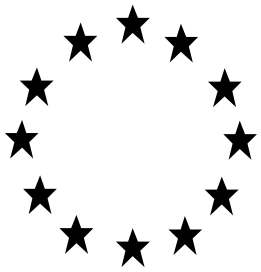
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Renewal of approval

Assessment Report



Chlorophacinone

Product-type 14
(Rodenticides)

July 2016

SPAIN

CONTENTS

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 chlorophacinone 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 the recommendations of the RMM report for anticoagulant rodenticides.

Chlorophacinone was approved as an existing active substance, in product-type 14 under the Biocidal Products Directive (DIRECTIVE 2009/99/EC). The renewal of the active substance has been requested by Liphatech S.A.S.

On 23rd December 2014, Spain competent authority (eCA) received a dossier from Liphatech S.A.S. The eCA accepted the dossier as complete for the purpose of the evaluation on 31st July 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 12th February 2016, the eCA submitted to the Agency the assessment report and on 5th April 2016, the eCA submitted it to the applicant.

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.

1.2. 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 chlorophacinone 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.

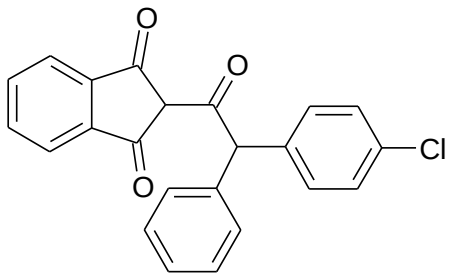
For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

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.

2. OVERALL SUMMARY AND CONCLUSIONS[2]

2.1. Presentation of the Active Substance

2.1.1. Identity

CAS-No.	3691-35-8
EINECS-No.	223-003-0
Other No. (CIPAC, ELINCS)	CIPAC No. 208
IUPAC Name	2-[2-(4-chlorophenyl)-2-phenylacetyl]indan-1,3-dione *
Common name, synonym	Chlorophacinone
Molecular formula	$C_{23}H_{15}ClO_3$
Structural formula	
Molecular weight (g/mol)	374.82
Purity: % w/w (specification):	>97.8%
Isomeric composition	Chlorophacinone contains one optically active carbon and therefore exists as two enantiomers. The ratio of the enantiomers is provided in the confidential file from the active substance approval
Impurities and additives:	Information on the impurities and additives in the technical grade active substance is confidential to Liphatech S.A.S. and is presented in the confidential attachment from the active substance approval.

* This is the correct IUPAC name for Chlorophacinone. Until 2007 the IUPAC name for this compound was considered to be 2-[(4-chlorophenyl)phenylacetyl]-1H-indane-1,3-(2H)-dione

The purity of the active substance (> 97.8%) is the minimum degree of purity as specified from the applicant for the active substance production process. The purity and specification of the active substances remains and is presented as per the agreed BPD specification.

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

Information on the purity and specification of the active substance is based on the five batch analysis provided in the original dossier.

The 5-batch analysis report is greater than 12-years old and, hence, a new five batch analysis for the renewal was requested. Quality control data was also requested, as an interim measure, prior to substance renewal and product approval in order to verify that the specification of the active substance still is in compliance with the specification from the original approval.

2.1.2. Intended Uses

Chlorophacinone is used as a rodenticide pest control substance (Main group 03, product type 14), to control *Rattus norvegicus* (Norway rat, Brown rat), *Rattus rattus* and *Mus musculus* (House mouse). Chlorophacinone was evaluated as a rodenticide against rats and mice for the following use patterns: in and around buildings (professional use and general public), sewers (professional use only), open areas (professional use only) and waste dump (landfill) perimeters (professional use only).' No new information of the evaluated products has been provided by the applicant.

2.2. Summary of the Assessment

2.2.1. Specification of the different sources of the active substances

No new information is available since the original approval and the conclusions remain the same, however the applicant has been asked to provide some confirmatory data*.

The purity of the active substance (> 97.8%) is the minimum degree of purity as specified from the applicant for the active substance production process. Specification of purity is based on the combined concentration of both enantiomers (R and S). Both enantiomers are considered as active substance. The ratio is considered confidential and can be found in the Confidential Document of the Competent Authority Report for the original evaluation (2008) of the active substance.

*Data Requirement:

It should be noted that the 5-batch analysis supporting the technical specification is 12 years old. The supporting 5-batch analysis should be ≤ 5 years old. The applicant has been asked to provide a new 5-batch analysis in order to confirm that the quality of technical material has remained unchanged compared to the original technical material. The applicant should provide this information at the latest by 1st October 2016. It should also be noted that the RMS has asked the applicant to provide quality control data.

The applicant should also give the RMS a thorough explanation with regards to the (eco)-toxicological acceptability of the specification when providing the new 5-batch analysis.

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

2.2.2.1. Phyisco-chemical properties and methods of analysis

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

However, it is noted by the eCA that for residue methods in soil, water and animal and human body fluids and tissues a data requirement is highlighted: The notifier must provide monitoring data for a second transition ion at the product authorisation stage. Besides, the applicant should submit a new residue method in air using the suitable LOQ (0.005 µg/m^3).

2.2.2.2. Classification and Labelling

Currently chlorophacinone has harmonized classification in accordance with Regulation (EC) No 1272/2008 (CLP Regulation).

The classification and labelling for chlorophacinone was updated and agreed by the REACH Committee on 4 February 2016 and it was approved in the 9th ATP in February 2016 (9th ATP, not yet published), as follows:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Repr. 1B; 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. 1B; H360D: C ≥ 0.003 % STOT RE 1; H372: C ≥ 0.1 % STOT RE 2; H373: 0.01 % ≤ C < 0.1 % M =1 M =1

2.2.2.3. Efficacy and resistance

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

2.2.2.4. Human health assessment

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

2.2.2.5. Environmental assessment

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

2.2.2.6. Fate and distribution in the environment

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

2.2.2.7. PBT and POP assessment

The available data are sufficient for a PBT assessment of chlorophacinone.

