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

Evaluation of active substances

Renewal of approval

Assessment Report

Brodifacoum

Product-type 14
(Rodenticide)

September 2016

eCA: NL and IT

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1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance brodifacoum as product-type 14 (rodenticides), carried out in the context of evaluation of applications for renewal provided for in Article 14 of the Biocidal Product Regulation (EU) No 528/2012 (BPR), with a view to the possible renewal of the approval of this substance.

With the intention to streamline the renewal of substance approvals and product authorisations of anticoagulant rodenticides[1] and their comparative assessments, at the 50th CA meeting the document "Substance approval and product authorisation renewals of the anticoagulant rodenticides" (CA-Feb13-Doc.5.2.b – Final) was endorsed. This was confirmed at the 61th CA meeting laid down in the document "Renewal of anticoagulant rodenticides active substances (CA-Sept15-Doc.5.3).

A workshop was held in Brussels on 26 February 2015 regarding the report on *Risk mitigation measures for anticoagulant rodenticides as biocidal products (Final Report October 2014; ISBN 978-92-79-44992-5)* prepared for the European Commission. The revised summary of the workshop was endorsed at the 62nd CA meeting (CA-Nov15-Doc.5.4). The BPC Efficacy Working Group discussed in WGI-2016 some recommendations of the RMM report for anticoagulant rodenticides.

Brodifacoum was approved as an existing active substance, in product-type 14 under the Biocidal Products Directive (Inclusion Directive 2010/10/EU). The renewal of the active substance has been requested by Syngenta Crop Protection AG.

On 31st of July 2015, the Dutch competent authority (eCA) received a dossier from Syngenta Crop Protection AG.

On 21st of July 2015, the Italian competent authority (eCA) received a dossier from Exponent International representing PelGar International Ltd and Activa s.r.l.

The Dutch eCA accepted the dossier as complete for the purpose of the evaluation on 1st of September 2016.

On the basis of the available information the eCA decided that only a limited evaluation in accordance with Article 14(2)(2) of the BPR of the application is necessary.

As all anticoagulant rodenticides meet the exclusion criteria. If approved, stringent risk mitigation measures will need to be applied. Where no new information was available in the application of renewal, the revision of the evaluation applying current guidance is postponed to product authorisation. This decision shall exclusively apply for the renewal of anticoagulant rodenticides. On the 25th of March 2016, the eCA submitted to the Agency and the applicant the assessment report.

In order to review the assessment report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by ECHA. Revisions agreed upon were presented at the 16th Biocidal Products Committee and the assessment report was amended accordingly.

[1] The concerned active substances are: brodifacoum, bromadiolone, chlorophacinone, coumatetralyl, difethialone, difenacoum, flocoumafen and warfarin.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and the decision on the renewal of the approval of brodifacoum for product-type 14, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

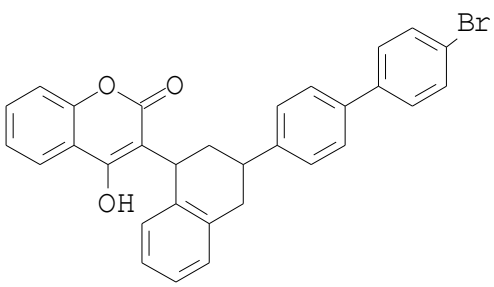
For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS[2]

2.1. Presentation of the Active Substance

2.1.1. Identity

CAS-No.	56073-10-0
EINECS-No.	259-980-5
Other No.	370 (CIPAC) 607-172-001 (Index number)
IUPAC Name	3-[(1*RS*,3*RS*;1*RS*,3*SR*)-3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin
CAS Name	*2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-*
Common name	Brodifacoum (ISO)
Molecular formula	$C_{31}H_{23}BrO_3$
Structural formula	
Molecular weight	523.4 g/mol

[2] See document CA-Sept15-Doc.5.3 - Renewal anticoagulant rodenticides.doc

Isomeric composition	*cis* isomer (CA Index name *2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-, cis-*, CAS-No. 72654-66-1) is a racemic mixture of (1R,3S) and (1S,3R); *trans* isomer (CA Index name *2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-, trans-*, CAS-No. 72654-67-2) is a racemic mixture of (1R,3R) and (1S,3S)
Purity	>95%w/w
The active substances contain no additives.	

2.1.2. Intended Uses

Syngenta

Brodifacoum is intended to be used for the control of brown rat (*Rattus norvegicus*), black rat (*Rattus rattus*) and house mouse (*Mus musculus*) in and around buildings and sewers. The intended users are professionals (trained and non-trained) and general public (non-professionals). The sewer use has not been assessed for the representative formulation of this applicant. When this use is claimed for a product, efficacy evaluation and risk assessment should be performed at product authorisation.

Below details on the intended use are summarised in Table 2.1.2-1. Compared to the intended use table in the original AR, the user categories and organisms to be controlled are better specified.

Activa-PelGar

Brodifacoum is used as a rodenticide pest control substance (Product type 14). *Brodifacoum* is used to control:

Rattus norvegicus	(Norway rat, Brown rat)
Rattus rattus	(Black rat or Roof rat)
Mus musculus	(House mouse)

Brodifacoum is used as the active substance in products for domestic, industrial and commercial buildings including in and around farm buildings, and in sewers.

The maximum concentration allowed is 50 mg/kg (ready to use bait only) according to the COMMISSION DIRECTIVE 2007/69/EC.

No new information of the evaluated products has been provided. Formulated products containing *Brodifacoum* are not applied directly on food or feeding stuffs. Products are not intended to be applied directly on surfaces intended for contact with food or feeding stuffs. However, *Brodifacoum* containing products are intended to be used in premises were food or feeding stuffs are prepared or stored.

Table 2.1.2-1: Uses supported for the active substance renewal

Object and/or situation	Organisms Controlled	Formulation		Application type	User categories
		Type	**Conc (w/w)**		
For the purpose of the protection of public health, including: • Prevention of transmission of disease; • Prevention of the contamination of food and feeding stuffs and other materials, at all stages of their production, storage and use; • Protection of buildings and structures including pipes, cables and overall integrity; • Protection of livestock, wild and domestic; • Social abhorrence and stigma; • Legal requirement	Rats (in and around buildings and sewers) and mice (in buildings)	RB, BB, AB	0.005% ≡ 0.05 g/kg ≡ 50 ppm	Bait	The products are intended for use by professionals, trained professionals and general public.

2.2. Summary of the Assessment

2.2.1. Specification of the different sources of the active substances

Syngenta

The applicant Syngenta has one representative source. Based on the agreements made in the WebEx telecom (November 2015), a new batch analysis is required. The applicant has submitted a batch analysis, which confirms that the reference specification can be maintained (see confidential annex to the AR for details).

Activa-PelGar

PelGar International Ltd and Activa s.r.l. formed a Task Force for the purpose of *Brodifacoum* approval. *Brodifacoum* is manufactured by Tezza s.r.l. in Italy for Activa and by PelGar International Ltd in Czech Republic, according to the same manufacturing process. At the time of the original approval, only five-batch analysis (5-BA) data from PelGar were found acceptable by the eCA-IT. Pelgar's 5-BA was carried out in 2001, by means of validated analytical methods for the a.s. and the only impurity present at quantity ≥0.1% w/w.

Also a 5-BA was available for Activa at that stage, but their study lacked acceptable data on impurities, whereas Activa's purity and isomeric composition proved to be in line with Pelgar's data. Therefore, Activa was requested to submit additional analytical data at the product authorization phase, in order to prove the impurity profile of their technical material.

This is also to underline that the specification proposed for *Brodifacoum* by the Activa-PelGAr Task Force relied on PelGar's 5-BA data only. Namely, the minimum purity was set based on the minimum *Brodifacoum* level found in batches, whereas the maximum level for impurities was set based on their maximum level in batches.

In the context of the authorization of *Brodifacoum*-based products by Activa at national level, Activa submitted evidence to the IT-CA (by means of a 5-BA analysis carried out in 2013) that, apart from water, the only significant impurity in their technical material was the same found in PelGar's *Brodifacoum*. The HPLC/UV analytical method for its determination was validated according to SANCO/3030/99 rev. 4 and therefore accepted by IT-CA. Activa's 5-BA data proved that also Activa's *Brodifacoum* is covered by the Activa-PelGar Task Force specification. Additionally, based on the available information on purity, isomeric composition and impurity profile from both members of the Task Force, a technical equivalence assessment (Tier I) was carried out by IT-CA in 2013, concluding that Activa's *Brodifacoum* and PelGar's *Brodifacoum* were technically equivalent.

