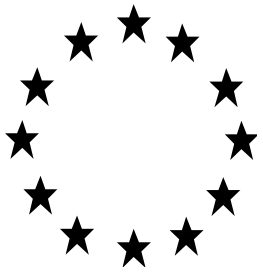
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Renewal of approval

Assessment Report



Difethialone

Product-type 14
(Rodenticides)

July 2016

Norway

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1. STATEMENT OF SUBJECT MATTER AND PURPOSE

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

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

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

Difethialone was approved as an existing active substance, in product-type 14 under the Biocidal Products Directive (Commission Directive 2007/69/EC). The renewal of the active substance has been requested by Liphatech.

The deadline for the application for renewal of approval for difethialone according to BPR was originally 29.04.2013. However, it was decided to postpone the deadline until the entry into force of the BPR. The applicant was to submit their applications as soon as possible after 1.09.2013. As Norway was the Rapporteur when difethialone was first approved as an existing active substance under the Biocidal Products Directive, the applicant chose Norway as the evaluating Competent Authority (eCA) also for the renewal of the approval of the active substance. However, as the BPR was not included in the EEA-agreement before 14.12. 2013, the deadline was, in dialogue with the Commision, ECHA and the applicant, further postponed. On 16.01.2014 the Norwegian competent authority (eCA) received the first part of the application (including a technical dossier) from Liphatech. Supporting documentation was submitted on 31.07.2015 in accordance with the document "Renewal anticoagulant rodenticides" (CA-Sept14-Doc.5.2 - Final.Rev1). The European Chemicals Agency (ECHA) accepted the application on 5.08.2015, and it was forwarded to the eCA for assessment. 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 was necessary.

As all anticoagulant rodenticides meet the exclusion criteria, if approved, stringent risk mitigation measures will need to be applied. Where no new information was available in the application of renewal, the revision of the evaluation applying current guidance is postponed to product authorisation. This decision shall exclusively apply for the renewal of anticoagulant rodenticides. On 21.03.2016, the eCA submitted to the Agency the assessment report. The applicant received the assessment report on the 05.04.2016.

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 meeting, and the assessment report was amended accordingly.

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

1.1. 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 difethialone for product-type 14, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

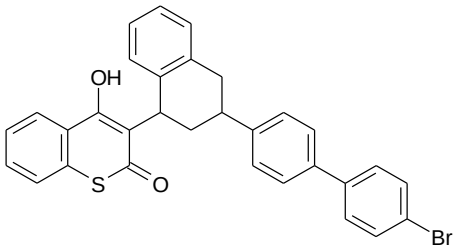
For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

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

2. OVERALL SUMMARY AND CONCLUSIONS[2]

2.1. Presentation of the Active Substance

2.1.1. Identity

CAS-No.	104653-34-1
EINECS-No.	None assigned
Other No. (CIPAC, ELINCS)	CIPAC No. 549
IUPAC Name	3-[3-(4'-bromo[1,1'biphenyl]-4-yl)-1,2,3,4-tetrahydronaphth-1-yl]-4-hydroxy-2H-1-benzothiopyran-2-one*
Common name, synonym	Difethialone
Molecular formula	$C_{31}H_{23}BrO_2S$
Purity	Specification > 97.6%
Structural formula	
Molecular weight (g/mol)	539.495

**From the 1980s until 2007, an incorrect IUPAC name (3-((1RS,3RS;1RS,3SR)-3-(4'-bromobiphenyl-4-yl-1,2,3,4-tetrahydro-1-napthyl)-4-hydroxy-1-benzothin-2-one) was in use.*

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

2.1.2. Intended Uses

Difethialone is used as a rodenticide pest control substance (Main group 03, Product type 14) for the control of rodents indoors (i.e. in grain silos, warehouses), in and around farms, buildings and in sewer systems.

The applicant has not supported a usage of difethialone in open areas, e.g. on waste dumps.

Difethialone is used to control:

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

by professionals and the general public

The maximum concentration allowed is 25 mg/kg (ready to use bait only) according to the Commission Directive 2007/69/EC.

No new information on the evaluated products (block bait, paste bait and pellet bait) has been provided.

Formulated products containing difethialone are not applied directly on food or feeding stuffs. Products are not intended to be applied directly on surfaces intended for contact with food or feeding stuffs. However, difethialone containing products are intended to be used in premises were food or feeding stuffs are prepared or stored.

2.2. Summary of the Assessment

2.2.1. Specification of the different sources of the active substances

Difethialone is produced at one location only.

The purity of the active substance (> 97.6%) 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 diastereoisomers (cis and trans). Both diastereomers are considered as active substance. The ratio is considered confidential and can be found in Document V of the Competent Authority Report for the original evaluation (2007) of the active substance.

The five batch analysis provided in the original dossier were considered to be of appropriate age (close to 10 years), hence a new five batch analysis for the renewal was not requested. Quality control data will be requested prior to product approval in order to verify that the specification of the active substance still is in compliance with the specification from the original approval.

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

2.2.2.1. Physico-chemical properties and methods of analysis

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

2.2.2.2. Classification and Labelling

Difethialone has no current harmonized classification in accordance with Regulation (EC) No 1272/2008 (CLP Regulation).

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

Difethialone 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 (Norway) 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-opinion was adopted on 14 March 2014.