Persistence

chlorophacinone can be classified as not readily biodegradable, and it is considered stable to hydrolysis at environmentally relevant temperatures hence, the screening criteria for persistence is met.

Rapid photolysis in water: DT_{50} (25ºC) = 2.2 d; pH~7, and soil. DT50 (12ºC) = 11.1 d are reported. In soil under dark aerobic conditions in the laboratory (12°C extrapolated from 25°C), chlorophacinone is degraded steadily with an estimated DT_{50} value of 128 days. According to section 1 of Annex XIII of REACH (Regulation (EC) Nº. 1907/2006), if the degradation half-life in soil is higher than 120 days, a substance fulfils the persistence criterion (P). Thus, chlorophacinone is considered persistent.

If the participant wishes to challenge the P criteria, a water/sediment degradation study is required.

Bioaccumulation

Chlorophacinone has a log Pow = 2.42 (pH~7 at 23ºC), as it is below 3 it is an accepted indication of very low bioaccumulation potential. This compound will not accumulate in tissues of organisms. Therefore the bioconcentration factor for fish has been calculated according to the TGD, showing no potential for bioaccumulation: BCF_{fish} = 22.75 l/kg. Thus, the substance does not fulfil the B criterion.

Toxicity

According to Section 1.1.3 of Annex XIII to REACH, a substance is considered to fulfil the toxicity criterion (T) when:

- the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms is less than 0.01 mg/L; or
- 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 the CLP Regulation; or
- there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: STOT RE 1, or STOT RE 2 according to the CLP Regulation.

The ECHA Committee for Risk Assessment, in their Opinion issued on March 2014, proposed the harmonised classification and labelling at EU level as Repr. 1B and a specific concentration limits for chlorophacinone of 0.003%. Therefore, chlorophacinone meets the criteria for classification STOT RE 1 according to the CLP Regulation. Thus, chlorophacinone fulfils the T criterion.

In conclusion, according to Annex XIII of REACH (Regulation (EC) Nº. 1907/2006), chlorophacinone does not fulfil the B criterion, and is not considered a PBT candidate.

POP criteria

The criteria for a substance being a persistent organic pollutant (POP) are P, B and having the potential for long range transport. In addition, high toxicity can breach the B criterion, in which

case a substance will be a persistent organic pollutant if it is P, demonstrates the potential for long range transport, and is either B or T.

Chlorophacinone has a low vapour pressure (4.76 x 10-4 Pa) and hence its Henry's Law Constant indicates that volatilisation is not expected to significantly contribute to the dissipation of chlorophacinone in the environment. Thus, it is not considered a POP candidate.

2.2.2.8. Assessment of endocrine disruptor properties

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

2.2.3. Assessment of the recommendations arising from the report[3] on RMM for anticoagulant rodenticides 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

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

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 chlorophacinone 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 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 products containing the least potent active substance that will effect complete control should be used first. However, as there currently is no rapid way to determine the resistance status of a rodent infestation prior to treatment, the proposed approach is neither realistic nor practical.

The eCA agrees in the above mentioned order of use of the substances. Where the resistance situation is known, the least potent substance that will effect complete control should be used. 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 is of the opinion that FGARs generally should not be restricted for use against mice, unless data on resistance is available.

Provided the other RMMs are applied (pack size, bait boxes see below), there is no reason to restrict the use of SGAR for general public, especially in order to control House mice populations, which are the number one problem in the general public 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 general public 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 general public 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 that SGARs can be authorized for use by the general public (non-professional users) and non-trained professionals (farmers) against mice as long as only small quantities are allowed, and the bait is provided in tamper resistant bait boxes.

Pack size should always be limited for general public 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 general public 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.

The applicant 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 general public use products a pack of 1.5kg will allow for a small number of bait points with one or two refills which should be sufficient to treat a very small rat infestation.

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.

General public 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 it 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 commented that 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. Virtually all rat infestations are of an outdoor origin as rats will live outdoors and search indoors for food etc.

eCA shares the opinion that the control of rats in and around buildings should be allowed for the general public and that it should be subject to derogations from the mutual recognition at the product authorization stage.

Dyes and bittering agents should always be included in the formulations.

At the workshop in was unanimously agreed that dyes and bittering agent should be included in bait formulations.

The applicant commented that it is usual practice of industry to include dyes and pigments in rodenticidal products to reduce the risk of accidental uptake by humans and birds etc. However, they considered it unnecessary and commercially unwarranted to specify which colours to be used.

The eCA agrees that the addition of dyes and bittering agents 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 boxes.

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.

The applicant commented that 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 be performed* by trained professionals (pest control operators) in order to determine the extent of the infestation Information should always be applied on the bait stations.

For general public use, tamper-resistant bait boxes should always be mandatory, with baits securely fixed inside the bait boxes when possible (wax blocks, paste). Loose baits (such as grain and pellets) cannot be excluded, even for general public use, because of their higher palatability. Using smaller packs and pre-packed bait boxes 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 boxes 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 general public use, because of their higher palatability.

The eCA is of the opinion that use of tamper resistant bait stations should be mandatory and only small packages should be authorized. Regarding loose formulations, individual pre-dosed sachets 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 boxes, 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.

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 is of the opinion tamper-resistant bait boxes should always be mandatory irrespective of the type of user, except in sewers. However, we consider that under certain circumstances in specific situations, covered bait stations might be accepted only for trained professionals.

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 pulse baiting by trained professionals could be supported as far as the efficacy is demonstrated. For FGARs the pulse baiting is not relevant.

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.

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.

