**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



 



  

Bromadiolone

Product-type 14 (Rodenticides)

July 2016

Italy

# CONTENTS

1. [STATEMENT OF SUBJECT MATTER AND PURPOSE 3](#_bookmark0)
	1. [Procedure followed 3](#_bookmark1)
	2. [Purpose of the assessment report 3](#_bookmark2)
2. [OVERALL SUMMARY AND CONCLUSIONS 5](#_bookmark3)
	1. [Presentation of the Active Substance 5](#_bookmark4)
		1. [Identity 5](#_bookmark5)
		2. [Intended Uses 6](#_bookmark6)
	2. [Summary of the Assessment 6](#_bookmark7)
		1. [Specification of the different sources of the active substances 6](#_bookmark8)
		2. [Assessment as to whether the conclusion of the initial assessment of approval remain valid 7](#_bookmark9)
			1. [Physico-chemical properties and methods of analysis 7](#_bookmark10)
			2. [Classification and Labelling 7](#_bookmark11)
			3. [Efficacy and resistance 8](#_bookmark12)
			4. [Human health assessment 8](#_bookmark13)
			5. [Environmental assessment 8](#_bookmark14)
			6. [Fate and distribution in the environment 8](#_bookmark15)
			7. [PBT and POP assessment 8](#_bookmark16)
			8. [Assessment of endocrine disruptor properties 11](#_bookmark17)
		3. [Assessment of the recommendations arising from the report on RMM for anticoagulant rodenticides, in connection with the conclusions in the workshop, inputs from the applicant and any other information available to the eCA that are relevant for the active substance 12](#_bookmark18)
	3. [Overall conclusions 20](#_bookmark19)
	4. [Requirement for further information 20](#_bookmark20)
		1. [Requirement for further information related to the active substance 20](#_bookmark21)
	5. [List of endpoints 20](#_bookmark22)

[APPENDIX I: LIST OF ENDPOINTS 21](#_bookmark23)

[Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling 21](#_bookmark24)

[Chapter 2: Methods of Analysis 24](#_bookmark25)

[Chapter 3: Impact on Human Health 25](#_bookmark26)

[Chapter 4: Fate and Behaviour in the Environment 31](#_bookmark27)

[Chapter 5: Effects on Non-target Species 35](#_bookmark28)

[Chapter 6: Other End Points 37](#_bookmark29)

[APPENDIX II: LIST OF STUDIES SUBMITTED FOR THE RENEWAL OF](#_bookmark30) [APPROVAL PROCESS 38](#_bookmark30)

# STATEMENT OF SUBJECT MATTER AND PURPOSE

## Procedure followed

This assessment report has been established as a result of the evaluation of the active substance bromadiolone 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 rodenticides1 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 the recommendations of the RMM report for anticoagulant rodenticides.

Bromadiolone was approved as an existing active substance, in product-type 14 under the Biocidal Products Directive (Commission Directive 2009/92/EC). The renewal of the active substance has been requested by Bromadiolone Renewal Group (BRG).

On 05/03/2015, IT competent authority (eCA) received a dossier from Bromadiolone Renewal Group (BRG). The eCA accepted the dossier as complete for the purpose of the evaluation on 05/03/2015. 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, stringent risk mitigation measures will need to be applied. It was decided where no new information is available 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 25/03/2016, 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 the assessment report was amended accordingly.

## 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 bromadiolone 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.

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

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.

# OVERALL SUMMARY AND CONCLUSIONS2

## Presentation of the Active Substance

#### Identity

|  |  |
| --- | --- |
| CAS-No. | 28772-56-7 |
| EINECS-No. | 249-205-9 |
| Other No. (CIPAC, ELINCS | CIPAC No. 371 |
| IUPAC Name\* | *3-[(1RS,3RS;1RS,3SR)-3-(4′-bromobiphenyl-4-yl)-3-hydroxy-1- phenylpropyl]-4-hydroxycoumarin* |
| Common name | Bromadiolone |
| Molecular formula | C30H23BrO4 |
| Structural formula | OH OHO OBr |
| Molecular weight (g/mol) | 527.40 |
| Purity of the active substance as manufactured | Min. 96.9% |
| Isomers | Isomeric mixture of the two racemic diastereomers (1*RS*,3*RS*) and (1*RS*,3*SR*). Both diastereoisomers are toxicologically active and considered as active substance. Hence, the specification of purity includes both.More detailed information on the isomers and their ratio is given for each applicant in the Confidential Annex to the CAR for the original approval of bromadiolone. |
| Impurities | None of the impurities present in technical bromadiolone are considered relevant. The information on impurities is found for each applicant in the Confidential Annex to the CAR for the original approval of bromadiolone. |
| Additives | None are present |

\*As published for the ISO common name bromadiolone. It is considered that the ISO-common name Bromadiolone covers all possible ratios of the two diastereomers and that it is thus applicable to the substance presented herein.

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

#### Intended Uses

Bromadiolone ( a l o w p o t e n t S G A R s ) is used in products for pest control (Product type 14, rodenticides). Bromadiolone is used to control:

*Rattus spp.* (rat)

*Mus musculus* (house mouse)

Bromadiolone has been evaluated as a rodenticide against rats and mice for the following use patterns: in and around buildings (general public, non-professional, and trained professional users), sewers (trained professional users only), open areas (trained professional users only) and waste dump (landfill) perimeters (trained professional users only).

No new information on efficacy and resistance has been provided since the original approval and hence the conclusions remain the same.

According to the conditions for granting an authorisation of a biocidal products in Article 19(1)(b)(ii) of the Biocidal Products Regulation (EU) No 528/2012, products should be "sufficiently effective and have no unacceptable effect on the target organisms such as resistance, or, in the case of vertebrates, unnecessary suffering and pain". It is recognised that slow acting anticoagulant rodenticides like bromadiolone do cause pain for several days in rodents and are generally not considered as a humane method to control rodents. Other, more humane control methods are available: alternative active substances or biocidal products as well as non-chemical alternatives. However, as there are concerns whether these alternatives are sufficiently effective or do present other practical or economical disadvantages, anticoagulant rodenticides containing biocidal products should be accepted.

## Summary of the Assessment

#### Specification of the different sources of the active substances

The original approval of bromadiolone was supported by two different applicants, Liphatech and the Bromadiolone Task Force (members: Activa, PelGar, Babolna-Bio, and Laboratorios Agrochem S.L.). Following a technical equivalence assessment in 2010, Liphatech’s bromadiolone and Task Force’s bromadiolone were concluded to be technically equivalent and a combined assessment report and a combined LoEPs were prepared by the evaluating Competent Authority (eCA) for the original approval (*i.e.* SE).

**Liphatech:** During the evaluation of the Liphatech’s dossier, in 2005 the manufacturing of bromadiolone was moved to a different plant location, while the synthesis pathway remained unchanged. Both the old five-batch analysis (5-BA) data and the 5-BA data from the new manufacturing site, obtained in 2003 and 2005 respectively, turned out to comply with the specification proposed by Liphatech.

**Bromadiolone Task Force**: The Bromadiolone Task Force specification was supported only by the 5-BA (2005) from one manufacturer/manufacturing site, which is the one used specifically by Activa and Babolna-Bio. Batch-data were compliant with the proposed specification.

However, a different manufacturer/manufacturing site is used by other members of the Bromadiolone Task Force, i.e. PelGar and Laboratorios Agrochem S.L., which had to seek for technical equivalence assessment at product authorization for their own sources. The batch- data used for that purpose were made available also to eCA-IT in the context of the renewal, by either PelGar (5-BA, 2011) and Laboratorios Agrochem S.L. (5-BA, 2006).

Additionally, the technical equivalence of a new source of bromadiolone (**Bell Laboratories**) was assessed in 2012 by the eCA for the original approval (*i.e.* SE). A 5-BA carried out in 2011 was relied on. The new source was compared vs. Liphatech.

As agreed at BPC-16, a new 5-BA should be submitted at the next renewal of the approval of bromadiolone, when a source is covered by batch-data older than 10 years.