The resulting Annex VI entry, agreed by the REACH Committee on 4 February 2016 (9th ATP to CLP, not yet published), is listed below:

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 Chronic 1; H410
Labelling	
Pictograms	GHS06 GHS08 GHS09 Dgr
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)	**EUH070**: Toxic by eye contact
Specific Concentration limits, M-Factors	Repr. 1B; H360D: C ≥ 0.003 % STOT RE 1; H372: C ≥ 0.02 % STOT RE 2; H373: 0.002 % ≤ C < 0.02 %

	M =100 for Aquatic Acute toxicity M =100 for Aquatic Chronic toxicity

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

2.2.2.3. Efficacy and resistance

No new information/studies were provided by the applicant since the original approval, and the conclusions remain the same.

2.2.2.4. Human health assessment

No new studies were provided by the applicant 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[3]) and dermal absorption should be taken into account.

2.2.2.5. Environmental assessment

No new studies were provided by the applicant since the original approval, and the conclusions remain the same.

2.2.2.6. Fate and distribution in the environment

No new studies were provided by the applicant, and the conclusions remain the same.

However, according to the new Guidance on the BPR (Volume IV. Part A, Section I: Introduction Version 1.1, November 2014, p. 26) four metabolites detected in the soil simulation study (A7.2.2.1.) would now be classified as relevant metabolites. The metabolites M2,M3, M4 and M7 which were observed at maximum levels of 8.3%, 13.5%,10.2% and 9.6 % applied radioactivity after 378, 189, 140 and 189 days, respectively.

2.2.2.7. PBT and POP assessment

PBT

Difethialone was assessed in the PBT working group in a meeting in March 2008. The conclusions from the meeting was that difethialone is a potential PBT and vPvB substance.

- P/vP criteria fulfilled when considering biodegradation in soil;
  screening criteria P/vP fulfilled regarding aquatic biodegradation
- Screening criteria B/vB fulfilled
- T criterion fulfilled

For the renewal approval, no new studies/information were provided by the applicant. However, an update of the PBT assessment has been performed, because the old TGD criteria were used in the CAR and in the PBT group in 2008.

[3] The Human Exposure Expert Group (HEEG) prepared opinions in the context of the BPD on harmonised approaches to biocide exposure assessment. The opinions are available from the ECHA web-site at http://echa.europa.eu/view-article/-/journal_content/title/support-biocides-heeg-opinions.

Assessment of PBT according to the REACH criterion from Commission Regulation (EU) No 253/2011 of 15 March 2011:

Persistency, P and vP criteria
Aerobic biodegradation of difethialone in soil shows an average half-life in soil of 635 days at a temperature of 20°C. The half-live in soil exceeds the criteria for P (120 days) and vP (180 days). This verifies the conclusion from the PBT group of difethialone as a P and vP substance.

Bioaccumulation, B and vB criteria
The original assessment of the B criterion was based on the experimentally derived log Kow (6.29) and calculated BCF (39,974; TGD and 14,000; Episuite3.1). In the new EU regulation 253/2011 point 1.1.2, a substance fulfils the B criteria when the BCF is higher than 2000 and vB if BCF > 5000. In addition to this point, point 3.2.2 b. (Other information on the bioaccumulation potential provided that its suitability and reliability can be reasonably demonstrated) should be considered in the PBT assessment. Under this point terrestrial studies, analysis of human body fluids or tissues, elevated levels in biota and toxicokinetic behaviour of the substance should be assessed for the B assessments. Monitoring data show that difethialone has been found in non-target animals throughout Europe. Elimination half-life of 18 weeks in rats and high prevalence in the non-target animals demonstrate a high potential for secondary exposure. Based on this information, it can be concluded that difethialone fulfils the B and vB criteria.

Toxicity, T criteria
A NOEC or EC10 for marine or freshwater organisms are not available. However, according to the criteria in Reg. (EU) 253/2011 point 1.1.3, it is possible to use human toxicity data. According to the RAC-opinion on difethialone (see 2.2.2.2), the substance should be classified as toxic for reproduction, category 1B and as STOT RE 1 H372 (blood). Difethialone therefore fulfils the T criterion.

POP

- 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 difethialone has a log Kow>5. There is evidence that the chemical has a high bioaccumulation potential in mammals/birds.

- 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 expected half-life in air is about 2 hours and thus does not fulfil the criterion (half-life more than 2 days). Moreover, the vapour pressure and Henry's law constant are low, and the adsorption potential to organic matter is high. However, atmospheric transport e.g. in particles cannot be excluded. There are no monitoring data available or other evidence indicating potential for long range environmental transport.
In conclusion, difethialone exhibits certain POP characteristics (persistence, bioaccumulation and adverse effects), but does not fulfil the screening criteria for long-range environmental transport. Difethialone 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. Difethialone is not considered to have endocrine disrupting properties.

2.2.3. Assessment of the recommendations arising from the report[4] on RMM for anticoagulant rodenticides, in connection with the conclusions in the workshop, inputs from the applicant and other information available to the eCA that are relevant for the active substance

Anticoagulant rodenticides (AR) have a common anti-vitamin K (AVK) mode of action, disrupting the normal blood clotting mechanisms, resulting in increased bleeding tendency and, eventually, profuse haemorrhage and death. Onset of symptoms may be delayed for several days after exposure.

Anticoagulant rodenticides are divided into First Generation AR (FGAR; warfarin, chlorophacinone, coumatetralyl), requiring several days of feeding to be fully active and Second Generation ARs (SGARs; bromadiolone, difenacoum, brodifacoum, flocoumafen and difethialone), which are more potent and effective after only one/a few times of feeding. Difethialone, brodifacoum and flocoumafen are often referred to as more potent than bromadiolone and difenacoum.