In the context of *Brodifacoum* renewal, a 5-BA carried out in 2011 was made available by PelGar, showing that their specification was still in line with the original specification. PelGar's 5-BA data (2011) also addressed the presence of a residual hazardous solvent, which was found below the LOD (<0.005% w/w) in all batches. This level does not trigger the classification of the a.s. itself. Therefore, the above-mentioned residual solvent is to be regarded as either a non-significant and a non-relevant impurity, and as such it does not need to be included in the specification.

In conclusion, for both members of the Task Force 5-BAs newer than 10 years are available, which confirmed the original specification. Therefore, only quality control data should be submitted to confirm that also their actual specifications are still in line with the original specification.

2.2.2. Assessment as to whether the conclusion of the initial assessment of approval remain valid

2.2.2.1. Physico-chemical properties and methods of analysis

No new data on the physical and chemical properties was provided. Both applicants have addressed the remaining data requirement for an analytical method for soil from the original approval of the substance.

Syngenta

A new monitoring method for soil was provided as none were available when the substance was approved (AR December 2010). The provided LC-MS/MS method was successfully validated for brodifacoum in two soil types, with an LOQ of 0.01 mg/kg soil. Validation was performed to SANCO/825/00 rev 7.

Activa-PelGar

The submitted LC-MS/MS method for the analysis of *Brodifacoum* residues down to 0.01 mg/kg in sandy loam and soil clay meets the requirements provided for by SANCO/825/00 and the Additional Guidance to TNsG on Data Requirements on analytical methods. It also supports the residue definition. The method is highly specific (LC-MS/MS, with two mass transitions validated), linear over the range 0.005–0.250 mg *Brodifacoum* /kg in soil, accurate (with recovery rates at LOQ and 10xLOQ in the acceptable range 70–110%) and precise ($\%RSD_n$ = 5 < 20% for each fortification level). The LOQ, as the lowest validated fortification level, complies with the relevant end-point (*Eisenia fetida* 14-d LC_{50} > 994 mg/kg dwt, corresponding to > 879.6 mg/kg wwt).

2.2.2.2. Classification and Labelling

Brodifacoum presently has a harmonised classification according to Regulation (EC) No 1272/2008 (CLP Regulation) with H300 'Fatal if swallowed', H310 'Fatal in contact with skin', H372 'Causes damage to the blood through prolonged or repeated exposure' and, H410 'Very toxic to aquatic life with long lasting effects'.

Brodifacoum belongs to a group of compounds known as anticoagulant rodenticides. The substances have a common anti-vitamin K (AVK) mode of action.

Brodifacoum was discussed by the Technical Committee on Classification and Labelling of Dangerous Substances (TC C&L) of the European Chemicals Bureau (ECB) together with seven other anticoagulant rodenticides (2006 – 2008) as well as by the Specialised Experts for Reproductive Toxicity (September 2006). However, as no final decision could be made on the human health classification of the substances (classification for reprotoxicity and setting of specific concentration limits for acute and repeated dose toxicity), the work was transferred to ECHA, and a CLH proposal was prepared by the evaluating Member State (Italy) and submitted to ECHA. The dossiers for the eight rodenticides were handled as a group, but the Committee for Risk Assessment (RAC) evaluated the proposals on a substance by substance basis comparing the data available for Warfarin and other AVKs and relying on a weight-of–evidence approach as required by Regulation 1272/2008 (CLP).

Based on the RAC Opinion (d.d. 14 March 2014). Brodifacoum warrants the following classification:

- Acute Tox. 1 H300 "Fatal if swallowed" (criterion: LD_{50}, oral $\leq$ 5 mg/kg) based on the oral LD_{50} in mice of 0.4 mg/kg and rats of <5 mg/kg

- Acute Tox. 1 H310 "Fatal in contact with skin"(criterion: LD_{50}, dermal, rat or rabbit ≤ 50 mg/kg) based on the dermal LD_{50} for rats in two dermal rat studies giving LD_{50}-values of 3.2 and 7.5 mg/kg
- Acute Tox. 1 H330 "Fatal if inhaled"(criterion: LD_{50}, inhalation, rat, of 50 mg/m^3) based on the inhalatory LD_{50} value of 3.0 mg/m^3
- STOT RE 1; H372 stating the blood as the main affected organ: H372: "Causes damage to the blood through prolonged or repeated exposure". Increased blood clotting times were found at the top doses in the two 90 day studies in rats (0.004 and 0.080 mg/kg/day, respectively), in the absence of other findings. In the 6 weeks dog study, the 2 dogs in the highest exposure group (0.01 mg/kg/day) had to be killed on day 36 when their blood clotting time reached termination criteria, which is well below 10 mg/kg bw/day the guidance value classification with STOT RE 1; H372. Using Haber's law, the effect level at day 36 was recalculated to give an equivalent 90 day effect level of 0.004 mg/kg/day (0.01 mg/kg/day x 36, which resulted in SCLs for STOT RE 1; H372 above 0.02% and STOT RE 2; H373 between 0.002 and 0.02%.
- Repr. 1A; H360D. The experimental animal studies on Brodifacoum do not indicate any developmental toxicity. This could either be because of no such inherent toxicity or that animal studies are not sufficiently predictive for effects in humans. A comparison of the animal and human effects of warfarin was therefore performed. In humans, Warfarin is known to cause death of embryos and foetuses and malformations, mainly nasal hypoplasia. Since deformation of the naso-maxial part of the face is very specific, it is also referred to as human "Warfarin embryopathy", and Warfarin is consequently classified as a known human developmental toxicant in category Repr. 1A (H360D). Brodifacoum and warfarin share the same mode of action, i.e., they inhibit vitamin K epoxide reductase, an enzyme involved with blood coagulation and bone formation. There are three case reports on effects of Brodifacoum in pregnant women that can be informative. Although there are only 3 cases, two of them indicate severe effects in the foetus, which in contrast to the coagulopathy in the mother was not curable with vitamin K administration, and thus led to more serious effects in the fetus than in the mother. These cases support the position that Brodifacoum may exert similar developmental toxicity to warfarin in humans.
  Overall, the RAC is of the opinion that Brodifacoum should be classified similarly to Warfarin when it comes to developmental toxicity, i.e., in category Repr. 1A (H360D). The reasons are the similar MOAs, some supporting human evidence of developmental toxicity of Brodifacoum and the other therapeutically used AVK coumarins, and the likelihood that experimental animal data derived from standard test protocols is not predictive for effects in humans.
  As the other AVK rodenticides are equally or more toxic than Warfarin, it is not considered appropriate to apply the generic concentration limit for these substances (0.3%), but instead to base the SCLs on that proposed for Warfarin. Thus, the RAC is of the opinion that the SCL for Warfarin can be used as a surrogate SCL for the other AVK rodenticides, resulting in a SCL of 0.003% for Brodifacoum.
- Based on CLP, the acute toxicity category should be based on the lowest $E(L)C_{50}$, in this case two trophic levels show similar toxicity, i.e. fish (*Oncorhynchus mykiss)* and algae *(Pseudokirchneriella subcapitata)* with $E(L)C_{50}$ of 0.042 mg/l and 0.04 mg/l, respectively. This value is ≤ 1 mg/l, therefore Brodifacoum classifies as Acute category 1 (H400) with a M-factor of 10, because both values are between 0.01 and 0.1 mg/l. No adequate chronic data was available for all three trophic levels and only chronic data from algae were submitted in the CLH report. According to this and taking into account that the substance is not rapidly degradable, a classification as Aquatic Chronic category 1 (H410) and an M-factor of 10 is applicable for Brodifacoum based on a NOErC of 0.01 mg/L, since 0.001 < NOEC ≤ 0.01. However, the surrogate approach should be applied due to the lack of chronic data for fish and invertebrates. Brodifacoum is not rapidly degradable and the log K_{ow} ≥ 4 and the highest acute toxicity was reported for fish, i.e. LC_{50} (fish) ≤ 0.1mg/L (0.042 mg/L), the resulting classification from the surrogate approach is Aquatic Chronic 1 (H410) with an M- factor

of 10 ($0.01 < L(E)C_{50} \leq 0.1$). Therefore, the long-term hazard classification based on the chronic algae toxicity and the surrogate approach (fish acute toxicity) is the same.