The above considered, a new 5-BA should be submitted by Liphatech, in order to prove that their manufacture is still in line with their original specification.

Likewise, a new 5-BA should be submitted by Activa and Babolna Bio, to show that their source still complies with the original Task Force specification. A new 5-BA should be submitted by Laboratorios Agrochem S.L., too. But where 5-BAs newer than 10 years are available, as for PelGar, the submission of Quality Control data from the past 5 years is sufficient to support their old batches (more than 5 years old). Quality Control data should be submitted as soon as possible, but not later than October 2016.

With regard to Bell Laboratories, Quality Control from the past 5 years are sufficient too, to support their 5-BA (more than 5 years old) and confirm that their actual specification is still in line with the specification evaluated for technical equivalence in 2012.

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

* + - 1. Physico-chemical properties and methods of analysis

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

* + - 1. Classification and Labelling

Bromadiolone presently has not a harmonised classification according to Regulation (EC) No 1272/2008 (CLP Regulation).

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

Bromadiolone 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 (Sweden) 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).

The RAC supported the proposal from Sweden. The RAC-opinion was adopted on 14 March 2014. The resulting Annex VI entry is listed below:

|  |
| --- |
| **Classification according to the CLP Regulation** |
| Hazard Class and Category | Repr. 1B; H360D |
| Codes | Acute Tox. 1; H300 |
|  | Acute Tox. 1; H310 |
|  | Acute Tox. 1; H330 |
|  | STOT RE 1; H372 (blood) |
|  | Aquatic Acute 1; H400 |
|  | Aquatic Chronic 1; H410 |
| **Labelling** |  |
| Pictograms | GHS06 |

|  |  |
| --- | --- |
|  | GHS08GHS09 |
| Signal Word | Danger |
| Hazard Statement Codes | H360D: May damage the unborn child H300: Fatal if swallowedH310: Fatal in contact with skin H330: Fatal if inhaledH372: Causes damage to the blood through prolonged or repeated exposureH410: Very toxic to aquatic life with long lasting effects |
|  |  |
| **Specific Concentration limits, M-Factors** | Repr. 1B; H360D: C ≥ 0,003%STOT RE 1; H372 (blood): C ≥ 0,005%STOT RE 2; H373 (blood) 0,0005% ≤ C < 0,005%M=1 (acute) M=1 (chronic) |

* + - 1. Efficacy and resistance

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

* + - 1. Human health assessment

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

However, 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.

* + - 1. Environmental assessment

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

* + - 1. Fate and distribution in the environment

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

* + - 1. PBT and POP assessment
				1. PBT assessment

No new information is available, but the assessment has been revised on the basis of the criteria set out under Regulation (EC) No. 1907/2006

The PBT assessment is similar to the one submitted to the TCNES Subgroup on Identification of PBT and vPvB Substances to their meeting in March 2008. It is based on data from both applicants of bromadiolone.

Persistence

According to the PTB assessment in the Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment (Version 2.0 November 2014), a substance fulfils the persistence criterion (P) in any of the following situations: (a) the

degradation half-life in marine water is higher than 60 days; (b) the degradation half-life in fresh or estuarine water is higher than 40 days; (c) the degradation half-life in marine sediment is higher than 180 days; (d) the degradation half-life in fresh or estuarine water sediment is higher than 120 days; (e) the degradation half-life in soil is higher than 120 days; and a substance fulfils the “very persistent” criterion (vP) in any of the following situations: (a) the degradation half-life in marine, fresh or estuarine water is higher than 60 days; (b) the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days; (c) the degradation half-life in soil is higher than 180 days.

The P screening criterion is fulfilled for bromadiolone since it is “not readily biodegradable” in water, which is further supported by that it is “not inherently biodegradable”. Bromadiolone is also stable to hydrolysis. The degradation rates in the soil studies show primary degradation with DT50 < 120 days in soil. Five metabolites are formed in quantities exceeding 10 % of AR and non-extractable residues are formed at maximum 21 % of AR. Although the TGD part II should be followed there is an additional P criterion in REACH Annex XIII, namely DT50 > 120 days in soil. One of the relevant metabolites, bromadiolone ketone, with a max formation of 39.6 % of AR, has a half-life in soil exceeding 120 days and a log Kow of 6.8 (as predicted using the software ECOSAR Kowwin v.1.67) which is higher than for bromadiolone itself. Also, it is evident from the structure of bromadiolone ketone that it has a similar level of toxicity as bromadiolone itself, which should be taken into account when the P criterion is evaluated. In conclusion, the P screening criterion for water is fulfilled and in addition, bromadiolone fulfils the soil P criterion of REACH taking the toxic and persistent metabolites into consideration. However, reading across from a structural analogue Difenacoum, considered to be persistent and very persistent, bromadiolone can be concluded to fulfil the P criterion.

Bioaccumulation

According to the PTB assessment in the Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment (Version 2.0 November 2014), a substance is considered to fulfil the B criterion when the bioconcentration factor in aquatic species is higher than the value of 2000 and fulfil the vB criterion if BCF exceeds 5000. If measured BCF values are not available, a substance is considered to potentially fulfil the B criterion if log Kow exceeds a value of 4.5.

The laboratory studies on bioconcentration in fish are both of low reliability and they are not used to assess the B criterion. BCF studies are technically difficult to conduct as bromadiolone including its metabolite bromadiolone ketone is highly toxic to fish. The calculation method uses log Kow as input value, and the BCF values, based on log Kow measured at pH 6 and pH 7, are both below the trigger value for fulfilment of the screening B criterion. Despite this, some uncertainty regarding the fulfilment of the B criterion remains since there are monitoring studies available that show residues of bromadiolone in wildlife in which most of the incidents of contamination are believed to be due to feeding of contaminated prey. However, it is not possible to draw any conclusions in relation to the B/vB criteria as the exposure situation is not known. The metabolite bromadiolone ketone has a predicted log Kow of 6.8 and thus fulfils the screening B criterion. Literature studies show that bromadiolone was found in the livers of non-target species feeding on rodents or their carcasses in some European studies (Newton et al. 1997; Geduhn et al. 2015; López- Perea 2015; Christensen et al. 2010; Elmeros et al. 2015). The 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 bromadiolone), bromadiolone should be considered as bioaccumulative and therefore, bromadiolone fulfils the B criterion.

Toxicity

According to the PTB assessment in the Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment (Version 2.0 November 2014), a substance fulfils the toxicity criterion (T) in any of the following situations: (a) the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms is less than 0.01 mg/L; (b) 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; (c) 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.

Bromadiolone is very toxic and is to classify the substance as fatal if swallowed, in contact with skin and if inhaled (Acute Tox. 1; H300, H310, H330), as causing damage to organs after prolonged or repeated exposure (STOT RE 1; H372 – blood) for all routes with blood as the target organ and Repr.1B presumed of damaging fertility (H360D). Bromadiolone is also classified as very toxic to aquatic life with long-lasting effects (Aquatic Acute 1 and Aquatic Chronic 1, M=1 in both cases). The substance should therefore be considered as fulfilling the T criterion. Based on structural similarities, there is reason to assume that some of the metabolites (particularly bromadiolone ketone) are as toxic as the mother substance. Regarding the T-criterion for environment bromadiolone is potentially toxic based on results from short-term toxicity data on aquatic organisms. In conclusion bromadiolone fulfils the T criterion.

Conclusion:

**Bromadiolone is considered a PBT substance.**

* + - * 1. POP assessment
* The substance fulfils the screening criteria (Annex D of the Stockholm Convention) for persistency (evidence that the half-life of the chemical in water/sediment might be greater than two/six months or that its half-life in soil is greater than six months).
* Screening criteria for bioaccumulation are also fulfilled (evidence that the bioconcentration factor in aquatic species for the chemical is greater than 5,000 or, in the absence of such data, that the log Kow is greater than 5). No measured bioconcentration factor in fish is available, but some uncertainty regarding the fulfilment of the B criterion remains since there are monitoring studies available that show residues of bromadiolone in wildlife in which most of the incidents of contamination are believed to be due to feeding of contaminated prey. However, it is not possible to draw any conclusions in relation to the B/vB criteria as the exposure situation is not known. The metabolite bromadiolone ketone has a predicted log Kow of

6.8 and thus fulfils the screening B criterion.