In addition to being more toxic, SGARs have a longer body retention time than FGARs with a higher tendency to accumulate in non-target species that feed on rodents.

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 offers a distinction between risk mitigation measures that might be appropriate for harmonisation by proposing conditions to be included 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

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

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 difethialone 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. The text below in bold (italic) is taken directly from the RMM report (section 1.1 and 1.2). This assessment includes the critical review of the applicant and a recommendation or conclusion by the evaluating Competent Authority.

Substance specific considerations as well as some specific measures proposed for difethialone are presented and discussed at the end of this section.

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).

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 difethialone 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.

General recommendations on RMMs for anticoagulant rodenticides

RMMs 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 at this moment 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 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 is of the opinion that FGARs generally should not be restricted for use against mice. In case of suspected lack of efficacy of the AR by the end of the treatment, the user should be recommended to call a pest control service.

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

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 is of the opinion 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. Furthermore, it is commented that 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, the applicant considers that there are currently insufficient pest control operators to treat the reported number of household infestations. Farmers are considered to be amateurs in some Member States and farmers should not according to the applicant be denied access to rodent control because of the risks that would present to the food chain.

The eCA is of the opinion that SGARs might be authorized for use by the general public against mice as long as only small quantities are allowed and the bait is provided in prefilled tamper resistant bait stations.

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 suggested maximum pack sizes given in the RMM report were considered as a good starting point, and CEFIC was asked to make a modified proposal.

The applicant agreed in principle with the restriction on pack size, but with a maximum pack sixe of 1.5 kg. It was argued that the list of pack sizes proposed in the RMM report does not consider potency and presumes only one bait point.

The eCA agrees that pack size 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 with some modifications. 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 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.

Rat control necessities the use of rodenticides in and around buildings. Due to different national situations, the eCa agrees that rat control in and around buildings could be subject to derogation from the mutual recognition at the product authorization stage.

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

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

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 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.

The applicant commented that Industry introduced the use of 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). It should be kept in mind though that the addition of bittering agent would be expected to significantly reduce, but not eliminate, the probability of an accidental ingestion by the youngest children.

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 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.

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 perform by professionals in order to determine the extent of the infestation. The bait stations should be clearly marked to show that they contain anticoagulant rodenticides and that they should not be disturbed. Contact information (e.g. to the Poison Information Centre) and measures to be taken in case of poisonings (most importantly information about antidote) should be included. In addition, contact information to the one responsible for the treatment should be given.

For amateur 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 amateur 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 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 and locked outbuildings, where bait stations would not be necessary.
Loose baits (such as grain and pellets) should in their opinion <u>not</u> be excluded for amateur use because of their higher palatability.

The general public is untrained and less likely to read and interpret correctly use instructions on product packaging. Furthermore, they will not have access to personal protective equipment (PPE), except possibly gloves. Hence, to reduce the risk of exposure to the user as well as poisoning of children, pets and other non target animals, the eCA is of the opinion that use of tamper resistant bait stations should be mandatory and only small packages should be authorized. Due to the high toxicity and high accumulation in organisms of the SGARs, the bait stations containing bait formulations with SGARs should be prefilled and not be possible to open.

For products applied in such prefilled tamper resistant bait stations, incidental exposure will most likely be limited, especially if the bait station is fixed to the ground/floor (anchored). However, rodents hoard food and will therefore translocate bait from bait stations, subsequently making bait available for non target animals (e.g. birds) and humans. Children and pets are most likely the group most at risk as they may stay inside or around buildings where baits have been placed.

As hoarding is more relevant for grain/pellet formulations, careful considerations should be taken before authorizing such formulations containing high potent SGARs for use by the general public.

The bait stations should be clearly marked to show that they contain anticoagulant rodenticides and that they should not be disturbed. Contact information (e.g. to the Poison Information Centre) and measures to be taken in case of poisonings should be included.

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 that covered bait points might be accepted in specific situations only by professionals trained to use rodenticides. However, due to the increased risk of poisoning of non target animals and humans, such covered bait points should only be accepted for indoor use and be restricted to locations where exposure to children and pets can be excluded.

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 considers generally that the principle of more targeted placement (pulse baiting) by professionals trained to use rodenticides with frequent visits could be supported as far as the efficacy is demonstrated.

As for difethialone, it can be a suitable SGAR for pulse baiting. However experience with pulsed baiting seems to be lacking according to the statement of the applicant. Hence, before authorizing such use, efficacy has to be demonstrated.

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.

Due to the risk to non-target species, the eCA agrees that permanent baiting outdoors should be restricted to locations with high potential for reinvasion and/or sites where quality assurance schemes require it.

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 that permanent baiting indoors should be restricted to locations with high potential for reinvasion and/or sites where quality assurance schemes require it. It should be defined in a code of best practice.

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 professional. 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"). For clients and other amateurs, 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 amateurs is considered to ensure that amateurs 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. To ascertain that dead bodies are disposed by the general public, the eCA agrees that sealing of dead bodies in two separate plastic bags before disposing the bodies in the household waste is appropriate.
Due to the risk of disease transmission and exposure to the anticoagulant rodenticide, advice on wearing of gloves when removing dead bodies should be given as well as washing of hands after disposal.