Due to the risk to non-target species, currently the eCA does not allow the permanent baiting neither indoors nor outdoors. Nevertheless, eCA agrees that it could be restricted to locations with high potential for reinvasion.

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 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.

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 trained professional. 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"). For clients and other general public, sealing the bodies in two separate plastic bags and safe disposal in the garbage can be considered.

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 general public is considered to ensure that general public will dispose of rodent bodies in a proper manner.

The eCA agrees that dead rodent bodies should be removed and disposed at the end of the treatment. The disposal should be in accordance with local requirements, and the method of disposal should be described specifically on the national SPC and on the label of the product.

Uneaten bait should always be removed and disposed of at the end of the treatment. General public may dispose of their remaining uneaten baits by sealing it within two plastic bags and safe disposal in the garbage.

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 general public 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.

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.

Monitoring based on sequencing of the VKORC1 gene was generally supported at the workshop. However, the organisation and funding of such a monitoring regime was questioned. The expert team offered to make a proposal in cooperation with CEPA and CAs on the set up of a monitoring system taking into account regional information.

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.

The eCA agrees that information on resistance throughout EU should be gathered.

RMM to be set at the stage of product authorisation

Bait stations should be mandatory for general public 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 general public.

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 general public.

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

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. Furthermore, tamper resistant bait stations should be mandatory.

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.

Substance specific considerations

Chlorophacinone is a first generation anticoagulant rodenticide. Considerations outlined above are relevant for chlorophacinone.

2.3. Overall conclusions

The outcome of the assessment for chlorophacinone 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.

2.4. Requirement for further information

2.4.1. 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 Chlorophacinone. However, additional information is required as outlined below:

Technical specification and 5-batch analysis: The applicant has been asked to provide a new 5-batch analysis in order to confirm that the quality of technical material has remained unchanged compared to the original technical material. The 5-batch analysis should be supported by fully validated methods of analysis. The applicant should provide this information at the latest by 1st October 2016.

The applicant should also give the RMS a thorough explanation with regards to the (eco)-toxicological acceptability of the specification when providing the new 5-batch analysis.

Residue methods of analysis: The monitoring methods for soil, water (drinking water and surface water), human body fluids and tissues were validated using a single ion transition. However, the applicant should provide validation data for the second ion transition. In addition, the applicant should submit a new residue method for air matrices using the appropriate LOQ.

The applicant should provide this information at the product authorisation stage so that monitoring methods are available for products.

Resistance information: However, it is recognised that resistance in rodent population is an important issue and should be monitored in order to use the appropriate products. A set up of a monitoring system taken into account regional information should be considered as a requirement in the future. Therefore applicants should provide within the application for the next renewal all data available to them on resistance to the active substance on the target organisms in the EU.

Soil study: a soil simulation study in line with OECD 307 conducted on a minimum of two further soils needs to be provided according to the information requirements of the BPR at product authorization level or at least before the next renewal.

2.4.2. Requirement for further information related to biocidal products

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions.

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

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.

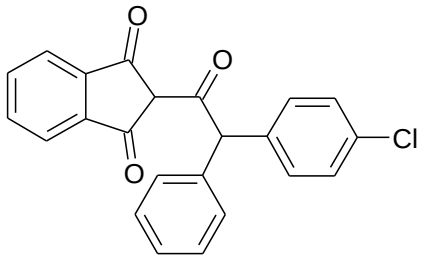
Appendix I: List of endpoints

[List all the endpoints valid for the active substance. If no change since the initial approval, make a copy-paste]

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

Active substance (ISO Name)	Chlorophacinone
Product-type	Main group 03: Pest control Product type 14: rodenticides, against rats and mice

Identity

Chemical name (IUPAC)	2-[2-(4-chlorophenyl)-2-phenylacetyl]indan-1,3-dione
Chemical name (CA)	
CAS No	3691-35-8
EC No	223-003-0
Other substance No.	CIPAC No. 208
Minimum purity of the active substance as manufactured (g/kg or g/l)	978 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None
Molecular formula	C23H15ClO3
Molecular mass	374.82
Structural formula	

Physical and chemical properties

Melting point (state purity)	143.0°C (99.74%)
Boiling point (state purity)	Decomposed below boiling point
Thermal stability / Temperature of decomposition	250 ºC
Appearance (state purity)	Pale yellow powder (99.85%)
Relative density (state purity)	1.4301g/mL (99.85%)
Surface tension (state temperature and concentration of the test solution)	68.9 mN/m (20.6 ºC)

Vapour pressure (in Pa, state temperature)	4.76 x 10^{-4} Pa at 23°C
Henry's law constant (Pa m^3 mol^{-1})	0.013725 Pa.m^3.mol^{-1} Log H: -1.86
Solubility in water (g/l or mg/l, state temperature)	Pure water: 13 mg/L at 20°C pH 4 at 20 ºC: 1 mg/L pH 7 at 20 ºC: 344 mg/L pH *[10]* at 20 ºC: 459 mg/L
Solubility in organic solvents (in g/l or mg/l, state temperature)	Hexane: 854 mg/L at 25ºC Methanol: 786 mg/L at 25ºC
Stability in organic solvents used in biocidal products including relevant breakdown products	Active substance is not formulated in solvents in biocidal products
Partition coefficient (log P_{OW}) (state temperature)	pH 4 at 23 ºC: 3.08 pH 7 at 23 ºC: 2.42 pH *[9]* at 23 ºC: 2.57 No pH control: 1.93 at 23°C
Dissociation constant	pKa = 8.0
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Approximately 260nm and 315nm - ε□ not stated
Photostability (DT_{50}) (aqueous, sunlight, state, pH)	Under artificial sunlight: DT_{50} 2.2 days (natural summer sunlight at latitude 50°N) in buffer solution (pH 7). DT_{50} 1.3 days (natural summer sunlight at latitude 50°N) in pond water (pH 8.4 post sterilisation).
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not determined
Flammability or flash point	Not highly flammable
Explosive properties	Not explosive
Oxidising properties	Not oxidising
Auto-ignition or relative self ignition temperature	no

Classification and proposed labelling

with regard to physical hazards	None
with regard to human health hazards	H360D H300 H310 H330 H372 (blood)
with regard to environmental hazards	H400 H410

Chapter 2:Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	The technical material is dissolved in the mobile phase (0.1 g ammonium acetate + 42 mL 0.05 N hydroxide tetrabutylammonium solution in phosphate buffer + 14 mL THF + 44 mL methanol). Determination is by reverse-phase HPLC/UV with a Spherisorb ODS 2 column with mobile phase as described above (230 nm).
Impurities in technical active substance (principle of method)	See Confidential Information document.