* The substance is also very toxic and fulfils the screening criteria for “adverse effect” (toxicity or ecotoxicity data that indicate the potential for damage to human health or to the environment).

The substance does not fulfil the numerical screening criteria for potential for long-range environmental transport: The rapid photolysis rate in air (t½ ca 2 hours), the low vapour pressure of bromadiolone and the low Henry’s law constant together show that bromadiolone is not expected to volatilise to or persist in air in significant quantities.

Moreover, the vapour pressure and Henry's law constant are low and the adsorption potential to organic matter is high. There is no monitoring data available or other evidence indicating potential for long range environmental transport. On basis of the available information can be concluded that the initial criteria for long-range transport potential are not met.

In conclusion, bromadiolone exhibits certain POP characteristics (persistence, bioaccumulation and adverse effects), but does not fulfil the screening criteria for long-range environmental transport. Bromadiolone therefore does not meet the criteria for being a persistent organic pollutant.

2.2.2.8. Assessment of endocrine disruptor properties

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

#### Assessment of the recommendations arising from the report3 on RMM for anticoagulant rodenticides, in connection with the conclusions in the workshop, inputs from the applicant and any other information available to the eCA that are relevant for the active substance.

Anticoagulant rodenticides (AR) are divided into First Generation AR (FGAR; warfarin, chlorophacinone, coumatetralyl) and Second Generation ARs (SGARs; bromadiolone, difenacoum, brodifacoum, flocoumafen and difethialone). Difethialone, brodifacoum and flocoumafen are often referred to as more potent than bromadiolone and difenacoum.

Anticoagulant rodenticides have been found in many studies in non-target animals. Some new studies were submitted for the renewal of the anticoagulant rodenticides: i) in Denmark coumatetralyl and several SGARs were found in stone martens and polecats; ii) in UK anticoagulant rodenticides are regularly detected in the Predatory Bird Monitoring Scheme and in incidents of suspected poisoning of animals by pesticides investigated under the Wildlife Incident Investigation Scheme; iii) in Germany several FGARs and SGARs were found in the red fox; iv) in Spain SGARs were found in birds of prey and hedgehogs; in France anticoagulant rodenticides have been found in buzzards, red kite and mustelids species; v) in Finland all anticoagulant rodenticides in use (i.e. coumatetralyl and SGARs) were found in predatory and scavenging non-target birds and mammals. More studies are publicly available but these show that there is a concern with respect to secondary exposure of non-target organisms.

Due to the identified risk for environment and human health, anticoagulant rodenticides have to be handled with great caution and all appropriate and available risk mitigation measures (RMMs) have to be applied. As several AR, which are quite similar regarding hazardous properties and associated risks, were assessed for possible renewal at the same time (see also the CA-document “Substance approval and product authorisation renewals of the anticoagulant rodenticides; CA-Feb13-Doc.5.2.b), the Commission initiated a project on possible risk mitigation measures which could be applied for all anticoagulant rodenticides. This resulted in the report “Risk mitigation measures for anticoagulant rodenticides as biocidal products” (Berny, P. et al., October 2014). The report distinguishes between risk mitigation measures at community level through imposing conditions in the approval for the active substance, and measures at national level when products are authorised.

As a follow-up to the report, the Commission organised a workshop on 26 February 2015 with the aim to discuss and agree on RMMs to be recommended for anticoagulant rodenticides. The workshop was attended by representatives of several Member State Competent Authorities, the Commission, the Rodenticide Resistance Action Group (RRAG, UK), CEPA (Confederation of European Pest Management Associations), CEFIC (the European Chemical Industry Council) and members of the Efficacy Working Group. A summary report presenting the results of the workshop was discussed at the CA meetings in March and November 2015 (“Revised version of the summary of the workshop on the RMM report held in Brussels on 26/02/2015”; CA-Nov15- Doc.5.4). The result of an internet survey on the relevant RMMs was included in the report.

A critical review of the RMM was submitted by the applicant of bromadiolone when submitting the application for renewal in line with the CA document “Complementary guidance regarding the renewal of anticoagulant rodenticide active substances and biocidal products” (CA-Sept14- Doc.5.2-Final.Rev1).

In this section the risk mitigation measures proposed in the report of Berny et al. (2014) are presented and assessed, distinguishing between the measures at approval and product

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

authorization stage. This assessment includes, if available, the critical review of the applicant and a recommendation or conclusion by the evaluating Competent Authority.

The detailed considerations in this section on the recommendations for renewal of the inclusion in the Union list of approved active substances formed the basis for the renewal conditions and the elements to be taken into account when authorising products as laid down in respectively sections 2.3 and 2.4 of the opinion of the Biocidal Products Committee (BPC).

### General recommendations on RMM for anticoagulant rodenticides

**RMM to be set at active substance approval**

In the survey reported in the summary of the workshop, most member states agreed that the order of use of methods and substances to control rodents, generally should be: Non chemical methods > FGARs > less potent SGARs > potent SGARs.

#### 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.

The applicant commented that 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. However, currently there is no rapid way to determine the resistance status of a rodent infestation prior to treatment. The proposed approach is therefore neither realistic nor practical.

The eCA agrees in the above mentioned order of use of the substances. It should be kept in mind that ineffective use of anticoagulant rodenticides can be misdiagnosed as resistance.

#### 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 it was concluded that there is not necessary information nor support to restrict FGAR at EU level for use against mice. The authorization of biocidal products should be decided upon the national or regional resistance situation. It was commented that there is a lack of data on resistance in house mice, and that there is a lot of variation throughout Europe. This was further supported in the Efficacy Working Group in January 2016.

The eCA agrees with the RMM reported above.

#### Provided the other RMMs are applied (pack size, bait stations see below), there is no reason to restrict the use of SGARs for amateurs, especially in order to control house mice populations, which are the number one problem in the amateur sector.

According to the internet survey referred in the summary of the workshop, the majority of member states authorize both FGARs and SGARs for use by the general public, both for control of mice and rats.

The applicant states that use of rodenticides by amateurs is essential for the wider control of rodent infestations in order to protect public health, property and the environment. If rodent control were to become completely reliant on professional operators, then this could be the cause of householders ignoring the need for treatment of infestations due to the higher cost and so increase the associated risks to public health. Furthermore, industry considers that there are currently insufficient pest control operators to treat the reported number of household infestations. The applicant noted also that farmers are considered to be amateurs in some Member States and farmers should not be denied access to rodent control because of the risks that would present to the food chain.

The eCA agrees with the RMM mentioned above.

#### 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.

At the workshop it was agreed that products for professionals and the general public should be placed at the market as different products with different pack size and separate labelling. The proposal for maximum pack size in the RMM report was considered as a good starting point and CEFIC was asked to make a proposal. However, such a proposal has not been provided.

Industry has always applied this restriction but with a practical maximum pack size – 1.5kg has been proposed. The list of pack sizes proposed in the RMM report is simplistic as it does not consider potency and presumes only one bait point. For all amateur use products a pack of 1.5kg will allow for a small number of bait points with one or two refills which would be sufficient to treat a very small rat infestation.

Considering the unacceptable risk calculated for infants ingesting the product, eCA considers appropriate to limit the pack size that should be limited for the general public with smaller amounts sold of SGARs. The proposal for pack size included in the RMM report could be used in the product authorisations. The products sold to the general public should be different from products sold to professionals.

#### 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).

At the workshop is was agreed that the control of rats in and around buildings should be allowed for the general public. However, it should be subject to derogations from the mutual recognition at the product authorization stage.

The applicant agrees as virtually all rat infestations are of an outdoor origin as rats will live outdoors and search indoors for food etc.