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

At the workshop 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 is of the opinion that uneaten bait should be searched for and removed during the treatment. All remaining uneaten bait should be removed and disposed at the end of the treatment. The disposal should be in accordance with local requirements. The method of disposal should be described specifically on the national SPC and on the label of the product as proposed in the summary of the workshop.
Advice on wearing of gloves when removing uneaten bait should be given as well as washing of hands after disposal.

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 , 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.

See comments above for the use of different AR against resistant populations of rodenticides.

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.

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.

RMMs to be set at the stage of product authorisation

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

According to the RMM report (table 6) protection level 1 is defined as "factory filled non refillable tamper resistant bait stations", level 2 as "baits to be used in refillable tamper-resistant bait stations and supplied as inner packs or units, each containing bait for one bait point" whereas level 3 is defined as "baits to be used in refillable tamper-resistant bait stations, and supplied loose in refill packs".

The eCA agrees that tamper resistant bait stations should be mandatory for products to be used by amateurs. Due to risk of primary and secondary poisoning to animals as well as poisoning of humans, bait stations of level one should be used rather than level 2 or 3 for products containing SGARs.

All bait formulations should be available to all user categories, with limited amounts and tamper-resistant bait boxes 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. Furthermore, tamper resistant bait stations should be mandatory.
Due to the high risk of poisoning of non-target animal (e.g. birds) to grain/pellets

(increased attractiveness of the formulation combined with the fact that rodent translocate bait from the bait station), careful considerations should be taken before authorizing such formulations containing high potent SGARs 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.

Substance specific considerations

Due to the high toxicity of difethialone and its accumulative nature (18 weeks liver half life in rats), its use poses a high risk of primary and secondary poisoning to non-target mammals and birds.

Monitoring data demonstrate that difethialone is found in non-target animals throughout Europe (Walker et al. 2013, Geduhn et al. 2015, López-Perea et al. 2015, Elmeros et al. 2015, Berny et al. 2014). Difethialone has not been found as frequent as some of the other SGARs, but the measured concentrations have been rather high in some cases. Generally, the frequency of incidents is assumed to correlate with the use volumes of the anticoagulant substances.

Risk to infants accidentally ingesting bait has been identified. There are a few reported incidents of poisonings of humans or pets due to difethialone containing products. However, the use of rodenticides containing difethialone has been rather limited, and many incidents of poisonings, both accidential and intentional, have been reported in literature for anticoagulant rodenticides in general.

There is a risk for development of resistant strains through the use of anticoagulant substances. In the interest of public health and hygiene there is a need for having a variety of active substances available due to the problems of resistant populations of rodents.

Resistance is not compound specific. However, whereas resistance has been demonstrated for bromadiolone and difenacoum, there is today no evidence of 'practical' resistance in the field to the three other SGARs according to the RMM report (low resistance factors; unlikely to have any perceptible effect on treatment outcome, Berny et al. 2014). It should be kept in mind though that the use of difethialone has been limited in volume and time.

As FGARs and low potency SGARs may not control rodent populations effectively, resistance selection will result with the resulting prolonged use and risk to non-target species (Buckle, 2012). Difethialone (as well as the other high potent SGARs) is an important substance in situations when problems with resistance occur.

However, due to the high toxicity of difethialone and the risk of primary and secondary poisoning of animals and humans, difethialone should be used as limited as possible and mainly when resistance to FGARs and low potent SGARs is shown to occur. Specifically, disregarding the use in open areas/waste dumps should be considered. Such use has not been applied for nor risk assessed.

2.3. Overall conclusions

The outcome of the assessment for difethialone 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 related to the biocidal product

No further information on the biocidal products is required for the purpose of 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 reevaluation performed for the renewal of approval, are listed in Appendix I.

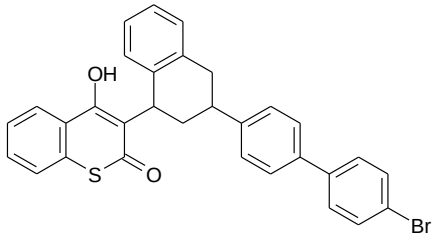
Appendix I: List of endpoints

No new studies relevant for the list of endpoints have been submitted since the Assessment report of difethialone was made in 2007. Hence, if not specifically commented, the endpoints listed in the annex are the ones from the Assessment Report of difethialone of 2007 (with only minor adjustment of text due to the revised template of the Assessment Report).

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

Active substance (ISO Name)	Difethialone
Product-type	Main group 3: Pest control. Product type 14: Rodenticides, against rats and mice

Identity

Chemical name (IUPAC)	3-[3-(4'-bromo[1,1'biphenyl]-4-yl)-1,2,3,4-tetrahydronaphth-1-yl]-4-hydroxy-2H-1-benzothiopyran-2-one *
Chemical name (CA)	2H-1-Benzothiopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-
CAS No	104653-34-1
EC No	None assigned
Other substance No.	CIPAC No. 549
Minimum purity of the active substance as manufactured (g/kg or g/l)	976 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None of relevance Information regarding impurities and additives in the active substance is confidential to LiphaTech
Molecular formula	$C_{31}H_{23}BrO_2S$
Molecular mass	539.495 g/mol
Structural formula	

* From the 1980s until 2007, an incorrect IUAC name (3-((1RS,3RS;1RS,3SR)-3-(4'-bromobiphenyl-4-yl-1,2,3,4-tetrahydro-1-napthyl)-4-hydroxy-1-benzothin-2-one) was in use.