A special note on sensitisation: in contrast to the CAR, the RAC has decided that no classification with H317 is warranted, as the LLNA and Maximisation test with negative results were considered more sensitive compared to the positive Buehler assay (where irritation also in the control group hampered the interpretation of the results).

For further details we refer to RAC opinion and the background document:

http://echa.europa.eu/documents/10162/13626/rac_clh_opinion_brodifacoum_adopted_final_en.pdf
http://echa.europa.eu/documents/10162/13626/rac_clh_bd_brodifacoum_en.pdf

The resulting Annex VI entry, if agreed by COM (draft 9 ATP to CLP), is listed below:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Repr. 1A; H360D Acute Tox. 1; H300 Acute Tox. 1; H310 Acute Tox. 1; H330 STOT RE1; H372 (blood) Aquatic Acute 1; H400 Aquatic Chronic1; H410
Labelling	
Pictograms	GHS06 GHS08 GHS09
Signal Word	Danger
Hazard Statement Codes	**H360D**: May damage the unborn child **H300**: Fatal if swallowed **H310**: Fatal in contact with skin **H330**: Fatal if inhaled **H372**: Causes damage to the blood through prolonged or repeated exposure **H410**: Very toxic to aquatic life with long lasting effects
Suppl. Hazard statement Code(s)	-
Specific Concentration limits, M-Factors	Repr. 1A; H360D: C ≥ 0,003 % STOT RE 1; H372: C ≥ 0,02 % STOT RE 2; H373: 0,002 % ≤ C < 0,02 % M =10 for Aquatic Acute toxicity M =10 for Aquatic Chronic toxicity

If the proposed classification is agreed, reference products containing 0.005% brodifacoum will be classified for reprotoxicity (H360D: May damage the unborn child) and repeated dose toxicity (H373. May causes damage to the blood through prolonged or repeated exposure). As for acute toxicity, no classification for oral and dermal toxicity is needed as the study results on the product do not meet the classification criteria. No acute inhalation studies on the products are presented, but the physical nature of these kind of products is such that classification for acute inhalational toxicity is not considered needed.

Additional labelling:

In addition to the phrases listed above, labelling, as specified in Article 69 of Regulation (EU) No 528/2012, as well as additional labelling for rodenticides, might become necessary (see chapter 2.3).

2.2.2.3. Efficacy and resistance

No new information on the efficacy is available since the original approval. The conclusions on the efficacy will therefore remain the same. To date, no incidences of resistance towards brodifacoum are known. This is in line with scientific evidence as referenced in the report on RMM for anticoagulant rodenticides where it is stated that 'there is no evidence of field resistance to brodifacoum, difethialone and flocoumafen'. However, given the resistance development against FGARs and less potent SGARs and the similar mode of action of the anticoagulant rodenticides, resistance development should be carefully monitored. It was therefore concluded at WG EFF that appropriate data for resistance monitoring should be provided by the applicants during the next renewal process depending on the feasibility of the implementation of a harmonised resistance monitoring programme at EU level. This has been added as a requirement of further information at 2.3.4.

2.2.2.4. Human health assessment

No new information is available since the original approval and the conclusions remain the same.

Compared to the HEEG opinion 12 on the Harmonised approach for the assessment of rodenticides (anticoagulants) the exposure calculation performed in the original approval report are based on a worst-case assumptions for the number of application/handling bait stations. Therefore, the final conclusion on the safe use of brodifacoum for the protected (gloves) professional user remains valid.

For the non-professional user new calculations are performed, considering placing and cleaning of 5 bait stations per day, but this does not change the conclusion (safe use without gloves).

Table 2.2.2.2-1 Exposure to brodifacoum for non-professional users using Klerat Pellets for the control of rats or mice with no PPE

Loading phase		
Number of manipulations	=	5 manipulations × 2.04 mg product/station
Exposure at loading	=	10.2 mg product/day × 0.005% w/w brodifacoum
Exposure at loading	=	5.1×10^{-4} mg a.s./day × 3% dermal absorption*
Systemic exposure	=	1.5×10^{-5} mg a.s./day
Cleaning phase		
Number of manipulations	=	5 manipulations × 3.79 mg product/station
Exposure at cleaning	=	18.95 mg product/day × 0.005% w/w brodifacoum
Exposure at cleaning	=	9.5×10^{-4} mg a.s./day × 3% dermal absorption
Systemic exposure	=	2.8×10^{-5} mg a.s./day
Total exposure	=	Loading phase + Cleaning phase
	=	$1.5 \times 10^{-5} + 2.8 \times 10^{-5}$ mg a.s./day
	=	4.4×10^{-5} mg a.s./day / 60 kg
	=	7.3×10^{-7} mg a.s./kg bw/day

Table 2.2.2.2-2 Exposure to brodifacoum in %AEL

Scenario	Exposure (µg/kg bw/day)	AEL (µg/kg bw/day)	%AEL
Non-professional – rat or mice control – no PPE	7.3×10^{-4}	$AEL_{chronic}$ – 0.0033	22
		$AEL_{medium\ term}$ – 0.0067	11
		AEL_{acute} – 0.0033	22

* regarding dermal absorption a very conservative worst-case assumption was made for the dermal exposure to Klerat Pellets of 5%. This was based on an in vitro study using human skin, where both in the epidermidis and receptor fluid the amount of brodifacoum was below the LOQ. A surrogate residue value was calculated to be <1.64% and <3.53%, respectively, leading to a conservative value of 5% for the risk assessment. However, as no data in the dossier of the other notifier was available, a value of 3% is used based on read-across to difenacoum. NL would propose to use 3% for pellets for the risk assessments.

At product authorization stage at national level, new guidance documents on exposure (including the harmonised approach for the assessment of anticoagulant rodenticides made by HEEG, i.e. HEEG opinion 10 and 12) should be taken into account.

2.2.2.5. Environmental assessment

No new information is available since the original approval and the conclusions of the AR for brodifacoum (PT14) drawn in the environmental section remain the same.

2.2.2.6. Fate and distribution in the environment

No new information is available and the conclusions of the AR for brodifacoum (PT14) drawn in the fate and distribution section remain the same.

2.2.2.7. PBT and POP assessment

PBT assessment

Substances that fulfil the PBT or vPvB criteria shall not be included in the Union list of approved substances unless releases to the environment can be effectively prevented.

Since December 2010 it is agreed that the PBT assessment is carried out on basis of the criteria set out under Regulation (EC) No. 1907/2006.

Persistence

The following information on degradation / transformation in different environmental compartments is available:

Brodifacoum is not readily biodegradable as in the test done according to the OECD 301D, 3.5% biodegradation was observed during the 28 days.

Brodifacoum is hydrolytically stable (DT50 = 300 d, pH 7 at 25°C), but its photolytic half-life in water is 12 hours.

The DT50 in soil is 157 days at 20 °C, the DT50 considering the temperature correction to 12°C is 298 days.

No data on degradation in marine water, freshwater or sediment are available. However, reading across from a structural analogue difenacoum, considered to be persistent and very persistent brodifacoum is considered to be persistent.

Bioaccumulation

There is not enough information available to finally be able to clarify the B-criterion. However, for the substance brodifacoum the screening B-criterion is fulfilled as the log Kow is above 4.5. Formally BCF testing with fish would be required in order to be able to clarify if brodifacoum meets the B-criterion. However, in the case of second generation anticoagulant substances, BCF testing with fish might not provide meaningful results. A BCF test with fish might be technically difficult to conduct as brodifacoum is highly toxic to fish. Furthermore, second generation anticoagulant substances, which are predominantly released to the terrestrial environment, can accumulate in the liver of target rodents and it can be assumed that they also accumulate in the livers of non-target mammals and birds. This is confirmed by the fact that the second generation anticoagulant substances are found in livers of wildlife. However, as no criteria exist for bioaccumulation via the terrestrial food chain and standardised test methods for bioaccumulation in other non-target animals than earthworms are not available these findings are merely an indication that brodifacoum may have B-properties.

The estimated BCF for brodifacoum, using an estimated log Kow value of 6.1, is 35645 L/kg using the TGD equation 75, and 568.9 L/kg using the US EPA EPIWIN program.

Monitoring data should be applied in addition as part of a weight of evidence approach. Based on the conclusion of the ad hoc follow up on difenacoum (analogue of brodifacoum) brodifacoum should be considered as bioaccumulative and therefore fulfils the criteria for B.

Toxicity

Brodifacoum is acutely very toxic to fish, for the rainbow trout the LC50 was 0.04 mg/L.