Analytical methods for residues

Soil (principle of method and LOQ)	Soil is extracted by shaking with aqueous methanol. Determination of the filtered and diluted extract is by reverse-phase LC-MS/MS (monitored ions 373.4/201.2 m/z). A Luna C-8 column is used with acetonitrile/water/ammonium acetate (gradient) mobile phase. The limit of determination is 0.01 mg/kg (defined as the lowest concentration at which acceptable recovery has been demonstrated).
Air (principle of method and LOQ)	Air is passed through Tenax absorption tubes which are eluted with acetonitrile. Determination is by reverse-phase HPLC, Luna C-8 column with acetonitrile/water/ ammonium acetate (gradient) mobile phase. The limit of determination is 0.03 $\mu g/m^3$ (defined as the lowest concentration at which acceptable recovery has been demonstrated).
Water (principle of method and LOQ)	Water is extracted by partition into dichloromethane. The extract is evaporated to dryness and reconstituted in aqueous methanol. Determination is by reverse-phase LC-MS/MS (monitored ions 373.4/201.2 m/z). A Luna C-8 column is used with acetonitrile/water/ ammonium acetate (gradient) mobile phase. The limit of determination is 0.05 $\mu g/L$ (defined as the lowest concentration at which acceptable recovery has been demonstrated).

Body fluids and tissues (principle of method and LOQ)	Blood Blood is diluted with methanol. Phosphate buffer, a mixture of ethanol/ethyl acetate and trichloroacetic acid solution is added. The sample is shaken and the organic phase removed. The sample is re-extracted with ethanol/ethyl acetate. The combined organic extracts are evaporated to dryness and reconstituted in methanol prior to determination. Determination is by HPLC with a Thermo Hypersil Keystone column and ammonium acetate/methanol (gradient) mobile phase (two ion transitions monitored 373>201 and 375>203). The limit of determination is 0.05 mg/L (defined as the lowest concentration at which acceptable recovery has been demonstrated). Liver Liver is blended with phosphate buffer (pH 5.5) and a mixture of ethanol and ethyl acetate (1+19, v/v). A solution of trichloroacetic acid is added and the sample is blended again. Clean-up of the centrifuged extract is by GPC. Determination is by HPLC with Thermo hypersil keystone column and ammonium acetate/methanol (gradient) mobile phase (two ion transitions monitored 373>201 and 375>203). The limit of determination is 0.05 mg/L (defined as the lowest concentration at which acceptable recovery has been demonstrated).
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Samples are extracted by blending twice with methanol (meat and lemon) or methanol/water (oilseed rape). After centrifugation the samples are diluted with methanol/water. Determination is by HPLC/MS-MS LOQ: 0.01 mg/kg’
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not available

Chapter 3:Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Compound is absorbed, enters the enterohepatic circulation and then is excreted through the faeces. Metabolism studies in rats with radiolabelled Chlorophacinone showed that it is absorbed following oral administration, with a relatively short (10.2 hours) plasma half-life. After a single low dose (1-1.4 mg/Kg), 90% radioactivity is excreted in faeces within 48 hours and 100% of the administered material is excreted within 4 days. Higher doses (2 mg/kg) showed that at 168 hours excretion is incomplete and 8% of dose was still present in the carcass. Elimination was mainly via faeces, with less than 1% of urinary excretion, and no excretion via expired air. About 19.6% of the faecal radioactivity (equivalent to 15% of dosed radioactivity) is unchanged parent compound and most were metabolised compounds. Two main metabolites was identified as hydroxylated metabolites accounting for the 45% of faecal radioactivity (36.2% of administered dose) with some "minor" unidentified metabolites representing 34% of faecal radioactivity. It is important to note that a peak representing 12.49 % of assigned peaks (representing about 8 % of dosed radioactivity) was detected but not identified.
Rate and extent of dermal absorption*:	• The in vitro topical application of ^{14}C-Chlorophacinone as a contact formulation or wheat flour bait to human split thickness skin samples maintained ***in vitro*** resulted in similar **rapid rates of absorption** with radioactivity appearing within 1.7 or 0.25 hours respectively **but absorption was minimal** and less than 0.1% (powder) or 0.5 % (bait) were detected in the receptor fluid. • **Total absorption in human skin is estimated to be not more than 1.7%., deduced in vitro test using** topical application of ^{14}C-Chlorophacinone as a contact formulation or wheat flour bait to human split thickness skin samples maintained *in vitro*, considering total absorption including radioactivity measured in receptor fluid, tape stripping and residual skin values.