Physical and chemical properties

Melting point (state purity)	233°C at the beginning of melting, 236 °C at the final stage of melting (purity 99%)
Boiling point (state purity)	No boiling point has been determined
Thermal stability / Temperature of decomposition	No decomposition below the melting point
Appearance (state purity)	Yellow powder (purity 99%)
Relative density (state purity)	1.36 g/ml at 25 °C (purity 99%)
Surface tension (state temperature and concentration of the test solution)	Not required, water solubility is below 1 mg/l
Vapour pressure (in Pa, state temperature)	< 1.33×10^{-5} Pa (22.6°C)
Henry's law constant (Pa m^3 mol^{-1})	< 1.8×10^{-2} $Pa.m^3.mol^{-1}$
Solubility in water (g/l or mg/l, state temperature)	Pure water: 0.39 mg/l at 25°C pH not stated
Solubility in organic solvents (in g/l or mg/l, state temperature)	Results at 20°C Dichloromethane: 10 to 14 g/l Hexane: 0.2 g/l
Stability in organic solvents used in biocidal products including relevant breakdown products	No studies available. However, the stability of the products, where solvent is used, is documented. Moreover, data on stability in the premix are available.
Partition coefficient (log P_{OW}) (state temperature)	6.29 at pH 7.3 (ambient temperature)
Dissociation constant	Due to low water solubility, difethialone is not considered ionisable
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Approximately 234nm, 260nm and 330nm (ε not stated).
Quantum yield of direct phototransformation in water at Σ > 290 nm	6.183×10^{-3} mol/photon from the study with artificial sunlight
Flammability or flash point	Not highly flammable
Explosive properties	Not explosive
Oxidising properties	Not oxidizing
Auto-ignition or relative self ignition temperature	No reactivity towards container material known

Classification and proposed labelling[5]

with regard to physical hazards	None

[5] 9 ATP to Regulation (EC) No 1272/2008 (CLP Regulation), agreed by the REACH Committee on 4 February 2016 (not yet published)

with regard to human health hazards	Repr. 1B; H360D Acute Tox. 1; H300 Acute Tox. 1; H310 Acute Tox. 1; H330 STOT RE1; H372 (blood) Supplemental hazard statement codes: EUH070
with regard to environmental hazards	Aquatic Acute 1; H400 Aquatic Chronic 1; H410
Specific concentration limits, M factors	Repr. 1B; H360D: C ≥ 0.003 % STOT RE 1; H372: C ≥ 0.02 % STOT RE 2; H373: 0.002 % ≤ C < 0.02 % M =100 for Aquatic Acute toxicity M =100 for Aquatic Chronic toxicity

Chapter 2:Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	The technical material is dissolved in a mixture of dichloromethane and methanol (1+1, v/v) containing an internal standard (biphenyl). Determination is by reverse-phase HPLC/UV at a wavelength of 260 nm. An Inertsil ODS-2 column is used with acetonitrile/ propan-2-ol/2M ammonium acetate (63/3/35, v/v/v) mobile phase
Impurities in technical active substance (principle of method)	The analytical method for determination of impurities is confidential and can be found in the confidential document[6]

Analytical methods for residues

Soil (principle of method and LOQ)	Soil is extracted by shaking with acetone. Determination of the concentrated extract is by reverse-phase LC-MS (target ion 539 amu, confirmatory ions 541 and 561 amu). A Lichrospher C-18 column is used with methanol/water/phosphoric acid (92.5/7.5/0.1, v/v/v) 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 bubbled through a tube containing 1-methoxyethanol collecting liquid. Determination is by reverse-phase HPLC/UV at a wavelength of 254 nm. A Nucleosil C-18 column is used with acetonitrile/ 0.0425% phosphoric acid (80/20, v/v/v) mobile phase. The limit of determination is 0.2 $\mu g/m^3$ (defined as the lowest concentration at which acceptable recovery has been demonstrated).

[6] See confidential Annex to the CA-report of difethialone of 2007.

Water (principle of method and LOQ)	Acetonitrile is added to the water sample and clean up is by passage through a C-8 column solid phase extraction cartridge. Determination is by reverse-phase HPLC/MS-MS (two ion transitions monitored 536.9>79 and 538.9>81). An Inertsil ODS-EP column is used with acetonitrile/water/acetic acid (85/15/0.1, v/v/v) mobile phase. The limit of determination is 0.05 μg/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 Phenomenex Luna phenyl-hexyl column and ammonium acetate/methanol (gradient) mobile phase (two ion transitions monitored 539>81 and 537>79). The limit of determination is 0.05 mg/l (defined as the lowest concentration at which acceptable recovery has been demonstrated). **Liver** Liver is ground with anhydrous sodium sulphate and extracted by shaking with a mixture of dichlormethane and acetone (1+1, v/v). Clean-up of the filtered extract is by GPC. Determination is by HPLC with a Phenomenex Luna phenyl-hexyl column and ammonium acetate/methanol (gradient) mobile phase (two ion transitions monitored 539>81 and 537>79).The limit of determination is 0.05 mg/kg (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)	**Oils seed rape and lemon:** Extracted by blending and then shaking with methanol/water 4+1 v/v (oil seed rape) or methanol (lemon). After centrifugation the samples are diluted with methanol/water. Determination with LC-MS-MS. Primary method (m/z: 81.0). Confirmation ion (m/z: 79.3). Calibration range 0.05 to 5.0 ng/ml. Limit of determination: 0.01 mg/kg Linearity R^2 = >0.9995 RSD < 20%, Recovery rates within 70-110%. **Cucumber and wheat:** Extraction by blending with ethyl acetate. Purification of filtered extract by SPE cartridge (cucumber) or gel permeation chromatography (wheat) and determination is by LC-MS-MS (primary ion m/z: 79-81). Calibration range 0.03 to 1.2 µg/ml. Limit of determination: 0.01 mg/kg Linearity R^2 (cucumber) = 0.951 and 0.955 Linearity R^2 (wheat) = 0.972 and 0.996 RSD < 20%, Recovery rates within 70-110%
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	**Meat:** Extracted by blending and then shaking with methanol. After centrifugation the samples are diluted with methanol/water. Determination with LC-MS-MS. Primary method (m/z: 81.0). Confirmation ion (m/z: 79.3). Calibration range 0.05 to 5.0 ng/ml. Limit of determination is 0.01 mg/kg Linearity R^2 = >0.9995 RSD < 20%, Recovery rates within 70-110%

