE (gloves) are worn. The use of protective gloves is recommended in all cases for hygiene reasons and always expected for trained professional users during pest control operations.

Additionally, it has been shown that the proposed roll on packaging is an appropriate risk mitigation measure, because it does prevent from any spillage.

As a consequence, we would like to conclude that the risk/exposure assessment presented is acceptable.

Risk for the general public

Adults or children may be present following application and may be incidentally exposed by touching unprotected bait under an hipothetical worse case as the product bottle is placed inside a bait station. For products applied in bait stations or outdoors, incidental exposure will be very limited.

Infants are potentially the group most at risk as they may play inside or around buildings where baits have been placed. They could be exposed orally by ingesting bait or touching their mouth with contaminated fingers.

Local effects

There is no need to consider local effects separately.

Conclusion

In the hypothetical case that a child may enter in contact with unprotected bait, the calculated toxic amount was 2.17 x 10^{-4} ml based on a 1.1 x 10^{-6} mg/kg bw/day AEL This value shows that infants and children ingesting bait might be at risk. In this hypothetical worst case scenario, firstly, the bait is located inside a sealed bait station and secondly, the product contains a bittering agent which would prevent ingestion of the baits. Therefore, in practice the margins of safety are expected to be much higher than those calculated. It is also important that product labels and good practice advise users to prevent access to bait by children for example:

- Place the product out of the reach of children, birds, pets and farm animals and other non-target animals.
- 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.
- 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.

The proposed uses therefore present an acceptable risk from indirect exposure.

Risk for consumers via residues in food

Neither new data was not provided nor had new guidance to be taken into account for re-assessment. Accordingly, the conclusion from the former assessment regarding risks for consumers via residues in food remain valid.

Risk characterisation from combined exposure to several active substances or substances of concern within a biocidal product

There is no risk derived from a combined exposure because indirect exposure via the environment is considered negligible, the product is not intended to be mixed with other biocidal or non biocidal products and the product does not contain any other active substance of concern.

Summary of risk characterisation

Scenario number	Exposed group	Tier/PPE	AEL mg/kg bw/d	Estimated uptake mg/kg bw/d	Estimated uptake/ AEL (%)	Acceptable (yes/no)
1.	Trained professional user	Tier 1/ no PPE (unrealistic)	1.1 x 10^{-6}	1.92 x 10^{-6}	175	No
1.	Trained professional user	Tier 2/ PPE	1.1 x 10^{-6}	1.92 x 10^{-7}	17.5	Yes
2.	Trained professional user	Tier 1/ no PPE (unrealistic)	1.1 x 10^{-6}	1,92 x 10^{-6}	175	No
2.	Trained professional user	Tier 2/ PPE	1.1 x 10^{-6}	1,92 x 10^{-7}	17.5	Yes
Combined: application and cleaning (1 + 2)	Trained professional user	Tier 1/ no PPE (unrealistic)	1.1 x 10^{-6}	3.85 x 10^{-6}	350	No
		Tier 2/ PPE	1.1 x 10^{-6}	3.85 x 10^{-7}	35	Yes

3.7 Risk assessment for animal health

Neither new data was not provided nor had new guidance to be taken into account for re-assessment. Accordingly, the conclusion from the former assessment regarding animal health remains valid.

3.8 Risk assessment for the environment

Neither new data was not provided nor had new guidance to be taken into account for re-assessment. Accordingly, the conclusion from the former assessment regarding the environment remains valid.

3.9 Assessment of a combination of biocidal products

A use with other biocidal products is not intended.

3.10 Comparative assessment

As difenacoum is a Candidate for Substitution, a comparative assessment must be carried out as part of the evaluation process.

The Biocidal Products Committee of the European Chemicals Agency published its Opinion on Questions regarding the comparative assessment of anticoagulant rodenticides on 02 March 2017 (Document no. ECHA/BPC/145/2017).

The opinion states that:

- In the absence of anticoagulant rodenticides, the use of rodenticide biocidal products containing other active substances would lead to an inadequate chemical diversity to minimize the occurrence of resistance in the target harmful organisms. These products also show some significant practical or economical disadvantages for the relevant uses.
- There is insufficient scientific evidence to prove that non-chemical alternative methods of rodent control are sufficiently effective according to the criteria established in agreed Union guidance with a view to prohibit or restrict the authorised uses of anticoagulant rodenticides.

The Opinion forms the basis of the 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.

On the basis of this comparative assessment, the authorisation of rodenticide products containing difenacoum is justified.