Distribution:	Compound is absorbed, enters the enterohepatic circulation and then is excreted through the faeces. Maximum blood concentration is reached after 4 hr. In a single dose oral study in the rat the tissue distribution was calculated 48 hours after dosing for several tissues: Liver (2.9 ppm), kidney (1.18 ppm), lung (0.39 ppm, heart (0.16 ppm), muscle (0.097 ppm), fat (0.673 ppm), carcass (0.306 ppm). The levels in the liver were five times higher than those in the kidney four hours after dosing and 2.8 fold at the 48 hour post-dosing sacrifice point.
Potential for accumulation:	The blood half-life for elimination is 10 hr. In a study dosing 1-1-4 mg/kg, the results indicate rapid absorption and relatively rapid metabolism in the liver and 100% elimination within four days. However, higher doses (2 mg/kg) showed that at 168 hours **excretion is incomplete** with **8%** of dose was still present in the carcass.
Rate and extent of excretion:	Elimination was mainly **via faeces**, with less than 1% urinary and CO2 excretion: Faecal excretion 101.6% after 4 days (Biliary excretion after 8 hr is 26%) Urinary excretion 0.75% after 4 days Most faecal excretion was as metabolised compounds accompanied with **unchanged parent compound (19.6%** of the faecal radioactivity, equivalent to 15% of dosed radioactivity). Two major **metabolites represented for 45%** of faecal radioactivity (equivalent to 36.2 % of total dosed radioactivity) as hydroxylated metabolites, with some "minor" unidentified metabolites.

Toxicologically significant metabolite(s)	Two main metabolites were identified as hydroxylated metabolites, one in the indandione group and the other in the biphenyl portion of the molecule. The two analogues constituted 46% of faecal radioactivity (36.2% of administered dose). A metabolite presented as 12% of faecal radioactivity (8% of extracted material) was not identified as well as other minor metabolites representing 34% of faecal radioactivity. After 168 hours excretion was incomplete and about 8% was detected in carcases. Applicant argues that "none of the metabolites identified for indandione derivatives used as rodenticides have been shown to be toxicologically significant". However no data is presented to justify this statement.

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

Acute toxicity

Rat LD_{50} oral	**Male: 3.15 mg/kg** (1.48 - 6.68) Female: 10.95 mg/kg (6.46 - 18.57) Combined: 6.26 mg/kg (3.96 - 9.89) Mortalities in males (4/10) observed from the lowest dose (2 mg/kg bw)
Rat LD_{50} dermal	LD_{50} (male and female) <<2mg/kg bw (all males died at all doses) Males **0.329 mg/kg bw**
Rat LC_{50} inhalation	Male: 7.0 µg/L (0.83-59.0) Female: 12.0 µg/L (7.80-18.0) Combined: 9.3 µg/L (2.30-38.0)

Skin corrosion/irritation	Average erythema score over 24, 48, 72 h = 0.00 for non-abraded skin Average oedema score over 24, 48, 72 h = 0.00 for non-abraded skin. Chlorophacinone does not meet EU criteria for classification as a skin irritant
Eye irritation	Average score over 24, 48, 72 h for : corneal reaction = 0.00 iridial reaction = 0.00 conjunctival redness = 0.00 conjunctival swelling = 0.00 Chlorophacinone does not meet EU criteria for classification as an eye irritant
Respiratory tract irritation	-

Skin sensitisation (test method used and result)	No signs of irritation were observed. Chlorophacinone does not meet EU criteria for classification as a skin sensitization
Respiratory sensitisation (test method used and result)	-
Repeated dose toxicity	
Species / target / critical effect	Rat (90 day oral administration) No target organs were identified. The mode of action for anticoagulant rodenticides is well characterised. The critical effect is death arising from persistent or severe haemorrhage. The clinical findings in the study were indicative of internal haemorrhagic events and were consistent with the established pattern of increasing prothrombin times associated with increasing severity of bleeding from orifices or abrasions, pallor, ataxia or weakness/limb paralysis and breathing difficulty. Death followed development of signs and necropsy confirmed presence of haemothorax and haemoperitoneum among other diffuse, non-specific haemorrhages and haematoma formation. Rabbit (15 day dermal administration, 5 days/week for 3 weeks) Widespread non-specific haemorrhage was the primary cause of death among rabbits dosed with a 2% formulation of Chlorophacinone. Necropsy also revealed centrilobular liver necrosis. In-life signs of haemorrhage were confirmed by necropsy observations of free fluid in many body cavities and pale organs. Increased prothrombin times were measured in-life as an indicator of progressive failure of the clotting cascade arising from non-replenishment of Vitamin K in the liver of intoxicated animals.
Relevant oral NOAEL / LOAEL	Rat: LOAEL = 0.010 mg/kg b.w. /day established on the basis of 16 weeks dosing period with minimal increase but statistically significant in coagulation time and other biochemical parameters alteration which are suggestive of hepatic and renal disorders NOAEL = 0.005 mg/kg b.w. /day (11 weeks exposure) (Some uncertainty due to shorter time at the dose of 5 µg/kg b.w. /day and no prothrombine time determination at this dose)

Relevant dermal NOAEL / LOAEL	Rabbit: LOAEL 0.40 mg/kg/day observation the alteration of prothrombin times NOAEL 0.08 mg/kg/day (21 day exposure)
Relevant inhalation NOAEL / LOAEL	Not established - study not scientifically justified

Genotoxicity

Results for in vitro bacterial gene mutation; in vitro cytogenicity in mammalian cells and in vitro mammalian cell gene mutation tests were negative. The mouse micronucleus test was also negative.