Chapter 3:Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Difethialone was rapidly and extensively absorbed by rats. Radioactivity was first detected in blood 30 minutes after dosing (0.5 mg ^{14}C-difethialone/kg bw), reaching the maximum level, 0.09 µg eq. LM 2219/mL, approximately 24 hours after dosing

Rate and extent of dermal absorption*[7]:	No studies on the end use formulations of difethialone. An in vivo human dermal absorption of 4% may be calculated by combining rat *in vivo* data and rat:human *in vitro* data. This represents a reasonable worst case value to be used in the risk assessments of the products, derived from the dermal delivery (absorbed dose and amounts retained in the epidermis and dermis layers of the skin, but excluding amounts in stratum corneum) of difethialone in glycol solvent (1.25 g/l)[8] 24h after application.
Distribution:	Difethialone was distributed to body organs with the highest levels found in liver
Potential for accumulation:	Difethialone has the potential to bioaccumulate in the liver. The plasma half-life was 2.3 days following an exposure to 0.5mg difethialone/kg bw. The liver concentrations reached a peak within 24 hours after administration (22.8 to 42.5% of administered dose in males and females). At the end of the six month observation period approximately 10% of the administered dose was still present in the liver. The half-life in the liver was in the region of 18 weeks for both males and females
Rate and extent of excretion:	Elimination was exclusively in the faeces as unchanged parent material, with 37% excreted in the first 3 days, 57% within 14 days following an exposure of 0.5mg difethialone/kg bw. There was no excretion via expired air or urine
Toxicologically significant metabolite(s)	Essentially the entire radioactivity found in liver and faecal samples was from unchanged labelled difethialone. No major metabolites were identified

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

Acute toxicity

Rat LD_{50} oral	Combined sexes - between 0.4 and 0.8 mg/kg bw. In a second study LD_{50} for males was 0.55 mg/kg bw and for females was calculated to be 0.58 mg/kg bw.
Dog LD_{50} oral	Combined sexes - 11.81 mg/kg bw

[7] Dermal absorption not evaluated using EFSAs guidance on dermal absorption (2012)
[8] Correction of misprint in the AR of 21 June 2007: The concentration of difethialone in the glycol solvent should read 1.25 g/l and not 25 g/l.

$LOAEL_{acute}$	Dog study (oral administration): 5 mg/kg bw (50 % reduction in plasma prothrombin level)
Rat LD_{50} dermal	Combined sexes - 6.5 mg/kg bw
Rat LC_{50} inhalation	Whole body exposure: $LC_{50} \leq 10.7$ µg/l/4h Nose only exposure: $LC_{50} \geq 5.0$ µg/l/4h but <19.3 µg/l/4h
Skin corrosion/irritation	Non-irritating
Eye irritation	Slightly irritating. EU criteria for classification not fulfilled.
Respiratory tract irritation	-
Skin sensitisation (test method used and result)	Maximisation test using Freund's Complete Adjuvant (test of low reliability) No indications of delayed contact hypersensitivity among guinea pigs subject to an induction and challenge regimen that included dose concentrations up to lethal levels.
Respiratory sensitisation (test method used and result)	No data available

Repeated dose toxicity

Short term/
Subchronic

Species/ target / critical effect	Pig (30 + 14 days, oral administration) Rat (13 weeks, oral administration) Dog (13 weeks, oral administration) Critical effect observed in the studies: Haemorrhagic effects (consistent with the known mode of action, impairment of the clotting cascade, and increased prevalence of haemorrhages, eventually leading to death), No toxic endpoints except haemorrhage reported.
Relevant oral NOAEL / LOAEL	Rat (90d) LOAEL = 4 µg/kg bw/day NOAEL = 2 µg/kg bw/day Dog (90d): LOAEL = 20 µg/kg bw/day NOAEL = 10 µg/kg bw/day
Relevant dermal NOAEL / LOAEL	No data available – not required.
Relevant inhalation NOAEL / LOAEL	No data available – not required

Long term

Species/ target / critical effect	No data available
Relevant oral NOAEL / LOAEL	No data available
Relevant dermal NOAEL / LOAEL	No data available
Relevant inhalation NOAEL / LOAEL	No data available

Genotoxicity

Difethialone showed no mutagenic potential in the in vitro and in vivo studies which have been performed.