No long-term data for aquatic organisms are available. Due to the lack of reliable long-term study with birds, a NOEC= 0.012 mg brodifacoum/kg diet was estimated by extrapolation from the reference anticoagulant difenacoum.

Regarding mammalian toxicity a substance fulfils T criterion when it is classified as the substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B, or 2) according to Regulation EC No 1272/2008; or there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to Regulation EC No 1272/2008.

Regarding toxic for reproduction, RAC decided that Brodifacoum is to be classified with H360D, because it contains the same chemical moiety responsible for teratogenicity of warfarin and it has the same mode of action that is a known mechanism of teratogenicity in humans.

Based on the RAC opinion, brodifacoum is classified as H300/310/330, H372 (blood) and H360D.

Overall conclusion is that brodifacoum fulfils the T criterion.

It is concluded that brodifacoum should be considered to meet the P, B and T criteria.

POP assessment

Protection goals and risk management of the UN-ECE POPs Protocol are control, reduction or elimination of discharges, emissions and losses of POPs. The following P (persistent) O (organic) P (pollutants) criteria are laid down in Executive Body decision 1998/2.

	POPs-criteria
Long-range transport potential	Vapour pressure <1000 Pa and half-life in air > 2 days or monitoring data in remote area showing that the substance is found in remote regions
Toxicity (1)	Potential to adversely affect human health and/or environment
Persistence	Half-life in water > 2 months or in sediment >6 months or in soils > 6 months
Bioaccumulation	(i) BCF or BAF >5000 or log Pow > 5 (ii) Alternatively, if the bio-accumulative potential is significantly lower than (i) above, other factors, such as the high toxicity of the substance, that make it of concern within the scope of the protocol.

(1) L(E)C50; NOEC - no observed effect concentration; CMR - carcinogenic, mutagenic or toxic to reproduction.

Considering that the vapour pressure of brodifacoum is << 1 x 10^{-6} Pa (1.18 10^{-18} Pa at 25°C estimated with EPIWIN) combined with a calculated half-life in air of 0.276 days, based on reaction with hydroxyl radicals (0.5x10^6 OH/cm^3; 24-h day time) the criterion for long-range transport potential not is fulfilled.

Brodifacoum is not readily biodegradable as in the test done according to the OECD 301D, 3.5% biodegradation was observed during the 28 days.

Brodifacoum is hydrolytically stable (DT50 = 300 d, pH 7 at 25°C), but its photolytic half-life in water is 12 hours.

The DT50 in soil is 157 days at 20 °C, the DT50 considering the temperature correction to 12°C is 298 days.

No data on degradation in marine water, freshwater or sediment are available. However, reading across from a structural analogue difenacoum, considered to be persistent and very persistent brodifacoum is considered to be persistent.

POPs Toxicity criteria are not clearly defined, but considering the lowest acute LC50 of brodifacoum for fish is of 0.04 mg/L the Toxicity criterion is met.

The estimated BCF for brodifacoum, using an estimated log Kow value of 6.1, is 35645 L/kg using the TGD equation 75, and 568.9 L/kg using the US EPA EPIWIN program.

Monitoring data should be applied in addition as part of a weight of evidence approach. Based on the conclusion of the ad hoc follow up on difenacoum (analogue of brodifacoum) brodifacoum should be considered as bioaccumulative and therefore fulfils the criteria for B.

Conclusion for the POP characterisation:

On basis of the available can be concluded that the initial criteria for long-range transport potential are not met. Therefore this substance is not a POPs candidate.

2.2.2.8. Assessment of endocrine disruptor properties

No new information is available. Brodifacoum is not considered to have endocrine disrupting properties.

2.2.3. Assessment of the recommendations arising from the report[3] on RMM for antiocoagulant rodenticides that are relevant for the active substance.

- For rat control, FGARs and less potent SGARs should always be considered as the first choice. SGARS should only be used against rats, where there is evidence that infestations are resistant.
Ideally where the resistance status is known prior to treatment, products containing the least potent active substance that will effect complete control should be used first, i.e.non-chemical methods > FGARs > less potent SGARs > potent SGARs. The authorisation of biocidal products should be decided upon the national or regional resistance situation. However, often this resistance status is not known. A harmonised programme to rapidly determine the resistance status of a rodent infestation prior to treatment should be developed. Currently such a programme is not available, but is under development. Given the uncertainties about the protocol to be used, the resources, data collection and sharing, etc. at the time of this renewal it was concluded at WG EFF that appropriate data for resistance monitoring should be provided by the applicants during the next renewal process depending on the feasibility of the implementation of a harmonised resistance monitoring programme at EU level. This has been added as a requirement of further information at 2.3.4.

- For mouse control, SGARs should always be considered as the first choice, as FGARs have low efficacy against House mice. FGARs should only be used against mice where there is evidence that the local strain is susceptible.
At the workshop in Brussels it was concluded that at this moment, there is not sufficient information and support to restrict FGAR active substances at EU level regarding resistance in mice. The proposed RMM is not relevant for this AR as it concerns a SGAR.

- Provided the other RMMs are applied (pack size, bait stations see below), there is no reason to restrict the use of SGAR for amateurs, especially in order to control House mice populations, which are the number one problem in the amateur sector.
- Pack size should always be limited for amateur use and SGAR should be sold in smaller amounts than FGARs. A precise computation and list of suggestions is provided. Products intended for use by amateurs should be clearly different from products intended for use by professionals and PCOs.
It is agreed that authorisations for general public and professionals can be covered under the same authorisation, but shall be placed on the market as different products (different pack size and separate labelling). The SPC format is already adapted to allow the different uses on one SPC. Looking at the different situations at MS level regarding the use of ARs by the general public MS can still derogate from MR when the refMS has authorised the product for general public. RMM on pack sizes is included in 2.3.3.

- Amateurs should have the option to use ARs in and around buildings for the control of rat infestations, since there is evidence that rat infestations almost invariably have an outdoor origin (burrows). Any restriction of an active substance, or a biocidal product, to use 'indoors only' is a de facto restriction preventing use against most rat infestations.
The control of rats in and around buildings for the general public can be approved at the substance approval stage but it may also be subject to derogation from MR at the product authorisation stage. RMM included in 2.3.2.

- Dyes should always be included in the formulations. Using specifically green/blue dyes for ARs which are not absorbed appears as an interesting RMM to monitor both bait uptake (efficacy) and non-target primary exposure.
RMM included in 2.3.2.

[3] Available at https://circabc.europa.eu/w/browse/d66ad096-37a1-4903-a3e0-24607ca3f3ea

- Bittering agents should be included in all bait formulations. Denatonium benzoate at 0.001% (10 mg/kg) is currently the most commonly used bittering agent in bait formulations.
RMM included in 2.3.2.

- Baiting area: professionals and trained professionals should conduct surveys prior to application of ARs that consider the extent of the rodent infestation, and the risks posed to humans and non-target species. Information should always be applied on the bait stations but not in the surrounding area.
Survey before baiting should be part of the training for all professionals including farmers. This RMM was agreed on at the workshop in Brussels and WG efficacy. The RMM is included in 2.3.3. No agreed position was reached on the RMM to avoid posting information on baiting areas, this will be left to the MSs to decide at product authorisation.

- For amateur use, tamper-resistant bait stations should always be mandatory, with baits securely fixed inside the bait stations when possible (wax blocks, paste). Loose baits (such as grain and pellets) cannot be excluded, even for amateur use, because of their higher palatability. Using smaller packs and pre-packed bait stations should reduce the risk of accidental human exposure, and possibly pet exposure.
At the workshop in Brussels a large majority agreed that tamper-resistant bait stations with securely fixed baits should always be mandatory for general public use and that products intended for use by the general public should be clearly different from products intended for professional use. The bait content of bait stations is to be defined at product authorisation stage as it may depend on rodent species, type of bait, etc. RMM on the use of bait stations for non-professional users is included in 2.3.2. Harmonisation on the use of loose grains and pellets in sachets for non-professional users seems possible.

- For PCOs and professionals, bait can either be presented in tamper-resistant bait stations, or in open trays that are protected from non-target species using a combination of natural cover, materials located on site and materials brought onto site specifically for that purpose.
Infestations are likely to be large, and non-target impact will be minimized by optimizing bait presentation to the rodents, and thus minimizing the duration of the treatment. The utility of tamper resistant bait points will vary from site to site and their use should be left to the discretion of the operator, in the light of the risk assessments conducted at the outset of the treatment.
At the workshop in Brussels it was concluded that the use of non-conventional bait stations (e.g. open trays or similar) by trained/certified professionals (PCOs) only should remain possible under certain circumstances. MSs may derogate from MR at the product authorisation stage. RMMs are included in 2.3.2.