Carcinogenicity

Species/type of tumour	The closely related molecule warfarin is not carcinogenic to humans. Study on Chlorophacinone is not available. Applicant argument for non submission of data was accepted.
Relevant NOAEL/LOAEL	-

Reproductive toxicity

- Study with Chlorophacinone

Developmental toxicity

Species/ Developmental target / critical effect	Rabbit Clinical of toxicity and necropsy pathology demonstrated that mortality was due to internal haemorrhage caused by the anticoagulant properties of the substance. Treatment-related clinical observations were limited to does causing mortality prior to death. There were no treatment-related clinical signs of toxicity at lower doses. At scheduled necropsy, there were no treatment-related findings in surviving pregnant animals. No developmental effects were noted at any tested evaluated dose. 100 % mortality was observed at 75 µg/kg bw/day and at 25 µg/kg bw/day, a high mortality (13 of 16) was also observed but no significant effect were detected in the foetus of the surviving does.
Relevant maternal NOAEL	10 µg/kg bw/day
Relevant developmental NOAEL	25 µg/kg bw/day

Fertility

Species/critical effect	Study on Chlorophacinone is not available. Applicant argument for non submission of data was accepted when the active substance was discussed.
Relevant parental NOAEL	-
Relevant offspring NOAEL	-
Relevant fertility NOAEL	-

- Read across with warfarin (please, see the information in the AR of warfarin)

Neurotoxicity

Species/ target/critical effect	Difethialone, a closely related molecule, showed no antianginal activity *in vivo* or *in vitro;* no antihypertensive activity; no sedative activity; no anticonvulsant activity; no antidepressant activity; no antispasmodic activity in a variety of *in vitro* tests and no analgesic, anti-inflammatory or gastric antiacid activity in various tests designed to investigate these pharmacological endpoints. Chlorophacinone, like difethialone, has a highly specific mode of action, blocking regeneration of Vitamin K in the liver and no other pharmacologic activity has been established for the molecule.

Developmental Neurotoxicity

Species/ target/critical effect	-

Immunotoxicity

Species/ target/critical effect	-

Developmental Immunotoxicity

Species/ target/critical effect	-

Other toxicological studies

One study in male rats investigated the efficacy of antidotal treatment. The animals were provided Chlorophacinone pellets (5ppm) as a diet replacement for 1, 2 or 3 days. Vitamin K1 antidote was injected intravenously to half of the animals in each group, 1-2 hours after completion of exposure period and followed by oral administration of phytomenadione for up to 13 days. Prothrombin times were monitored to detect increases during treatment and decreases following antidotal treatment. All animals given 1, 2 or 3 meals with Chlorophacinone died. Antidotal treatment was successful following 24 hour exposure but less successful with longer periods of exposure. The study demonstrated the effectiveness of Vitamin K1 (phytomenadione) as an antidote to anticoagulant intoxication in the rodent if the exposure is limited to around the LD50, but not if the dose is excessive.

Medical data

There are no published data on specific cases of Chlorophacinone intoxication, and no case reports from the manufacturer concerning adverse effects in users applying the products.

Anticoagulant rodenticides such as Chlorophacinone function by inhibiting the ability of the blood to clot at the site of a haemorrhage, by blocking the regeneration of vitamin K in the liver.

Information relating to medical supervision of staff involved in research and development, production and packaging of second generation rodenticides is included; a description of the well researched mode of action and specific medical effects arising from accidental or intentional exposure of humans to anti Vitamin K rodenticides.

The closely-related active substance warfarin has been in use for over forty years as an anticoagulant drug in human medicine. Its use is described in more detail in 3, but in summary it has been used in millions of patients with clotting disorders, heart disease, atrial valve replacement, and more recently, deep vein thrombosis. Use is life-long for most patients with heart disease, clotting disorders or valve replacement. There have been no reports of any increase in tumour incidence or of any adverse effects on human fertility. There have been no reports of neurotoxic or neurodegenerative disease, or neuro-muscular disease associated with the use of warfarin.

The specific medical effect can be recognized by simple tests such as clotting time, Quick test or prothrombin rate determinations and the antidotal treatment regimen is well characterized – parenteral injection of Vitamin K1 (phytomenadione) followed by long term oral administration of the antidote to stabilize prothrombin times. This regimen has been effectively and successfully used within the manufacturing plants and no cases of intoxication have been reported between 1987 and 1999 (last available information).

Summary

	Value	Study	Safety factor
AEL	0.000017 mg/kg bw/day (repeated dose). No acceptable acute dose study for risk characterization 0.000033 mg/kg bw/day (acute exposure)	90 day rat oral toxicity A 6.4.1-01 NOAEL = 0.005 mg/kg bw/day Maternal toxicity in teratogenicity study in rabbit (NOAEL= 0.010 mg/kg bw/day)	300
ADI[4]	Not applicable		
ARfD	Not applicable		

MRLs

Relevant commodities	-

Reference value for groundwater

According to BPR Annex VI, point 68	-

[4] If residues in food or feed.

Dermal absorption

Study (*in vitro/vivo*), species tested	In an *in vitro* test of dermal penetration with human skin
Formulation (formulation type and including concentration(s) tested, vehicle)	Chlorophacinone showed rapid absorption but with minimal total absorption. The highest proportion detected in the receptor fluid was 0.44 % which represents the actual systemic proportion. Total absorption was estimated to be 1.7% for the human including radioactivity measured in receptor fluid, tape stripping and residual skin values.
Dermal absorption values used in risk assessment*	1.7%

*Footnote: the dermal absorption was not evaluated using EFSA guidance (2012)

Acceptable exposure scenarios (including method of calculation)

Formulation of biocidal product	Not applicable
Intended uses	See below
Industrial users	Not applicable
Professional users	