Carcinogenicity

Species/type of tumour	There is no indication of any higher incidence of cancer in humans following long term therapy with the closely related molecule, warfarin. Study on difethialone waived.
Relevant NOAEL/LOAEL	Not appropriate

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	Difethialone did not cause any observed teratogenic effects in experimental animal studies. **Rat** In the absence of effects on dams or foetuses and with no maternal mortality or signs of toxicity, no critical effects were identified at the doses used in the main study (up to 50 µg/kg bw/day). Maternal death resulting from haemorrhages was evident in a preliminary study (dosed at 50 or 70 µg/kg bw/day). **Rabbit** No embryofoetal toxicity and no developmental toxicity indicative of teratogenicity observed. Maternal toxicity: Haemorrhages, mortality
Relevant maternal NOAEL	Rat maternal NOAEL – ≥50 µg/kg bw/day. Rabbit maternal LOAEL – 10 µg/kg bw/day Rabbit maternal NOAEL – 5 µg/kg bw/day
Relevant developmental NOAEL	Embryofoetal toxicity (rat) – NOAEL - ≥50 µg/kg bw/day. Embryofoetal toxicity (rabbit) – LOAEL - >10 µg/kg bw/day

Fertility

Species/critical effect	A two generation study is waived

Relevant parental NOAEL	Not appropriate
Relevant offspring NOAEL	Not appropriate
Relevant fertility NOAEL	Not appropriate

Neurotoxicity

Species/ target/critical effect	Difethialone was investigated, in various screening tests for potential pharmacological activity other than its known anticoagulant properties. Difethialone 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 endpoints. 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	No data available

Immunotoxicity

Species/ target/critical effect	No data available

Developmental Immunotoxicity

Species/ target/critical effect	No data available

Other toxicological studies

Studies to investigate antidotal treatment of intoxicated rats or dogs were completed.

Two studies in dogs demonstrated the effect of antidotal vitamin K1 therapy (phytomenadione) following single lethal doses of difethialone.

In another study in rats (25 ppm end use product given as a diet replacement for 1, 2 or 3 days) antidotal treatment was successful following 24 hour exposure, but less successful with longer periods of exposure (the majority of rats died after 48 or 72 hours exposure to difethialone).

Medical data

Many incidents of human poisoning, both accidental and intentional, of anticoagulant rodenticides have been reported in literature. Difethialone is manufactured in small quantities worldwide, and only one published case report of difethialone intoxication has been found. A few cases of intoxications from occupational exposure to anticoagulants have been reported.

The working physicians responsible for Liphatech personnel since 1987 did not encounter any signs of toxicity in routine medical monitoring of the staff. However a previous practitioner met one case of intoxication, due to nail biting.

Summary

	Value	Study	Safety factor
$AEL_{long\text{-}term}$ $AEL_{medium\text{-}term}$	0.007 µg/kg bw/day (repeated dose)	90 day oral toxicity to rat	300 Interspecies and intraspecies safety factor of 100 and an additional assessment factor of 3 due to the severity of the potential developmental effect
$AEL_{short\text{-}term}$[9]	0.017 µg/kg bw/day	rabbit developmental study	300 Interspecies and intraspecies safety factor of 100 and an additional assessment factor of 3 due to the severity of the potential developmental effect
ADI[10]	**Not applicable**		
ARfD	**Not applicable**		

MRLs

Relevant commodities	-

Reference value for groundwater[11]

According to BPR Annex VI, point 68	0.07 *µ*g/L

[9] Previously only two threshold values were derived, an Acceptable Operator Exposure Level (AOEL) for acute/short term exposure and one for repeated/chronic exposure. At the Technical Meeting on Biocides, May 2007 it was decided to derive the short term AOEL from the maternal NOAEL established in a teratogenicity study with the most sensitive species, applying a safety factor of 300. The decision was taken after finalisation of the assessment of difethialone (AR of 21 June 2007). It was agreed that it should be taken into account if performing a comparative assessment of the anticoagulant rodenticides and in future revisions of the risk assessment of difethialone. The threshold value has been revised according to this decision.

[10] If residues in food or feed.

[11] Agreed at the Technical meeting on Biocides in November 2013

Dermal absorption[12]

Study (*in vitro/vivo*), species tested	*in vivo* rat study and *in vitro rat and human studies*
Formulation (formulation type and including concentration(s) tested, vehicle)	No studies on the end use formulations of difethialone. An in vivo human dermal absorption of 4% may be calculated by combining rat *in vivo* data and rat:human *in vitro* data. This represents a reasonable worst case value to be used in the risk assessments of the products, derived from the dermal delivery (absorbed dose and amounts retained in the epidermis and dermis layers of the skin, but excluding amounts in stratum corneum) of difethialone in glycol solvent (1.25 g/l)[13] 24h after application.
Dermal absorption values used in risk assessment	4%

Acceptable exposure scenarios (including method of calculation)[14]

Formulation of biocidal product	Three representative ready to use products have been evaluated: Block bait, paste bait and pellet bait containing difethialone at 25ppm (0.0025 % w/w).
Intended uses	Rodenticide for use by professionals and the general public "in and around buildings" and in sewers" Difethialone is used to control: *Rattus norvegicus* (Norway rat, Brown rat) *Rattus rattus* (Roof rat, Black rat) *Mus musculus* (House mouse).
Industrial users	Not relevant.