The eCA agrees with what stated above. However, this RMM could be subject to derogation from the mutual recognition at the product authorization stage.

#### Dyes should always be included in all formulations containing bromadiolone. 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.

At the workshop in was unanimously agreed that dyes should be included in bait formulations (including red dyes).

The applicant commented that industry has always included dyes and pigments in rodenticidal products to reduce the risk of accidental uptake by humans and birds etc. To specify which colours is an unnecessary restriction and commercially unwarranted.

The eCA agrees that the addition of a colouring agent to baits should be mandatory for bait formulations.

#### Bittering agents should be included in all bait formulations. Denatonium benzoate at 0.01% (10 mg.kg-1)\* is currently the most commonly used bittering agent in bait formulations.

*[\*Correction by the applicant: The bittering agent is commonly incorporated at 0.001% (10mg/kg)]*

At the workshop it was unanimously agreed that bittering agents should be included in bait formulations.

Industry itself introduced the use denatonium benzoate as a human taste deterrent in the 1980’s and will continue to do so.

The eCA agrees on the importance to include bittering agents (e.g. denatonium benzoate) in the bait formulations to reduce the likelihood of oral consumption in humans (i.e. to reduce the amount ingested in case of accidental/intentional intake of bait). However, the presence of the bittering agent would significantly reduce the probability of an accidental ingestion by the youngest children but not totally avoid it.

#### 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.

At the workshop it was agreed that surveys before baiting should be included in code of best practice or be included as a RMM at active substance renewal. As for information in the surrounding area, no position was agreed. Hence, this RMM will be left to the Member States to decide.

Conducting site surveys prior to treatment is considered Best Practice. It is impossible to conduct efficient and effective rodent control with minimal environmental risks without having conducted a survey. Attention should not be drawn to treated areas as this would present evidence of an infestation which could have deleterious effects e.g. on nearby businesses and it would invite the abuse and vandalism of bait points. The text of notices on bait stations should be essential and relevant.

The eCA agrees that a pre-treatment survey of the infested area is necessary to perform by professionals in order to determine the extent of the infestation. Information should always be applied on the bait stations.

#### 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.

A large majority of the member states in the survey (reported in the summary of the workshop) agreed that tamper resistant bait stations with securely fixed baits should be mandatory for use by the general public. As for use of loose baits for the general public there were mixed responses.

The applicant commented that the proposal fails as there is no European definition of tamper- resistant. As the use of bait stations reduces efficacy especially for rat control their use should not be mandatory. Furthermore, there would be situations, e.g. roof voids, locked outbuildings, where bait stations would not be necessary. Loose baits (such as grain and pellets) should in their opinion not be excluded for amateur use, because of their higher palatability.

The eCA agrees with the RMM mentioned above. Regarding loose formulations, individual pre- dosed sachets to be opened and poured into the bait station should be considered and, in general, no decanting operation should be allowed for non-professional users.

#### 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 it was agreed that the use of non-conventional bait stations (e.g. open trays or similar) by trained/certified professionals should be possible under certain circumstances. Member states might derogate from mutual recognition at the product authorization stage.

According to the applicant optimizing bait presentation to the rodents is important to 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. Current Best Practice requires the use of protected bait points. Bait points may be protected by use of bait stations or under covers made from materials found on the site. The use of bait stations is known to limit efficacy as they deter rats from feeding on the bait. The use of materials from the site will result in more efficacious rat control as it will reduce neophobia.

The eCA thinks that tamper-resistant boxes only should have to be used; other solutions to manage the baiting could be too subjective and rise up the risk of dispersal of the bait. Nevertheless, such alternative solutions to manage or cover the bait points could be considered in extraordinary documented situations.

#### 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. At the workshop it was pinpointed that efficacy needs to be demonstrated. Pulsed baiting, if approved, must be mentioned specifically on the SPC/label of the product.

According to the applicant, pulse baiting is authorised only for products containing brodifacoum and flocoumafen. It is uncertain whether products containing bromadiolone and difenacoum could be used in this manner because of their lower potency. Field trial data would have to be generated to support or dismiss this proposal.

The eCA agrees that efficacy of pulsed baiting needs to be demonstrated and, if approved, must be mentioned specifically on the SPC/label of the product. However, even if pulsing baiting could have positive aspects, the eCA believes that this measure could rise resistance in rodent populations.

#### 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.

At the workshop it was agreed that permanent baiting outdoors should be possible for trained/certified professionals under certain circumstances. This could be defined in a code of Best practice. Member States should be allowed to derogate from mutual recognition (MR) of such use at the product authorization.

The applicant commented that permanent baiting for specific locations could be appropriate as part of an IPM strategy based on site specific risk assessments.

The eCA agrees with the RMM mentioned above.

#### 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.

At the workshop it was agreed that permanent baiting indoors should be possible for trained/certified professionals under certain circumstances. This could be defined in a code of Best practice.

The applicant agrees on the statement.

The eCA agrees with the RMM mentioned above.

#### 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. The choice of a baiting treatment beyond 35 days shall be justified.

At the workshop it was agreed that an evaluation should be made after 35 days.

The applicant commented that best practice requires that if control has not been achieved within 35 days then the reasons should be investigated and the risk assessment updated accordingly. In some situations, e.g. sensitive areas or areas subject to constant reinvasion, baiting beyond 35 days will be justified.

The eCA agrees that anticoagulant rodenticides shall not be used beyond 35 days without an evaluation of the state of the infestation and of the efficacy of the treatment, even if in this case eCA believes it is better a longer period of baiting with ARs; moreover this period should have to be adjusted by monitoring.

#### 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 agreed that the frequency of visit should be left to the professionals. A reference to code of best practice should be made by the MS.

The applicant commented that the frequency of visits is dependent on the infestation and site and should be evaluated in the risk assessment. Furthermore, the applicant agrees that treated sites should be visited at least once a week.

The eCA agrees that the frequency of visit should be left to the operator. Member states should encourage the application of Codes of Best Practices in rodent control. Reference to code of best practice should be made by the MS in relation to frequency of visits.

#### 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”). However the method of disposal should be described specifically on the national SPC and product label.

At the workshop the importance to remove and dispose of dead rodent bodies was agreed. However, there were mixed opinions on the method of disposal. Hence, it was proposed to leave the method of disposal and the classification of waste to the Member State.

According to the applicant, disposal of dead and moribund rodents on every site visit is considered to be Best Practice and has been included on product labels for decades.

It was further commented that making specific recommendations for disposal on product labels which are mutually recognised is difficult as different legislation will apply. Thus, the preference is to indicate that the disposal should be done in accordance with local regulations.

The pragmatic proposal for disposal by clients and other amateurs is considered to ensure that amateurs will dispose of rodent bodies in a proper manner.

The eCA agrees with the RMM mentioned above.

#### 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. However the method of disposal should be described specifically on the national SPC and product label.

At the workshop the importance to remove and dispose uneaten bait was agreed. However, there were mixed opinions on the method of disposal. Hence, it was proposed to leave the method of disposal and the classification of waste to the Member State.

The applicants commented that removal of uneaten bait at the end of a treatment is Best Practice and has been included on product labels for decades. Furthermore, the pragmatic proposal for disposal by amateurs will ensure that they will dispose of uneaten bait in a proper manner.

The eCA agrees with the RMM mentioned above.

#### 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.

Applicant states that 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. FGAR-, bromadiolone- and difenacoum-containing products should not be used where there is evidence of resistance. If there is no evidence of resistance, any authorised product can be used. Evidence includes failing to control an infestation after exclusion of all factors other than resistance. This reflects the position held by Industry as developed by CropLife’s Rodenticide Resistance Action Committee, the Rodenticide Resistance Action Group in the UK and similar groups within the EU.

#### 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.

The applicant comment is that the industry is doing this through rodenticide resistance action groups.

Depending on the feasibility of implementation of a resistance monitoring programme at EU- level, the eCA agrees that information on resistance throughout EU should be made available online.