PRODUCT 1: Professional user: assessment based on default values

Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Repeated dose Toxicity			
			Systemic NOAEL (mg/kg bw/day)	Systemic AOEL (mg/kg bw/day)	MOE	Exposure / AOEL
Treating 75 cesspools/day in sewers to control rats; unused product not collected.	Gloves	0.0000201	0.005	0.000017	249	1.206
	None	0.0001992	0.005	0.000017	25	11.952
Treating 75 bait points/ day to control rats in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.00001215	0.005	0.000017	412	0.729
	None	0.0001197	0.005	0.000017	42	7.182
Treating 75 bait points/ day to control mice in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.00000816	0.005	0.000017	613	0.490
	None	0.0000798	0.005	0.00017	63	4.788
Treating 75 bait points/ day (burrows) in open areas to control rats and mice; unused product not	Gloves	0.00000618	0.005	0.000017	809	0.371
	None	0.00006	0.005	0.000017	83	3.600

collected						

PRODUCT 1: Professional user: assessment based on measured values						
Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Repeated dose Toxicity			
			Systemic NOAEL (mg/kg bw/day)	Systemic AOEL (mg/kg bw/day)	MOE	Exposure/ AOEL
Treating 75 cesspools/day in sewers to control rats; unused product not collected.	Gloves	0.0000019125	0.005	0.000017	2614	0.115
	None	0.000019125	0.005	0.000017	261	1.148
Treating 75 bait points/ day to control rats in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.00000201	0.005	0.000017	2488	0.121
	None	0.0000201	0.005	0.000017	249	1.206
Treating 75 bait points/ day to control mice in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.00000201	0.005	0.000017	2488	0.121
	None	0.0000201	0.005	0.000017	249	1.206
Treating 75 bait points/ day (burrows) in open areas to control rats and mice; unused product not collected	Gloves	0.0000019125	0.005	0.000017	2614	0.115
	None	0.000019125	0.005	0.000017	261	1.148

PRODUCT P2: Professional user: assessment based on default values						
Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Repeated dose Toxicity			
			Systemic NOAEL (mg/kg bw/day)	Systemic AOEL (mg/kg bw/day)	MOE	Exposure/ AOEL
Treating 80 bait points/day to control rats in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.000000625	0.005	0.000017	8000	0.0375
	None	0.00000445	0.005	0.000017	1124	0.267
Treating 80 bait points/day to control mice in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.000000625	0.005	0.000017	8000	0.0375
	None	0.00000445	0.005	0.000017	1124	0.267
Treating 80 bait points/ day (burrows) in open areas to control rats and mice; unused product not collected	Gloves	0.000000625	0.005	0.000017	8000	0.0375
	None	0.00000445	0.005	0.000017	1124	0.267

PRODUCT P2: Professional user: assessment based on measured values			
Workplace operation	PPE	Total systemic	Repeated dose Toxicity

		dose (mg/kg bw/day)	Systemic NOAEL (mg/kg bw/day)	Systemic AOEL (mg/kg bw/day)	MOE	Exposure/ AOEL
Treating 80 bait points/day to control rats in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.00000064	0.005	0.000017	7813	0.038
	None	0.00000352	0.005	0.000017	1420	0.211
Treating 80 bait points/day to control mice in/around buildings and waste dump (landfill) perimeters; unused product collected	Gloves	0.000000415	0.005	0.000017	12048	0.025
	None	0.00000217	0.005	0.000017	2304	0.130
Treating 80 bait points/ day (burrows) in open areas to control rats and mice; unused product not collected	Gloves	0.00000065	0.005	0.000017	7692	0.039
	None	0.0000036	0.005	0.000017	1389	0.216

PRODUCT P3: Risk assessment for professional operators

Workplace operation	PPE	TOTAL SYSTEMIC DOSE (mg/kg bw/day)	Repeated dose Toxicity		MOE	Exposure/ AOEL
			Systemic NOAEL (mg/kg bw/day)	Systemic AOEL (mg/kg bw/day)		
Professional user: assessment based on default values (HSL model)						
Treating 8 points/day; unused product not collected.	Gloves	0.000011	0.005	0.000017	454	0.64
	None	0.0000722	0.005	0.000017	70	4.25
Professional user: assessment based on default values (BBA model)						
Treating 8 points/day; unused product not collected.	Gloves	0.0000021	0.005	0.000017	2380	0.123
	None	0.0000129	0.005	0.000017	387	0.76

General public

PRODUCT P1: General publicr: assessment based on default values

Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Acute toxicity	
			NOAEL (mg/kg bw/day) (a)	MOE
Treating 5 bait points/day to control rats; unused product collected	None	0.00000816	0.010	1225
Treating 5 bait points/day to control mice; unused product collected	None	0.00000551	0.010	1815

PRODUCT P1: General public: assessment based on measured values

Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Acute exposure	
			NOAEL (mg/kg bw/day) (a)	MOE
Treating 5 bait points/day to control rats; unused product collected	None	0.00000178	0.010	5618
Treating 5 bait points/day to control mice; unused product collected	None	0.00000178	0.010	5618

PRODUCT P2: General public: assessment based on default values

Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Repeated dose toxicity		Acute toxicity	
			NOAEL	MOE	NOAEL (mg/kg bw/day) (a)	MOE
Treating 5 bait points/day to control rats; unused product collected	None	0.000000465	NA	NA	0.010	21505
Treating 5 bait points/day to control mice; unused product collected	None	0.000000465	NA	NA	0.010	21505

PRODUCT P2: General public: assessment based on measured values

Workplace operation	PPE	Total systemic dose (mg/kg bw/day)	Repeated dose toxicity		Acute toxicity	
			NOAEL	MOE	NOAEL (mg/kg bw/day) (a)	MOE
Treating 5 bait points/day to control rats; unused product collected	None	0.000000135	NA	NA	0.010	74074
Treating 5 bait points/day to control mice; unused product collected	None	0.00000009	NA	NA	0.010	111111

Secondary exposure

Non users: assessment based on measured values

Workplace operation	Exposure path	Total systemic dose (mg/kg bw/day)	Repeated dose Toxicity	
			Systemic NOAEL (mg/kg bw/day)	MOE
In and around buildings for control of rats and mice.	Non-users will not be present during application. Infants may ingest part of wax blocks: 10 mg.	0.00005	0.010	200
In and around buildings for control of rats and mice.	Non-users will not be present during application. Infants may ingest part of wax blocks: 5 g	0.025	0.010	0.4