- Pulsed baiting should be used when SGARs are applied to reduce the quantity of bait applied provided data is available to support the efficacy of this practice with particular active substance and biocidal product.
Pulsed baiting is specific for products containing the most potent SGARs only (i.e. flocoumafen, brodifacoum and difethialone) and will be restricted to trained/certified professional users only (PCOs). Efficacy for pulsed baiting needs to be demonstrated and needs to be mentioned specifically on the product SPC/label. Weekly controls are required for pulsed baiting. RMM is included in 2.3.2.

- Permanent baiting should not be conducted outdoor unless there is a high risk of re-invasion, because it poses a very high risk to non-target species.
- Permanent baiting may be conducted indoors, particularly where there is a regulatory requirement, or where there is a high risk of re-invasion, because it can be managed to pose a low risk to non-target species.
Permanent baiting indoors and outdoors by trained/certified professionals only should remain possible under certain circumstances. This could be defined in a code of best practice e.g. (http://www.thinkwildlife.org/crru-downloads/crru-guidance-on-permanent-baiting-april-2016/?wpdmdl=16399). Permanent baiting for specific locations could be appropriate as part of an IPM strategy based on site specific risk assessments. For outdoor permanent baiting, MSs

may derogate from MR at the product authorisation stage. RMM included in 2.3.2.

- In the first instance, the duration of outdoor baiting should always be limited to 35 days (5 weeks). Subsequent continued rodent activity could indicate that the rodents are resistant to the rodenticide, or that a significant proportion of the infestation are not being treated, and are continually moving into the treated area.
At the workshop in Brussels a large majority agreed, but it was also concluded that in some situations, e.g. sensitive areas or areas subject to constant reinvasion, baiting beyond 35 days will be justified. RMM that products shall not be used beyond 35 days without an evaluation of the state of the infestation and of the efficacy of the treatment is is included in 2.3.3.

- Frequency of visits should be left to the discretion of the operator, in the light of the risk assessments conducted at the outset of the treatment. The wide diversity of sites with rodent infestations precludes any strict frequency. However, as a minimum treated sites should be visited once a week.
At the workshop it was concluded that it is preferable that MSs decide to make reference to code of best practices (e.g. http://www.thinkwildlife.org/crru-downloads/crru-uk-code-of-best-practice/?wpdmdl=3220) *and that frequency of visits is left to the professional. There should be a link between the SPC and the code of best practice which might be difficult for certain MSs which do not yet have such codes available. A general RMM is added to 2.3.3.*

- All rodent bodies should be disposed of on each visit by the PCO, and clients should be encouraged to dispose of rodent bodies, taking necessary steps to ensure their safety (providing advice on wearing gloves, minimizing contact, and washing hands after disposal).
Specific recommendations for disposal of rodent bodies should be specified (avoid the general sentence "according to local regulations"). For clients and other amateurs, sealing the bodies in two separate plastic bags and safe disposal in the garbage can be considered.
- Uneaten bait should always be removed and disposed of at the end of the treatment.
Amateurs may dispose of their remaining uneaten baits by sealing it within two plastic bags and safe disposal in the garbage.
At the workshop in Brussels it was concluded that the RMM 'Removal and disposal of uneaten bait and dead bodies at the end of treatment' can be included at active substance renewal, but the method of disposal and classification of waste will be left to the MSs (e.g. sentence "in accordance with local requirements"). However, the method of disposal should be described specifically on the national SPC and product label. RMM included in 2.3.3.

- Resistance in rodent populations should be managed by ensuring that only effective ARs are used to control population rodents. For House mice, first generation anticoagulants should be avoided unless there is good evidence that populations can be controlled with a particular active ingredient, and for House mice and Norway rats, resistance surveys involving the sequencing of the VKORC1 gene should be conducted for any population of rodents where physiological resistance is suspected. Where mutations of the VKORC1 gene are detected, subsequent use of ARs should be restricted to the active ingredients currently believed to be efficacious against that particular mutation. Such information should be made widely available across all MSs in a format similar to that of the Rodenticide Resistance Action Group (see RRAG, 2010), and should be regularly updated in the light of results generated across all member states.
- In the long term, mapping of the different VKORC1 mutations across all MSs should also be made available online, to allow predictions to be made for new infestations located within areas that have previously been surveyed.
At the workshop in Brussels, a need for a harmonised methodology for monitoring resistance was identified. A first proposal on the set up of a monitoring system taking into account regional information has been received from the expert team. Given the uncertainties about the protocol to be used, the resources, data collection and sharing, etc. at the time of this renewal, it was decided at WG EFF that appropriate data for resistance monitoring should be provided by the applicants during the next renewal process depending on the feasibility of the implementation of a harmonised resistance monitoring programme at EU level. This has been added as a requirement of further information at 2.3.4.

2.3. Overall conclusions

The outcome of the assessment for brodifacoum in product-type 14 is specified in the BPC opinion following discussions at the 16thmeeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. Requirement for further information related to the biocidal product[3]

None identified.

2.5. List of endpoints

The most important endpoints for the active substance, based on the original evaluation and the revaluation performed for the renewal of approval, are listed in Appendix I.

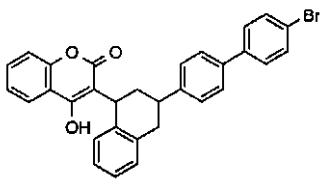
Appendix I: List of endpoints

The List of Endpoints is a combined set of data from two applicants, indicated by **A** (Syngenta) and **B** (Activa-Pelgar). Additions or changes compared to the AR (December 2010) are highlighted in yellow.

Chapter 1:Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Brodifacoum (ISO 1750 published)
Product-type	PT14, Rodenticide

Identity

Chemical name (IUPAC)	3-[(1*RS*,3*RS*;1*RS*,3*SR*)-3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin
Chemical name (CA)	3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2*H*-1-benzopyran-2-one
CAS No	56073-10-0
EC No	259-980-5
Other substance No.	370 (CIPAC No), 607-172-001 (Index no Annex VI Reg (EC) 1272/2008)
Minimum purity of the active substance as manufactured (g/kg or g/l)	950 g/kg **A.** 950 g/kg **B.** 992 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None
Molecular formula	$C_{31}H_{23}BrO_3$
Molecular mass	523.4 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	**A.** 232°C with decomposition (98.7 %w/w) **B.** *Brodifacoum* was observed to darken and decompose (100% w/w)
Boiling point (state purity)	Not applicable
Thermal stability / Temperature of decomposition	**A.** 232 °C (98.7 %w/w) **B.** 235.8 ºC (100% w/w)

Appearance (state purity)	**A.** fine powdery cream solid (92.5 %w/w) **B.** white to off-white solid, fine powder (pure) Odour: not tested due to the toxicity of *Brodifacoum*
Relative density (state purity)	**A.** 1.42 g/cm^3 at 25°C (92.5 %w/w) **B.** 1.530 at 20°C (purity: >99% w/w)
Surface tension (state temperature and concentration of the test solution)	Not applicable (as solubility is < 1mg/L)
Vapour pressure (in Pa, state temperature)	**A. <<**10^{-6} Pa at 20°C **B.** 2.6E-22 Pa at 20°C; 1.9E-21 Pa at 25°C (estimated by the vapour pressure curve)
Henry's law constant (Pa m^3 mol $^{-1}$)	**A.** **<<**2.18 x 10^{-3} Pa m^3 mol^{-1} at pH 7, and <<5.23 x 10^{-5} Pa m^3 mol^{-1} at pH 9 **B.** 2.35E-18 Pa m^3 mol^{-1} (calculation based on vapour pressure at 20°C estimated by the vapour pressure curve and water solubility at pH 7 and 20°C)
Solubility in water (g/l or mg/l, state temperature)	**A.** pH 5.2: 3.8 E-06 g/l (at 20 °C) **B.** pH 5: 5.65E-07 g/l (10°C); ≤3.17E-06 g/l (20°C); 6.57E-07 g/l (30°C) **A.** pH 7.4: 2.4E-04 g/l (at 20 °C) **B.** pH 7: 8.16E-06 g/l (10°C); 5.80E-05 g/l (20°C); 1.60E-05 g/l (30°C) **A.** pH 9.3: 1.0E-02 g/l (at 20 °C) **B.** pH 9: 6.27E-04 g/l (10°C); 1.86E-03 g/l (20°C); 7.96E-04 g/l (30°C)
Solubility in organic solvents (in g/l or mg/l, state temperature)	**A.** Hexane 0.088 g/l (20 °C) Toluene: 7.2 g/l (20 °C) Dichloromethane: 50 g/l (20 °C) Ethyl acetate: 12 g/l (20 °C) Methanol: 2.7 g/l (20 °C) Acetone: 23 g/l (20 °C) Acetonitrile: 3.2 g/l (20 °C) **B.** Toluene: 5.81 g/l (10°C); 5.89 g/l (20°C); 5.85 g/l (30°C) Dichloromethane: 29-33 g/l (10°C); 29-33 g/l (20°C); 40-50 g/l (30°C) Ethyl acetate: 10.2 g/l (10°C); 10.1 g/l (20°C); 10.8 g/l (30°C) Methanol: 1.67 g/l (10°C); 1.61 g/l (20°C); 1.64 g/l (30°C) Acetone: 20.7 g/l (10°C); 21.2 g/l (20°C);