### RMM to be set at the stage of product authorisation

#### Bait stations should be mandatory for amateur products. Various levels of protection can be obtained with the different bait stations and it is suggested to develop

***specific requirements for bait stations qualification. Different levels of protection are described in the document and levels 2-3 should be considered for amateurs.***

This particular issue was apparently not discussed at the workshop, as not reflected in the summary.

The eCA agrees that tamper resistant bait stations should be mandatory for products to be used by amateurs.

#### All bait formulations should be available to all user categories, with limited amounts and tamper-resistant bait stations for amateurs.

This particular issue was only partly discussed at the workshop as referred earlier in the text. The eCA agrees that limited amounts of bait should be available for use by the general public.

#### A standardized Summary of Product Characteristics (SPC) template should be completed for all products and readily available to all potential users. It should be the basis for label recommendations. It is strongly suggested to have a common and simplified label across MSs.

A work is ongoing in EU to harmonise as far as possible the relevant section of the SPCs for anticoagulant rodenticides. A Working Party (WP) was set up in autumn 2015 to discuss the relevant SPC sections, keeping in mind that the risk mitigation measures (RMMs) are also affected by the BPC discussions in the context of the renewal of the active substances.

#### Product manufacturers should provide a list of the information media available for the various user categories. Information leaflets or labels should be provided at this stage.

Ensuring that appropriate information (label, leaflet) is supplied to the user is essential. In addition easily understandable online information should be available.

## Overall conclusions

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

## Requirement for further information

#### Requirement for further information related to the active substance

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal of renewal the approval of bromadiolone*.* However, the following data should be provided to the evaluating Competent Authority Italy:

* Quality Control data from the past 5 years should be submitted by one member of the Bromadiolone Task Force (*i.e.* PelGar) and by Bell Laboratories, as soon as possible but not later than Oct 2016;
* As regards the remaining members of the Task Force, new 5-BAs should be submitted at the next renewal of the approval of bromadiolone by Activa, Babolna-Bio and Laboratorios Agrochem S.L.. A new 5-BA should be submitted at the next renewal also by Liphatech;
* According to the latest guidance, a method for drinking water fulfilling the relevant toxicological standard should be provided as soon as possible, but at the latest by the next renewal of the active substance.

Appropriate data from/on resistance monitoring may be provided by the applicant during the next renewal process4.

Applicants should provide within the application for the next renewal all new data available to them on resistance to the active substance on the target organisms in the EU.

A general discussion will take place on data requirements for renewal at the BPC APCP and Environment Working Groups. It may be possible that a Working Group requests additional data to be submitted for the following renewal of the active substance approval.

## 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](#_bookmark24).

4 depending on feasibility of the implementation of resistance monitoring programme at EU level.

# Appendix I: List of endpoints

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

|  |  |
| --- | --- |
| Active substance (ISO Name) | *Bromadiolone\** |
| Product-type | PT14 |

### Identity

|  |  |
| --- | --- |
| Chemical name (IUPAC) | *3-[(1RS,3RS;1RS,3SR)-3-(4′-**bromobiphenyl-4-yl)-3-hydroxy-1- phenylpropyl]-4-hydroxycoumarin* |
| Chemical name (CA) | *3-[3-(4'-bromo[1,1'-biphenyl]-4-yl-)-3-**hydroxy-1-phenylpropyl]-4-hydrox-2H-1- benzopyran-2-one* |
| CAS No | 28772-56-7 |
| EC No | 249-205-9 |
| Other substance No. | CIPAC: 371 RTECS: GN493470 |
| Minimum purity of the active substance as manufactured (g/kg or g/l) | 969 g/kg[relates to the mixture of two racemic diastereomers: (1*RS,*3*RS)* and (1*RS*,3*SR*). Both diastereoisomers are toxicologically active and considered as active substance ] |
| Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg) | None |
| Molecular formula | C30H23BrO4 |
| Molecular mass | 527.4 g/mol |
| Structural formula |  |

\* It is considered that the ISO-common name bromadiolone covers all possible ratios of the two diastereomers and that it is thus applicable to the substance presented herein.

### Physical and chemical properties

|  |  |
| --- | --- |
| Melting point (state purity) | 172.4-201.7 °C (98.8%)198.3-199.8 C (~100%) |
| Boiling point (state purity) | Decomposition before boiling |
| Thermal stability / Temperature of decomposition | Decomposition before boiling |
| Appearance (state purity) | White powder (98-100%)Odourless (99-100%) |
| Relative density (state purity) | 1.45-1.46 g/cm3 at 20-21°C (98.7-98.8%) |
| Surface tension (state temperature and concentration of the test solution) | 71.3-72.1 mN/m at 20-21°C and a concentration of 1.47-17.4 mg/l (98.8-98.9%) |
| Vapour pressure (in Pa, state temperature) | 2.13 x 10-8 Pa at 25°C (extrapolated; 100%)< 0.05 x 10-3 Pa at 45°C (99.9%) |
| Henry’s law constant (Pa m3 mol-1) | 4.25 x 10 - 4 Pa m3 mol-1 (using a published vapour pressure of 2.0 x 10-6 Pa at 20°C and a water solubility of 2.48 mg/l at pH 7)8.99 x 10 - 7 Pa m3 mol-1 (using a vapour pressure of 2.13 x 10-8 Pa at 25°C and a water solubility of 12.5 mg/L at 25°C in purified water) |
| Solubility in water (g/l or mg/l, state temperature) | In buffered solutions at 20°C:pH 4-5: 0.10-0.11 mg/l (98.7-98.8%)pH 7: 18.4 mg/l (98.7%)pH 9: 0.18 g/l (98.8%)pH 10: 1.23 g/l (98.7%)In purified water:12.5 mg/l at 25°C (98.7%; pH not stated) 2.48 mg/l at 20°C (98.8%; pH 7) |
| Solubility in organic solvents (in g/l or mg/l, state temperature) | n-heptane: 3.1-3.4 mg/l at 15-25°C (98.8%)n-hexane: 7.15 mg/l at 25°C (100%)methanol: 6.93-15.0 g/l at 25°C (98.8-100%) |
| Stability in organic solvents used in biocidal products including relevant breakdown products | Not applicable. Neither technical bromadiolone as manufactured nor the representative products contain any organic solvents. |
| Partition coefficient (log POW) (state temperature) | In buffered solutions:pH 4-5: log Pow ≥ 5 (20-25°C; 98.7-98.8%) |

|  |  |
| --- | --- |
|  | pH 6-7: log Pow = 3.8-4.1 (20-25°C; 98.7-99.1%)pH 9-10: log Pow = 2.5-3.2 (20-25°C; 98.7-98.8%)In purified water:log Pow = 4.3 at 23°C (100%; pH not stated) |
| Dissociation constant | Technically not feasible to experimentally determine the dissociation constant, due to low water solubility.Predicted pKa (ACD/PhysChem Suite): pKa1=4.5 (deprotonation of the hydroxyl- group in the coumarine moiety of the enolicform of bromadiolone)pKa2=9.06 (deprotonation of the carbon between the ketone and the lactone in the coumarine moiety of the keto form of bromadiolone) |
| UV/VIS absorption (max.) (if absorption> 290 nm state  at wavelength) | In buffered 96% ethanolic solution (98.4-99.5%):maxima: 259 nm (ε = 29637 L mol-1 cm-1), 313 nm (ε = 13949 L mol-1 cm-1)In methanol (98%):maxima: 263 nm (ε = 32325 L mol-1 cm-1), 310 nm (ε = 11095 L mol-1 cm-1) |
| Flammability or flash point | Not flammable(technical material, purity not stated) |
| Explosive properties | Not explosive (theoretical consideration) |
| Oxidising properties | Not oxidising |
| Auto-ignition or relative self ignition temperature | No self-ignition below the melting point |