Exposure via residue in food

Not applicable

*Footnote: at product authorisation new human exposure calculations should be performed taking into account HEEG opinion 10 and 12

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)	
pH 4	pH~4_____: > 1 year at environmentally relevant temperatures (50ºC pre-test; 60, 70ºC).

pH 7	pH~7_____: > 1 year at environmentally relevant temperatures (50ºC pre-test).
pH: *9]*	pH~9_____: > 1 year at environmentally relevant temperatures (50ºC pretest).
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Under artificial sunlight (25ºC): DT_{50} 2.2 days (natural summer sunlight at latitude 50°N) in buffer solution (pH~7). DT_{50} 1.3 days (natural summer sunlight at latitude 50°N) in pond water (pH~8.4 post sterilisation).
Readily biodegradable (yes/no)	No. No significant biodegradation of chlorophacinone was observed after an incubation period of 28 days according to the OECD TG 301F.
Inherent biodegradable (yes/no)	-
Biodegradation in freshwater	-
Biodegradation in seawater	Not applicable (exposure to seawater unlikely).
Non-extractable residues	Not available
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)	61% AR after $_{ca}$ 100 days.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	
DT_{50lab} (20°C, aerobic):	At 25°C DT_{50} value 47.3 days (1 soil, 75% 1/3 bar moisture).
DT_{90lab} (20°C, aerobic):	At 25°C DT_{90} value > 200 days (1 soil, 75% 1/3 bar moisture).
DT_{50lab} (10°C, aerobic):	Estimated at 12°C from data available at 25°C. DT_{50} value 128 days (1 soil).
DT_{50lab} (20°C, anaerobic):	Not applicable.
degradation in the saturated zone:	Not applicable.
Field studies (state location, range or median with number of measurements)	
DT_{50f}:	Not applicable.
DT_{90f}:	Not applicable.

Anaerobic degradation	Not applicable.
Soil photolysis	DT_{50} =11.1 d (12ºC) Degradation of Chlorophacinone results in the formation of a major metabolite o-phthalic acid (37.1% AR), carbon dioxide (potentially 50% AR) and three minor degradation products (< 10% AR)
Non-extractable residues	9.0% AR after *ca* 100 days.
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Degradation of chlorophacinone resulted in the formation of a major metabolite o-phthalic acid (37.1% AR), carbon dioxide (potentially 50% AR) and three minor degradation products (< 10% AR).
Soil accumulation and plateau concentration	Not applicable (not applied directly to soil).

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Soil distribution (partition) coefficient (KD) = 36 to 492 ml/g. Freundlich soil adsorption coefficient (KF) = 80 to 1000 ml/g. Freundlich soil adsorption coefficient normalised for organic carbon content (Koc) = 15,600 to 136,000 ml/g.

Fate and behaviour in air

Direct photolysis in air	The photochemical oxidative degradation half-life of Chlorophacinone in air was estimated using the Atmospheric Oxidation Program v1.90 (AOPWIN), which is based on the structural activity relationship (QSAR's) methods developed by Atkinson, R (1985 to 1996). The half-life for the hydroxyl reaction in air is estimated to be 14.3 hours, indicating that if present in air, Chlorophacinone would not be expected to persist.
Quantum yield of direct photolysis	Latitude: ....n.a... Season: ... ..n.a... DT_{50} .. ..n.a....
Photo-oxidative degradation in air	Latitude: ..... Season: ..... DT_{50} .....
Volatilization	Vapour pressure at 22.8°C is 4.76 x 10^{-4} Pa (OECD 104). Henry's law constant = 0.013725 $Pa.m^3.mol^{-1}$ (based on a water solubility of 13.0 mg/l). Chlorophacinone 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	LC_{50} = 0.45 mg/l
Invertebrates			
Daphnia magna	48 hours	Immobility	EC_{50} = 0.64 mg/l
Algae			
Desmodesmus subspicatus (formerly known as *Scenedesmus subspicatus*)	72 hours	Biomass Biomass Growth rate Growth rate	E_bC_{50} = 1.7 mg/l $NOEC_b$ = 0.72 mg/l E_rC_{50} = 2.2 mg/l $NOEC_r$ = 0.72 mg/l
Microorganisms			
Activated sludge	3 hours	Respiration inhibition	EC_{50} > 1.000 mg/l; above the water solubility limit EC_{15} > 775 mg/l; above the water solubility limit

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia foetida*	14-day LC_{50} > 300 mg/kg wwt soil (synthetic OECD substrate).
Reproductive toxicity to	Not appropriate.

Effects on soil micro-organisms

Nitrogen mineralization	Waived.

Carbon mineralization	Waived.

Effects on terrestrial vertebrates

Acute toxicity to mammals	LD_{50} = 1.48 to 18.57 mg/kg bw (rats)
Acute toxicity to birds	5-daysLD_{50} = 257 mg/kg bw (Bobwhite quail)
Dietary toxicity to birds	5-days LC_{50} = 95 mg/kg food (Bobwhite quail)
Reproductive toxicity to birds	Lowest 90-days NOEC (mortality) = 1 mg/kg food (Japanese quail)

Effects on honeybees

Acute oral toxicity	Not appropriate.
Acute contact toxicity	Not appropriate.

Effects on other beneficial arthropods

Acute oral toxicity	Not appropriate.
Acute contact toxicity	Not appropriate.
Acute toxicity to	Not appropriate.

Bioconcentration

Bioconcentration factor (BCF)	Waived. No study available. The BCF_{fish} was calculated from the log K_{ow} of 2.42; pH~7, 23ºC according to the TGD and resulted in BCF_{fish} of 22.75 l/kg.
Depration time (DT_{50})	Waived.
Depration time (DT_{90})	Waived.
Level of metabolites (%) in organisms accounting for > 10 % of residues	Waived.

Chapter 6: Other End Points

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

No new data were submitted for renewal.