	21.8 g/l (30°C)
Stability in organic solvents used in biocidal products including relevant breakdown products	Not required since the active substance does not include any organic solvent
Partition coefficient (log P_{OW}) (state temperature)	**A.** 8.5 (calculated by CLOGP algorithm of Hansch and Leo) 6.12 (estimated from measured Koc) **B.** pH 5: 6.16-6.27 (10°C); 5.99-6.13 (20°C); 5.80-5.98 (30°C) pH 7: 5.09 (10°C); 4.92 (20°C); 4.78 (30°C) pH 9: 4.91 (10°C); 4.78 (20°C); 4.58 (30°C)
Dissociation constant	pKa = 4.50 (QSAR estimation)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	**A.** 263 nm and 308 nm **B.** 266 nm and 308 nm (methanol; 10% 1N HCl methanolic solution); 263 nm and 312 nm (10% 1N NaOH methanolic solution) ε_{308} (l $mol^{-1}cm^{-1}$) = 14089 (methanol), 15629 (10% 1N HCl methanolic solution) ε_{312} (l $mol^{-1}cm^{-1}$) = 16677 (10% 1N NaOH methanolic solution)
Flammability or flash point	Not classified as a flammable solid
Explosive properties	Not explosive
Oxidising properties	Not oxidising
Auto-ignition or relative self ignition temperature	Not a self-heating substance.

Classification and proposed labelling

with regard to physical hazards	none
with regard to human health hazards	GHS06 GHS08 Repr. 1A; H360D Acute Tox. 1; H300 Acute Tox. 1; H310 Acute Tox. 1; H330 STOT RE 1; H372 (blood)
with regard to environmental hazards	GHS09 Aquatic Acute 1; H400 Aquatic Chronic 1; H410
SCLs and/or M-Factors	Repr. 1A; H360D: C ≥ 0,003% STOT RE 1; H372 (blood): C ≥ 0,02% STOT RE 2; H373 (blood) 0,002%≤ C <0,02% M=10 (acute) M=10 (chronic)

Chapter 2:Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	**A.** HPLC with UV detection at 254 nm using an internal standard **B.** Dissolution in methanol/dichloromethane (3:2,v/v). Determination by RP-HPLC/UV. LOQ = 0.79 µg/ml RP-HPLC/UV method for the isomeric content determination also available
Impurities in technical active substance (principle of method)	**A** HPLC with UV detection using either an internal or an external standard, or with fluorescence detection using an external standard **B.** RP-HPLC/UV

Analytical methods for residues

Soil (principle of method and LOQ)	**A.** LC-MS/MS, LOQ 0.01 mg/kg (brodifacoum) **B.** Extraction from spiked samples (sandy loam soil and clay soil) with acetone/hexane (80:20, v/v). Analysis by LC-MS/MS, with two mass transitions validated: 521.1→135.1 (quantification) 521.1→142.9 (confirmation) LOQ = 0.01 mg/kg
Air (principle of method and LOQ)	Not relevant, since *Brodifacoum* is a non-volatile substance intended to be used only in solid formulations
Water (principle of method and LOQ)	Extraction from spiked samples (drinking, ground, and surface water) with dichloromethane. Extract evaporation by rotary evaporator. Residue re-dissolution in 0.5 ml of methanol for RP-HPLC/MS/MS analysis (scan in SIM and SRM mode). LOQ = 0.05 µg/l for drinking and ground water, 0.5 µg/l for surface water
Body fluids and tissues (principle of method and LOQ)	**A.** Extraction from spiked samples of plasma and liver with acetonitrile:ether (9:1) and acetonitrile, respectively. Evaporation to dryness by nitrogen. Residue redissolution in 2 ml of acetonitrile. Determination by RP-HPLC with fluorescence detection, using *Difenacoum* as internal standard. LOQ in plasma = 0.010 mg/l, LOQ in liver tissue = 0.01 mg/kg **B.** Blood serum: extraction from spiked samples (blood aqueous solution) with dichloromethane after centrifugation. RP-HPLC/MS/MS analysis. LOQ = 0.06 mg/l Body tissues covered under food of animal origin

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Extraction from spiked samples with ethyl acetate for cucumber, wheat, and lemon, with acetone in case of oilseed-rape. Clean-up procedure (if necessary) suited to the sample properties, *i.e.* water/fat/acid content. Determination by LC-MS/MS. LOQ = 0.01 mg/kg in all 4 matrices
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Extraction from spiked samples with dichloromethane: acetone (7:3, v/v). Purified extracts analysed by LCMS/MS. LOQ = 0.01 mg/kg

Chapter 3:Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	**A.** Brodifacoum (0.21 mg/kg) was rapidly absorbed in rat (Tmax in blood= 8 h after dosing; Cmax 16.1 ng/ml). The oral absorption was>75%, based on the radioactivity associated to the tissues After a single higher oral radiolabelled dose of Brodifacoum (10 mg/kg) about 64.0% was absorbed (residues in the liver, carcass and bile 48h after dosing). The rest was recovered in the faeces, as unabsorbed material. **B.** **Oral absorption is assumed to be 100%,** on the basis of amount of radioactivity recovered in the excreta and retained in the tissues
Rate and extent of dermal absorption*:	**A.** Absorption through human skin assessed on **pellet baits** (Brodifacoum 0.0048%w/w). Over 24 h, Brodifacoum was below the limit of quantification (<3.53% of the applied dose) in the receptor fluid and in the epidermis (<1.64%), after tape stripping. Total recovery (108 ±6.25%) in the washing fluid. A calculated 'surrogate value' of 5% dermal absorption has been considered as the worst case. **B.** The read across from Difethialone and Difenacoum data is applied, based on the close structural relationship, the similar physico-chemical properties and the same mode of action. A dermal absorption value for Difethialone =4%; for Difenacoum two different values depending on the type of formulation: **3% (pellets and grains)** or **0.047% (wax block bait).**

Distribution:	**A.** **Widely distributed.** 10 days following a single oral dose (0.25 mg/kg bw), the retained dose was highest in the rat liver (22.8 %), followed by the pancreas (2.3 %), kidney (0.8%), heart (0.1%) and spleen (0.2%). Approximately 50% of the dose was in the carcass and skin. **B.** Widely distributed, although the liver is by far the major site of distribution and retention
Potential for accumulation:	**A.** High potential for accumulation: the liver retained the largest % of the dose, very long time after dosing. Data from feeding studies indicate a non-linear accumulation in rat livers. **B.** **High potential for bioaccumulation in the liver** (t ½ for hepatic residues unchanged a.s.>200 days).
Rate and extent of excretion:	**A.** A small amount (**11–14%)** was slowly eliminated in **urine and faeces** over 10 days following a single oral dose (0.25 mg/kg bw). Biliary and renal routes are of equal significance in the elimination. The elimination from the liver was biphasic at high doses. The rapid phase (days 1-4) corresponded to a reduction in clotting factor synthesis and a slower terminal phase (days 28-84), during which blood clotting function was normal **The half-life in the liver was calculated in the range of 282-350 days.** **B.** Faecal excretion (mainly by mechanism other than biliary excretion) is the major route of elimination, independently of gender, dose, single or repeated treatment. Parent compound accounted for the vast majority (50-80%) of radioactivity found in the feaces.
Toxicologically significant metabolite(s)	**A.** **Parent compound** **B.** Parent compound