**Classification and proposed labelling**

|  |  |
| --- | --- |
| with regard to physical hazards | none |
| with regard to human health hazards | GHS06 GHS08Repr. 1B; H360DAcute Tox. 1 ; H300 Acute Tox. 1; H310 Acute Tox. 1; H330 STOT RE 1; H372 (blood) |
| with regard to environmental hazards | GHS09Aquatic Acute 1; H400 Aquatic Chronic 1; H410 |

|  |  |
| --- | --- |
| **Specific concentration limits for the aquatic hazard classification** | Repr. 1B; H360D: C ≥ 0,003%STOT RE 1; H372 (blood): C ≥ 0,005%STOT RE 2; H373 (blood) 0,0005% ≤ C < 0,005%M=1 (acute) M=1 (chronic) |

## Chapter 2:Methods of Analysis

**Analytical methods for the active substance**

|  |  |
| --- | --- |
| Technical active substance (principle of method) | Method provided by Liphatech (see further the Confidential Annex to the CAR for the original approval of bromadiolone):1. Qualitative step (spectroscopy, isomeric distribution, melting point)
2. Quantitative step (titration)

Method provided by Task Force: HPLC-UV |
| Impurities in technical active substance (principle of method) | See the Confidential Annex to the CAR for the original approval of bromadiolone for each applicant |

**Analytical methods for residues**

|  |  |
| --- | --- |
| Soil (principle of method and LOQ) | HPLC-MS (LOQ 0.22 µg/kg) LC-MS/MS (LOQ 0.01 mg/kg) |
| Air (principle of method and LOQ) | HPLC-UV (LOQ 0.5 µg/m3)No confirmatory method available - not considered needed due to the low vapour pressure |
| Water (principle of method and LOQ) | HPLC-FD (LOQ 0.05 µg/l), HPLC-MS(LOQ 0.05 µg/l)confirmation: LC-MS/MS |
| Body fluids and tissues (principle of method and LOQ) | LC-MS/MS (LOQs 0.05 mg/l blood,0.05 mg/kg liver)LC-MS/MS (LOQs 0.01 mg/l blood,0.01 mg/kg liver) |
| Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) | Multi residue method:LC-MS/MS (LOQ 0.01 mg/kg cucumber and wheat)Single method:LC-MS/MS (LOQ 0.01 mg/kg lemon and oilseed rape) |
| Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) | LC-MS/MS (LOQ 0.01 mg/kg meat) |

## Chapter 3:Impact on Human Health

**Absorption, distribution, metabolism and excretion in mammals**

|  |
| --- |
| Bromadiolone was rapidly and extensively absorbed by rats. An exact oral absorption value could not be set based on Liphatech data but maximum levels in the plasma were attained after 9 hours.**The oral absorption was >70% (71- 77% based on carcass, urinary- and biliary excretion, Task Force data)** Absorption fairly slow with peak plasma levels of total radioactivity not being seen until 4-8 h post dose. Peak tissue concentrations of radioactivity wereobserved at 4 and 24 h post dose. |
| Based on in vitro studies on products a value of 1.6% was obtained that was used for the risk assessment. However, data for both applicants suggest low absorption of wax block formulations i.e. approx 0.3% for SUPER CAID BLOC (Liphatech).Based on an in vitro study of formulated active (bait:saline incorporated bromadiolone 0.00255 w/w) and a representative wax block formulation (0.005 % w/w) a worst case value of 0.36% was obtained that was used for this risk assessment (Task Force).No study on the pure active substance for Liphatech or Task Force. **Based on MW (>500) and log Pow (>4) a default value of 10% can be estimated for the active substance if no other studies are available.** |
| Extensively bound to plasma proteins (>98.8%). Liver and GI tract were only tissues investigated. Radioactivity in theG.I tract at 48 hours accounted for a mean of 18.0% of the dose. The majority of the dose is eliminated unchanged in faeces via bile and no other tissues show evidence of any molecule retention (Liphatech).Tissue levels above plasma levels, low dose: liver, adrenal glands, kidney, and spleen (1h post dose and 24h post dose) and thyroid (1h post dose) lungs (24h post dose). High dose: liver and kidney (1h post dose) and liver, kidney, adrenal glands and lungs. (24h post dose) (Task Force) |

Rate and extent of oral absorption:

Rate and extent of dermal absorption\*:

Distribution:

|  |  |
| --- | --- |
| Potential for accumulation: | Bromadiolone has the potential for bioaccumulation in the liver. The liver half life is approximately 318 days (Liphatech). 33-48% of dose was retained in the animal 7 days post dose, mainly in liver (Task Force). |
| Rate and extent of excretion: | Bromadiolone is excreted relatively slowly and almost entirely via the bile and faeces. As a maximum around 5% of radioactivity was excreted into urine (Task Force, but contained no parent bromadiolone). Around 20% of the bromadiolone dose was excreted unchanged into faeces (Task Force). |
| Toxicologically significant metabolite(s) | The sole major metabolite was identified as a hydroxylated analogue of bromadiolone (hydroxlation proposed as occurring on the benzylic carbon atom). None of the metabolites identified for hydroxy coumarin derivatives used as rodenticides have been shown to be toxicologically significant (Liphatech).Investigation of metabolites was not performed (Task Force). |

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

|  |
| --- |
| **Acute toxicity** |
| Rat LD50 oral | 1.31 mg/kg bw (male and female rats combined) 95% confidence limits 1.17 to1.49 mg/kg bw/day (Task Force)Between 0.56 and 0.84 mg/kg bw (female rat) (Liphatech) |
| Rat LD50 dermal | 23.31 mg/kg bw (male and female rabbits combined) (Task Force)1.71 mg/kg bw (male and female rats combined) (Liphatech) |
| Rat LC50 inhalation | No data no study (Task Force)0.43 µg/L (males and females combined) (Liphatech) |

|  |  |
| --- | --- |
| **Skin corrosion/irritation** | Not irritating |

|  |  |
| --- | --- |
| **Eye irritation** | Not irritating |

|  |  |
| --- | --- |
| **Respiratory tract irritation** | - |

|  |  |
| --- | --- |
| **Skin sensitisation (test method used and result)** | Not a skin sensitizer |

|  |  |
| --- | --- |
| **Respiratory sensitisation (test method used and result)** | - |

### Repeated dose toxicity

|  |  |
| --- | --- |
| Species / target / critical effect | Anticoagulant effects (dog, rat, rabbit) |
| Relevant oral NOAEL / LOAEL | Task Force: NOAEL 2.5 µg/ kg bw/day (rat)**NOAEL 0.5 µg/kg bw/day (rabbit)**Liphatech: NOAEL 8 µg/ kg bw/day (dog) |
| Relevant dermal NOAEL / LOAEL | No studies, not required |
| Relevant inhalation NOAEL / LOAEL | No studies, not required |

|  |  |
| --- | --- |
| **Genotoxicity** | No genotoxic effects |

|  |  |
| --- | --- |
| **Carcinogenicity** |  |
| Species/type of tumour | Study waived |
| Relevant NOAEL/LOAEL | Study waived |

|  |
| --- |
| **Reproductive toxicity***Developmental toxicity* |
| Species/ Developmental target / critical effect | Rabbit, rat |
| Relevant maternal NOAEL |  |
| Relevant developmental NOAEL | Task Force:**Maternal toxicity (rabbit):****LOAEL 2 μg/kg bw/day/ NOAEL < 2 μg/kg bw/day****Developmental toxicity (rabbit):****LOAEL 2 μg/kg bw/day/NOAEL 4 μg/kg bw/day**Liphatech:Maternal toxicity (rabbit):LOAEL 4 μg/kg bw/day/ NOAEL 8 μg/kg bw/dayDevelopmental toxicity:LOAEL >8 μg/kg bw/day/ NOAEL ≥8 μg/kg bw/dayMaternal toxicity (rat):LOAEL 70 μg/kg bw/day/ NOAEL 35 μg/kg bw/dayDevelopmental toxicity:LOAEL >70 μg/kg bw/day/ NOAEL ≥70 μg/kg bw/day |
| *Fertility* |
| Species/critical effect | Study waived |
| Relevant parental NOAEL | - |
| Relevant offspring NOAEL | - |

|  |  |
| --- | --- |
| Relevant fertility NOAEL | - |

|  |  |
| --- | --- |
| **Neurotoxicity** |  |
| Species/ target/critical effect | No studies, not required |
| **Developmental Neurotoxicity** |  |
| Species/ target/critical effect | No studies, not required |

|  |  |
| --- | --- |
| **Immunotoxicity** |  |
| Species/ target/critical effect | - |

|  |  |
| --- | --- |
| **Developmental Immunotoxicity** |  |
| Species/ target/critical effect | - |

|  |
| --- |
| **Other toxicological studies** |
| Studies in rats and dogs demonstrated the effectiveness of vitamin K as an antidote toanticoagulant intoxication. The effectiveness varied with duration of exposure to bromadiolone (Liphatech). |

|  |
| --- |
| **Medical data** |
| 1991-1999 115 calls related to bromadiolone (Milan Poisons Center), 98 of which involved clinical cases among humans or animals. Exposure mostly via ingestion, 55% of cases under the age of 4 years.Symptoms: Symptoms reported for 11 cases and included vomiting, gastric pyrosis itching, and haematological problems in 1 case (Task Force).Symptoms may be associated to increased bleeding tendency. Diagnosis: changes in prothrombin time (symptoms and clotting tests)Treatment: vitamin K1. |

**Summary**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Value** | **Study** | **Safety factor** |
| AELlong-term | 0.0012 µg/kg bw/day | Developmental toxicity study rabbit (Task Force) | 600\* |
| AELmedium-term | 0.0012 µg/kg bw/day | Developmental toxicity study rabbit (Task Force) | 600\* |
| AELshort-term | 0.0023 µg/kg bw/day | 90-day rabbit (Task Force) | 300\* |
| ADI5 | Not required | Not required | Not required |
| ARfD | Not required | Not required | Not required |

**MRLs**

5 If residues in food or feed.

|  |  |
| --- | --- |
| Relevant commodities | - |

### Reference value for groundwater

|  |  |
| --- | --- |
| According to BPR Annex VI, point 68 | - |

**Dermal absorption**

|  |  |
| --- | --- |
| Study (*in vitro/vivo*), species tested | In vitro |
| Formulation (formulation type and including concentration(s) tested, vehicle) |  |
| Dermal absorption values used in risk assessment | In vitro studies on products a value of 1.6% was obtained that was used for the risk assessment. However, data for both applicants suggest low absorption of wax block formulations i.e. approx 0.3% for SUPER CAID BLOC (Liphatech).In vitro study of formulated active (bait:saline incorporated bromadiolone 0.00255 w/w) and a representative wax block formulation (0.005 % w/w) a worst case value of 0.36% was obtained that was used for this risk assessment (Task Force).No study on the pure active substance for Liphatech or Task Force. **Based on MW (>500) and log Pow (>4) a default value of 10% can be estimated for the active substance if no other studies are available.** |

**Acceptable exposure scenarios (including method of calculation)6**

|  |
| --- |
| The products Super Caid Bloc, Protect-B and Super Caid AS Appat (a coated grain reparation) are ready to use formulations containing bromadiolone at 50 ppm. Super Caid Bloc are wax block formulations, SUPER CAID AS APPAT is non-dusty and bromadiolone is not volatile so the risk of inhalation exposure to bromadiolone for professional or amateur users during use isconsidered to be negligible. |
| - |
| - |

Formulation of biocidal product

Intended uses Industrial users

6 The information reported is from the original text of the Assessment Report for the first approval of bromadiolone. However, at product authorization stage new scenarios should be developed on the basis of the most update guidance document endorsed for biocides (i.e., HEEG opinions 10 and 12).

|  |  |
| --- | --- |
| Professional users | Repeated exposure to products used in sewers against rats. Exposure expressed as % of AELmedium, chronic when based on measured values and gloves were used.Protect-B:35Super Caid Bloc:155Repeated exposure to products used in and around buildings against rats and mice. Exposure expressed as % of AELmedium, chronic when based on default or measured values and gloves were used.Protect-B: 56 (mice, default) 30 (rat, mice, measured) Super Caid Bloc: 373 (mouse, default) 163 (rat, mice, measured)Super Caid AS Appat: 40,(rat, default) 57 (rat, measured) 40 (mice, default)33 (mice, measured)Repeated exposure to products used in open areas against rats and mice. Exposure expressed as % of AELmedium, chronic when based on measured or default values and gloves were used.Super Caid Bloc: 467 (rat and mice, default), 156 (rat and mice, measured)Super Caid AS Appat: 33 (rat and mice, default), 47 (rat and mice, measured) |
| Non professional users | Single exposure to products used in and around buildings against rats and mice. Exposure expressed as % of AELacute when based on default or measured values and without gloves:Protect-B: 81 (rat, default), 33 (mice, default) 17 (rat, mice, measured)Super Caid Bloc: 326 (rat, default), 217 (mouse, default) 23 (rat, mice, measured)Super Caid AS Appat: 22,(rat, mice, default) 7 (rat, measured), 5 (mice, measured) |
| General public | - |
| Indirect Exposure | No safe use under the assumption that infants/children may ingest bait. Exposure expressed as % of AELacute for infants ingesting 10 mg bait was 2170% and 793130% for children ingesting 5 g bait. |
| Exposure via residue in food | - |

## Chapter 4: Fate and Behaviour in the Environment

### Route and rate of degradation in water

|  |  |
| --- | --- |
| Hydrolysis of active substance and relevant metabolites (DT50) (state pH and temperature) | pH 5; 25°C: not possible to calculate due to poor linear correlation. Assumed very little degradation at environmentally relevant conditions. (LT)pH 7; 25°C: not possible to calculate due to poor linear correlation. Assumed no significant degradation at environmentally relevant conditions. (LT)pH 7, 50°C: no hydrolysis of bromadiolone during the 120 days test. (TF)pH 9; 25°C: not possible to calculate due to poor linear correlation. Assumed no significant degradation at environmentally relevant conditions. (LT)pH 9, 50°C: no hydrolysis of bromadiolone during the 120 days test. (TF) |
| Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites | Liphatech:Under artificial sunlight:DT50 = 11.5 minutes in buffer solution, pH 7 (corresponding to 29.4 minutes in “natural summer sunlight” at latitude 50°N).DT50 = 14.0 minutes in sterile pond water, pH 8.4 (corresponding to 36.0 minutes in “natural summer sunlight” at latitude 50°N).Task Force:Natural sunlight at latitude 52° N, aqueous solution: DT50 = 2.98 minutes (summer) and30.4 minutes (winter) at a quantum yield of 0.25.DT50 = 74.5 minutes (summer) and 768 minutes (winter) at a quantum yield of 0.01.Photolysis was biphasic with a combination of the two above rates.Metabolites not identified by any of the applicants. |
| Readily biodegradable (yes/no) | No (both applicants) |
| Inherent biodegradable (yes/no) | - |
| Biodegradation in freshwater | - |
| Biodegradation in seawater | Not applicable (exposure to seawater unlikely). |
| Non-extractable residues | Not applicable (exposure to aquatic systems unlikely). |
| Distribution in water / sediment systems (active substance) | Not available |
| Distribution in water / sediment systems (metabolites) | Not available |