* the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Acute toxicity

Rat LD_{50} oral	**A.** **0.4 mg/kg bw** (M rat and mouse). **B.** <5 mg/kg
Rat LD_{50} dermal	**A.** **3.16 mg/kg bw** **B.** 7.48 mg/kg bw (F)
Rat LC_{50} inhalation	A. **3.05 mg/m3** (F) B. No study provided
Skin corrosion/irritation	A. Not irritant according to the score. B. **Not irritant**
Eye irritation	A. Not irritant according to the score. B. **Not irritant**
Respiratory tract irritation	No data
Skin sensitisation (test method used and result)	A. **Skin sensitiser** (Maximisation test of Ritz and Buehler). B. No sensitizing reaction (LLNA test on mice) Negative (guinea pig maximization test) for a 0.25% technical product Final conclusion RAC no sensitizer
Respiratory sensitisation (test method used and result)	No data
Repeated dose toxicity	
Subchronic	
Species / target / critical effect	**A. /B.** Rat/Coagulation system/ Increase in blood coagulation time

Relevant oral NOAEL / LOAEL	**A.** **0.001 mg/kg bw /day** **B.** 0.04 mg/kg/day
Relevant dermal NOAEL / LOAEL	**A.** No study available **B.** No study available
Relevant inhalation NOAEL / LOAEL	**A.** No study available **B.** No study available

Long term

Species/ target / critical effect	**A./B.** Chronic study waived as infeasible and unnecessary

Genotoxicity	**A.** Negative in Ames test, in vitro cytogenetic assay in human lymphocytes and mouse lymphoma L5178Y cells. Negative in in vivo mouse micronucleus test. **B.** Negative in Ames test, in vitro cytogenetic assay in human lymphocytes and mouse lymphoma L5178Y cells

Carcinogenicity

Species/type of tumour	**A./B.** Chronic study waived as infeasible and unnecessary
Relevant NOAEL/LOAEL	-

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	**A.** Rabbit (maternal toxicity): deaths with internal haemorrhages. No developmental effects Rat (maternal toxicity): internal haemorrhages. No developmental effects **B.** Rabbit (maternal toxicity): increased prothrombin time. No developmental effects Rat no significant maternal toxicity or developmental effects

Relevant maternal NOAEL	**A.** NOAEL (rat): 0.001 mg/kg/day **B.** NOAEL (rabbit): 0.002 mg/kg/day
Relevant developmental NOAEL	**A.** NOAEL (rabbit): ≥0.005 mg/kg/day **B.** NOAEL (rabbit): 0.004 mg/kg/day

Fertility

Species/critical effect	**A.** Not performed **B.** Rat High dose F_1: haemorrhagic diathesies
Relevant parental NOAEL	**A.** Not performed **B.** 0.001 mg kg bw/day
Relevant offspring NOAEL	**A.** Not performed **B.** 0.003mg kg bw/day
Relevant fertility NOAEL	**A.** Not performed **B.** -

Neurotoxicity

Species/ target/critical effect	**A./B.** No potential for neurotoxicity

Developmental Neurotoxicity

Species/ target/critical effect	No data available, no data required.

Immunotoxicity

Species/ target/critical effect	No data available, no data required.

Developmental Immunotoxicity

Species/ target/critical effect	No data available, no data required.

Other toxicological studies

-

Medical data

A.

Routine monitoring of workers (industrial users) producing the active substance and formulating products has been carried out for the last forty years. Between June 1981 and September 1982, three poisoning incidents occurred with successful recovery. With the exception of these incidents, routine monitoring has shown no clinical effects in any workers. During this time there has been no evidence of allergenicity, sensitisation or any other abnormal effects induced by repeated and continual exposure to these anticoagulant rodenticides.

B.

No significant effects caused in personnel with occupational exposure have been observed.

Summary

	Value	Study	Safety factor
$AEL_{short\text{-}term}$	**A.** **0.0000033 mg/kg/day**	**Rat: developmental toxicity study (maternal toxicity; NOAEL=0.001 mg/kg bw/d)**	**300**
	B. 0.00000667mg/kg/day	Rabbit: Maternal toxicity from a Developmental study (NOAEL = 0.002 mg/kg bw/d)	300
$AEL_{medium\text{-}term}$	**A.** Not derived		
	B. **0.0000067 mg/kg/day**	Rabbit: Maternal toxicity from a Developmental study (NOAEL = 0.002 mg/kg bw/d)	300
$AEL_{long\text{-}term}$	**A.** **0.0000033 mg/kg/day**	**90-day oral rat toxicity study (NOAEL = 0.001 mg/kg bw /d)**	**300**
	B. 0.0000033 mg/kg/day	Reproductive 2-generation study rat (NOAEL = 0.001 mg/kg bw /d)	300
ADI[4]	**A.** 1x 10^{-6} mg kg/day	90-day oral rat toxicity study	1000
	B. **3x 10^{-6} mg kg/day**	**Two generation study**	**300**
ARfD	Not applicable		

MRLs

Relevant commodities	Product is not intended to come into contact with food or feeding stuffs, contamination of food and feeding stuff can be excluded.

Reference value for groundwater

According to BPR Annex VI, point 68	0.1 µg/L

Dermal absorption

Study (*in vitro/vivo*), species tested	**A.** In vitro, human skin **B.** Not performed
Formulation (formulation type and including concentration(s) tested, vehicle)	**A.** Pellet Baits **B.** Not performed. Read across from data on difenacoum

[4] If residues in food or feed.

Dermal absorption values used in risk assessment	**A.** 5% (worst case approach, as value in epidermis and receptor fluid were below LOQ. A surrogate residue value was calculated to be <1.64% and <3.53%, respectively) **B.** 3% (pellets and grain) 0.047% (wax block bait)

Acceptable exposure scenarios (including method of calculation) [5]

Formulation of biocidal product	-
Intended uses	Klerat Pellets, containing brodifacoum 0.005% w/w (50 mg/kg), is a ready to use product for the control of rats and mice in and around buildings.
Industrial users	-

[5] At product authorisation new human exposure calculations should be performed taking into account HEEG opinion 10 and 12.

Professional users	A: Exposure scenario: Application + post application •Decanting, loading of bait station with ready to use baits and emptying and disposing of bait stations Frequency of daily use: •Decanting: 80 manipulations per 50g (4kg bait handled per day) •Loading and placement: 80 manipulations per day •Clean-up: 16 manipulations per day 50g bait per bait point Concentration of active substance: 0.005 % w/w Level of protection: Gloves For products used on a single occasion, the % AEL is 40.5% for total exposure (dermal + inhalation exposure) derived from exposure study for decanting, loading, placing and cleaning up scenarios assuming no use of gloves. For the products used on a repetitive or daily basis, the % AEL is 81.8% for total exposure (dermal + inhalation exposure) derived from exposure study for decanting, loading, placing and cleaning up scenarios. B: Exposure scenario: Application + post application Concentration of active substance: 0.005 % w/w Level of protection: Gloves worn For products used on a single occasion, the exposure accounted for 2.88-46.5% of AELacute when based on an Operator Exposure study,and assuming use of gloves. Acceptable exposure for all use areas of the products used on a repetitive or daily basis, occurs when gloves are worn (5.8-93.9 % of AELchr) and calculations are based on an Operator Exposure study
Non professional users	A: Exposure scenario: Application + post application Frequency of daily use: • Loading and placement: 5 manipulations per day • Clean-up: 5 manipulations per day Level of protection: No Gloves % AEL is 22%

General public	A+B Infants ingesting 10 mg bait For an infant body weight of 10 kg, this corresponds to an estimated acute dose of 5 x 10^{-5} mg brodifacoum/kg bw Compared to the $AEL_{short\ term}$, the % AEL is 1515
Exposure via residue in food	Not applicable

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	DT_{50} values (at 25 °C): **A.** At pH5 estimated by extrapolation to be approximately 173 days; At pH7 estimated by extrapolation to be approximately 300 days; At pH9 stable to hydrolysis. **B.** pH 4: stable to hydrolysis pH 7: stable to hydrolysis pH 9: stable to hydrolysis
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	**A.** Study available. Half life < 1 day. **B.** t1/2 = 0.083days
Readily biodegradable (yes/no)	No
Biodegradation in seawater	Not applicable.
Non-extractable residues	Not available.
Distribution in water / sediment systems (active substance)	Not available. Brodifacoum is expected to rapidly partition into sewage sludge/sediment due to its high log Pow and poor water solubility.
Distribution in water / sediment systems (metabolites)	Not available. Brodifacoum is hydrolysed relatively slowly under environmentally relevant conditions (300 d, pH 7, 25°C), degrades slowly in soil with a half-life of 157 d. The parent will adsorb to the sediment and there will be a slow transformation with low levels of degradation products (< 10% of the applied a.s.)

Route and rate of degradation in soil

Mineralization (aerobic)	**A.** Mineralisation occurs, with a mean total of 35.80% of applied radioactivity (as radiolabelled brodifacoum) being recovered as $^{14}CO_2$ at 52 weeks. The levels of radioactivity accounted for by volatiles other than $^{14}CO_2$ were less than 2% over the study period of 52 weeks.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	
DT_{50lab} (aerobic):	DT_{50lab} (19.0 – 22.5°C, aerobic): 157 days DT_{50lab} (12°C, aerobic): 298 days DT_{50lab} (10°C, aerobic): not determined.
DT_{90lab} (20°C, aerobic):	DT_{90lab} (20°C, aerobic): not determined.
DT_{50lab} (20°C, anaerobic):	DT_{50lab} (20°C, anaerobic): not determined.
	degradation in the saturated zone: not determined.
Field studies (state location, range or median with number of measurements)	
DT_{50f}:	not determined.
DT_{90f}:	not determined.
Anaerobic degradation	**B.** Brodifacoum was not degraded in anaerobic condition.
Soil photolysis	Not determined.
Non-extractable residues	**A.** Max. 23.6 % after 365 d
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	**A.** Up to 5 minor radiolabelled components, none exceeding 10% of the applied radioactivity at any time point, were present in the soil extracts of the aerobic soil metabolism study.
Soil accumulation and plateau concentration	**A.** Manner of use of products containing brodifacoum precludes soil accumulation with concentrations of Brodifacoum in soil predicted to be negligible/low, and occurring only sporadically according to bait treatment timings.

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	K_a values determined: **A.** - 635, 337, 263, 252, 301 for coarse sand soil (pH 7.6). - 1495, 811, 1280, 1379, 1358 for sandy clay loam soil (pH 7.1). - 1280, 1194, 1119, 1194, 842 for calcareous sandy loam soil (pH 7.6). K_d values could not be determined due to very slow desorption and therefore much less than required for a reversible reaction. Ka_{oc} , Kd_{oc} not determined but the adsorption of brodifacoum was the lowest to the soil having the lowest organic carbon content (the coarse sand). The average value for Koc of 9155 l/kg was determined from the three Kocs. Dependence upon pH not determined. **B.** Koc = 50000 (The Pesticide Manual 13th edition)

Fate and behaviour in air

Direct photolysis in air	**B.** According to TGD the t1/2 has been recalculated considering a concentration of OH radicals of 0.5 x 10^6 molec/cm^3 and the time 24 h; the new value is t1/2 = 6.61 h.
Quantum yield of direct photolysis	**B.** 1.28 x 10^{-3} (first 60 minutes) 3.29 x 10^{-3} minutes (60 to 180 minutes)
Photo-oxidative degradation in air	Latitude: ..... Season: ..... DT_{50} ..... Not applicable
Volatilization	Not applicable

Monitoring data, if available

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	Not available.
Ground water (indicate location and type of study)	Not available.
Air (indicate location and type of study)	Not available.

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity
Fish			
Rainbow trout (*Oncorhynchus mykiss*)	96 hours	Lethality	**A.** LC50 = 0.04 mg/l **B.** **LC50 = 0.042 mg/l**
Invertebrates			
Daphnia magna	48 hours	Immobilisation	**A. /B.** EC50 = 0.25 mg/l (same study)
Algae			
Selenastrum capricornutum	72 hours	Growth rate	A. /B. **ErC50 = 0.04 mg/l** (same study)
Microorganisms			
Pseudomonas putida	6 hours	EC_{10}	**A.** **>0.0038 mg/l (based on water solubility at pH 5.2 and T = 20°C)** **B.** >0.058 mg/l (based on water solubility at pH 7 and T = 20°C)

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia foetida*	**A. /B.** **14-d LC50 >994 mg/kg dwt (> 879.6 mg/kg wwt)** (same study)
Reproductive toxicity to ……	Not available. Waived.

Effects on soil micro-organisms

Nitrogen mineralization	Not available. Waived.
Carbon mineralization	Not available. Waived.

Effects on terrestrial vertebrates

Acute toxicity to mammals	**A.** **LD50 = 0.4 mg/kg bw (rat)**

	B. LD50 = <5 mg/kg bw (rat)
Lowest endpoint from chapter 3 Teratogenicity study Two-generation reproduction study in rat	**A.** NOEL = 0.001 mg/kg bw/d (rat). **B.** **NOAEL 0.001mg/kg bw/d** (rat, parent females), corresponding to **NOEC 0.02 mg/kg food.**
Acute toxicity to birds	**A.** **LD50: 0.31 mg/kg bw** (Mallard Duck) **B.** LD50: 19 mg/kg bw (Japanese quail)
Dietary toxicity to birds	**A.** **LC50 = 0.72 mg/kg food** (Laughing Gull) **B.** Not submitted
Reproductive toxicity to birds	**A.** **NOEC = 0.0038 mg/kg food** **NOEL = 0.000385 mg/kg bw/d** (read across to avian reproduction NOEC > 0.01 mg/Kg diet with Difenacoum applying an extrapolation factor of 26) **B.** NOEC = 0.012 mg/kg food NOEL = 0.0012 mg/kg bw/d (read across to avian reproduction NOEC > 0.01 mg/Kg diet with Difenacoum applying an extrapolation factor of 8.05)

Effects on honeybees

Acute oral toxicity	Not applicable.
Acute contact toxicity	Not applicable.

Effects on other beneficial arthropods

Acute oral toxicity	Not applicable.
Acute contact toxicity	Not applicable.
Acute toxicity to ……..	-

Bioconcentration

Bioconcentration factor (BCF)	**A.** **BCF_{fish} = 35645** calculated according to TGD eq. 75, using log K_{ow} = 6.12 (estimated from measured K_{oc})

	BCF earthworm =15820 calculated according to TGD eq. 82d, using log K_{ow} = 6.12 (estimated from measured K_{oc}) **B** No reliable estimate
Depuration time (DT_{50}) Depuration time (DT_{90})	**A.** Waiving for a bioaccumulation study acceptable. Using the estimated log Kow=6.12 and the equation for the depuration phase indicated in OECD 305 (Annex 4), the following values have been obtained: (DT50) = 7.96 d, (DT95) = 34.4 d **B.** No data available. Waiving for a bioaccumulation study acceptable.
Level of metabolites (%) in organisms accounting for > 10 % of residues	**A.** No data. Waived. **B.** No data. Waived

Chapter 6: Other End Points

Appendix II: List of studies submitted for the renewal of approval process

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
-	[redacted]	2009	Brodifacoum - Validation of Analytical Methodology for the Determination in Soil Central Science Laboratory Sand Hutton York, Y041 lLZ, UK Report no. PGD – 320 GLP Unpublished	Y	SYN
-	[redacted]	2015	Brodifacoum : Model Description to evaluate the secondary poisoning risk to wildlife from brodifacoum under different use scenarios Syngenta International Research Centre Jealott's Hill Bracknell RG42 6EY UK Report No. PI0002596	Y	SYN

[6] ***Section Number/Reference Number*** should refer to the section number in Doc III-A or III-B. If the study is non-key, and hence not summarised in Doc III but mentioned in Doc II, it should be included in the reference list alongside related references and its location in Doc II indicated in brackets. (If there is a need to include a cross-reference to PPP references then an additional column can be inserted).

[7] ***Author's Name*** should include the author's surname before initial (s) to enable the column to be sorted alphabetically. If the Human Rights Charter prevents author's surnames on unpublished references being included in non-confidential documents, then it will be necessary to consider including 'Unpublished [number/year & letter] ' in Doc II, and both ' Unpublished [number/year & letter]' and the 'Authors Name' in the reference list'. This may necessitate the need for an additional column to state whether a reference is unpublished which can then be sorted.

[8] ***Title, Source (where different from company), Company, Report No., GLP (where relevant), (Un)Published*** should contain information relevant to each item (ideally on separate lines within the table cell for clarity). If useful, the name of the electronic file containing the specific study/reference could be added in brackets.