|  |
| --- |
| **Route and rate of degradation in soil** |
| Mineralization (aerobic) | 1.7 to 22.9% after *ca* 100 days. (LT) Study waived (TF) |
| Laboratory studies (range or median, with number of measurements, with regression coefficient) | Liphatech:DT50lab (20°C, aerobic):At 20°C DT50 value 2 to 7days (4 soils, 40% MWHC).At 25°C DT50 value 19 days (1 soil, 75% 1/3 bar moisture).At 12°C (calculated from the above values) DT50 value 4 to 53 days (5 soils).Bromadiolone Task Force: DT50lab (20°C, aerobic):At 20°C DT50 value of bromadiolone 5.8 to23.6 days (4 soils, 18-69% MWHC).At 12°C (calculated from the above values) DT50 value 12.4 to 50.4 days (4 soils).Major metabolite (maximum level 24.3 at day28) identified as bromadiolone ketone.PEC calculation was performed assuming that no degradation occurs and that bromadiolone does not migrate beyond the initial soil mixing depth between applications |
|  | Liphatech:DT90lab (20°C, aerobic):At 20°C DT90 value 14 to 49 days (4 soils, 40% MWHC).At 25°C DT90 value 585 days (1 soil, 75% 1/3 bar moisture).At 12°C (calculated from the above values) DT90 value26 to 1630 days (5 soils)Bromadiolone Task Force: DT90lab (20°C, aerobic):At 20°C DT90 value of bromadiolone 76 to 183 days (4 soils, 18-69% MWHC)..At 12°C (calculated from the above values) DT50 value 162 to 391 days (4 soils). |
| degradation in the saturated zone: | Not applicable |
| Field studies (state location, range or median with number of measurements) |  |
| DT50f: | DT50lab (20°C, anaerobic): Not applicable |
| DT90f: | DT90f: Not applicable |

|  |  |
| --- | --- |
| Anaerobic degradation | No degradation (TF) Study waived (LT) |
| Soil photolysis | Not applicable |
| Non-extractable residues | 8.8 to 21% after *ca* 100 days. (LT) Study waived (TF) |
| Relevant metabolites - name and/or code, % of applied a.i. (range and maximum) | Liphatech:Degradation of bromadiolone led to the formation of five unidentified metabolites which were present in significant quantities:Ketone/M2 2 1.1 % of AR (14 d, 25°C), 39.6 % of AR (28 d, 20°C)M4 15.9 % of AR (56 d, 20°C) M5 14.3 % of AR (56 d, 20°C)Unk 1 19.2 % of AR (120 d, 25°C) Unk 3/M9 24.8 % of AR (270 d, 25°C) 24.8 % of AR (154 d, 20°C)A cluster of non-identified metabolites amounting to 11.7% and 12.4% on two consecutive days were detected.Task Force:Study waived, metabolites not identified. |
| Soil accumulation and plateau concentration | Not applicable (not applied directly to soil). |

**Adsorption/desorption**

|  |  |
| --- | --- |
| Ka , Kd Kaoc , KdocpH dependence (yes / no) (if yes type of dependence) | Liphatech:Soil distribution (partition) coefficient (KD):5.3 to 10.4 mL/g (adsorption)13.2 to 22.3 mL/g (desorption).Freundlich soil adsorption coefficient (KF):5.3 to 10.4 mL/g (adsorption)13.2 to 22.3 mL/g (desorption).Freundlich soil adsorption coefficient normalised for organic carbon content (KOC):1563 to 1709 mL/g (adsorption)2157 to 6651 (desorption). No pH dependence observed.Task Force:Soil distribution (partition) coefficient (KD): 71.2-1250 mL/g (adsorption)Soil adsorption coefficient normalised for organic carbon content (KOC):3530 to 41600 mL/g (adsorption), average value 14770 mL/g used for calculations.No pH dependence observed.bromadiolone is considered slightly mobile to non-mobile in soil. |

**Fate and behaviour in air**

|  |  |
| --- | --- |
| Direct photolysis in air | The photochemical oxidative degradationhalf-life of bromadiolone in air was estimated using the EPIWIN v 3.12, which is based on the structure activity relationship (QSAR's). The half-lives for the hydroxyl and ozone reactions in air are estimated to be 2.09 and2.015 hours respectively, indicating that if present in air, bromadiolone would not be expected to persist (both applicants). |
| Quantum yield of direct photolysis | Not determined. |
| Photo-oxidative degradation in air | Latitude: n.a Season: n.a DT50 n.a |
| Volatilization | Vapour pressure at ambient temperature is 2.13 x 10-8 Pa (OECD 104) (LT); 2.0 x 10-6 Pa (TF)Henry's law constant = 8.99 x 10-7Pa m3 mol-1 (based on a water solubility of 12.5 mg/L) (LT); 4.25 x 10-4 Pa m3 mol-1 (TF)Bromadiolone is therefore not considered volatile and is not expected to volatilise to air in significant quantities. |

**Reference value for groundwater**

|  |  |
| --- | --- |
| According to BPR Annex VI, point 68 | - |

|  |
| --- |
| **Monitoring data, if available** |
| Soil (indicate location and type of study) | No monitoring data available. |
| Surface water (indicate location and type of study) | No monitoring data available. |
| Ground water (indicate location and type of study) | No monitoring data available. |
| Air (indicate location and type of study) | No monitoring data 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** |
| *Oncorhynchus mykiss* | 96 hours | mortality | LC50 = >8.0 mg/L(nominal) (LT)LC50 = 2.86 mg/L(nominal) (TF) |
| **Invertebrates** |
| *Daphnia magna* | 48 hours | lethality immobilisation | LC50 = 2.0 mg/L (LT)EC50 = 5.79 mg/L(nominal) (TF) |
| **Algae** |
| *Scenedesmus subspicatus* | 96 hours(72hours) | growth inhibition(b) growth inhibition (gr) | EbC50 = 0.17 mg/L (LT) (ErC50= 1.0 mg/L)ErC50 = 1.14mg/L (TF) (geometric mean of the initial measured conc.and half the LOQ) |
| *Pseudokirchneriella subcapitata* |  |  |
|  | 72 hours | growth inhibition (gr) |
| **Microorganisms** |
| Activated sludge | 3 hours | respiration inhibition | EC50 = 31.6 mg/L(nominal) (LT)EC50 = 132.8 mg/L(extrapolated) (TF) |

**Effects on earthworms or other soil non-target organisms**

|  |  |
| --- | --- |
| Acute toxicity to *Eisenia fetida* | 14-day LC50 > 8.4mg/kg wet soil (synthetic OECD substrate) (LT)13 days LC50 = 918 mg/L wet soil (TF) |
| Reproductive toxicity to ………………………… | Waived |

**Effects on soil micro-organisms**

|  |  |
| --- | --- |
| Nitrogen mineralization | Waived |
| Carbon mineralization | Waived |

**Effects on terrestrial vertebrates**

|  |  |
| --- | --- |
| Acute toxicity to mammals | LD50 between 0.56 and 0.84 mg/kg bw (rat) (LT)LD50 = 1.31 mg/kg bw (rat) (TF) |
| Acute toxicity to birds | LD50 = 138 mg/kg bw (bobwhite quail) (LT) LD50 = 134 mg/kg bw (Japanese quail) (TF) |
| Dietary toxicity to birds | 5-day LC50 = 62 mg/kg food (bobwhite quail) (LT)10-day LC50 = 28.9 mg/kg food (partridge, study presented as acute study) (TF) |
| Dietary toxicity (secondary poisoning) to birds | 7-day LD100 = 0.056 mg/kg bw/d (great horned owl)(LT) |
| Reproductive toxicity to birds | NOEC = 0.1 mg/kg food (Japanese quail, tested substance difenacoum) (LT)NOEC = 0.26 mg/L drinking water (Japanese quail) (TF) |

**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 ………………………………….. | Not applicable. |

|  |
| --- |
| **Bioconcentration** |
| Bioconcentration factor (BCF) | Liphatech:Whole fish: 460 (*Lepomis macrochirus*)BCF (calculated from a log Kow of 4.07) = 575Task Force:Bioconcentration tests failed due to high mortalities.BCF (calculated from a log Kow of 3.8) = 339 |
| Depration time (DT50) | > 14 days (LT) |
| Depration time (DT90) |  |
| Level of metabolites (%) in organisms accounting for > 10 % of residues | Metabolites not quantified. |

## 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 /****Referen ce No7** | **Author(s)8** | **Year** | **Title9****Source (where different from company) Company****Report No.****GLP (where relevant)****(Un)Published** | **Data Protec tion Claim ed (Yes/ No)** | **Owner** |
| - |  |  |  |  |  |

7 ***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).

8 ***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.

9 ***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.