[12] Dermal absorption not evaluated using EFSAs guidance on dermal absorption (2012)
[13] Correction of misprint in the AR of 21 June 2007: The concentration of difethialone in the glycol solvent should read 1.25 g/l and not 25 g/l.
[14] New guidance on exposure has been made after the exposure assessment was made (Assessment Report of 2007). More specifically, a harmonised approach for the assessment of anticoagulant rodenticides was made by HEEG in 2010-2012 (HEEG opinion 10 and 12), including agreed numbers of daily manipulations and proposals for harmonised exposure values from the CEFIC Operator exposure studies to be used in the exposure assessment.
The revised AEL short term (see above) would also influence the outcome of the risk assessment.

Professional users	Exposure scenario: Application + post application • Decanting (pellet bait only), loading of bait station with ready to use baits and emptying and disposing of bait stations Frequency of daily use: • Sewers: Maximum 75 cesspools • Wax and paste used in and around buildings: Maximum 75 bait points treated/day plus remains of 15 bait points collected • Pellets used in and around buildings: Maximum 79 bait points treated/day plus remains of 16 bait points collected [90 gram (rats) or 60 gram (mice) pellets per bait station] Concentration of active substance: 0.0025 % w/w Level of protection: Gloves (90 % reduction in exposure from use of gloves) For products used on a single occasion, the exposure accounted for 0.015-0.088% of $AOEL_{acute}$ when based on an Operator Exposure study,and assuming use of gloves. Acceptable exposure for all use areas of the products used on a repetitive or daily basis, occurs when gloves are worn (5.9 - 35 % of $AOEL_{RDT}$) and calculations are based on an Operator Exposure study.
Non professional users	Exposure scenario: Application + post application • Loading of bait station with ready to use baits and emptying and disposing of bait stations Frequency of daily use: • Wax and pellet used in and around buildings: Maximum 5 bait points treated/day plus remains of 5 bait points collected • Pastes used in and around buildings: Maximum 4 bait points treated/day plus remains of 4 bait points collected Concentration of active substance: 0.0025 % w/w Level of protection: No gloves worn MOE: $2.3 \times 10^6 - 3.8 \times 10^7$when calculations are based on an Operator Exposure study.

General public	Exposure scenario: Infants ingesting 10 mg (TNsG on Human Exposure to Biocidal products – default of bait treated with reppelent) or 5 gram bait (User Guidance to TNsG on Human Exposure – Poison Information Specialists general estimate of "one bite"). MOE= 2 x 10^5 (Infants ingesting 10 mg), 400 (Infants ingesting 5 gram) Scenario concerning handling of dead rodents is not presented as it is considered as unrealistic
Exposure via residue in food	Formulated products containing difethialone are not applied directly on food or feeding stuffs. Products are not intended to be applied directly on surfaces intended for contact with food or feeding stuffs. However, difethialone containing products are intended to be used in premises were food or feeding stuffs are prepared or stored. Exposure not assessed.

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)	Results at 25°C No specific degradation products were detected.
pH 5	> 1 year
pH 9	155 days
Other pH: 7	175 days
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Study with natural sunlight at 28-35°C: DT 50 (pH 5) = 59.7 min DT 50 (pH 7) = 61.9 min DT 50 (pH 9) = 54.5 min Study with artificial sunlight at 20°C: DT 50 (pH 7) = 23.4 min In both studies photolysis of difethialone led to the formation of multiple components but none of these were identified with respect to its chemical identity
Readily biodegradable (yes/no)	No. Ready biodegradability test (aerobic, ISO 14593 (equivalent to OECD 301B, CO_2 headspace test): Less than 6 % biodegradation within 28 days.

Inherent biodegradable (yes/no)	An investigation of the inherent biodegradability (OECD 302 A, B or C) has not been carried out.
Biodegradation in freshwater	Not applicable (exposure to aquatic systems limited in space and levels).
Biodegradation in seawater	Not applicable (exposure to seawater limited in space and levels).
Non-extractable residues	Not applicable (exposure to aquatic systems limited in space and levels).
Distribution in water / sediment systems (active substance)	Not available (exposure to aquatic systems limited in space and levels).
Distribution in water / sediment systems (metabolites)	Not applicable (exposure to seawater limited in space and levels).

Route and rate of degradation in soil

Mineralization (aerobic)	In percent of applied radioactivity: < 2% after 100 days (3 soils).
Laboratory studies (range or median, with number of measurements, with regression coefficient)	Two aerobic biodegradation studies available:
DT_{50lab} (20°C, aerobic):	1. DT_{50lab}, (20°C aerobic): - Speyer 2.2, (loamy sand, DE) 524 days (1^{ST} order, R^2=0,54) - Collombey, (sand, Switzerland) 224 days (1^{ST} order, R^2=0,46) 2. DT_{50lab}, (25°C aerobic) Maryland, (sandy loam, US) 190 days (1^{ST} order, R^2= 0,982)
DT_{90lab} (20°C, aerobic):	1. DT_{90lab}, (20°C aerobic) - Speyer 2.2, (loamy sand, DE) 1741 days (1^{ST} order, R^2=0,54) - Collombey, (sand, Switzerland) 746 days (1^{ST} order, R^2=0,46) 2. DT_{90lab}, (25°C aerobic) Maryland, (sandy loam, US) 613 days (1^{ST} order R^2= 0,982)
DT_{50lab} (12°C, aerobic):	1. - Speyer 2.2, (loamy sand, DE) 976 days - Collombey, (sand, Switzerland) 417 days 2. Maryland, (sandy loam, US) 513 days
DT_{50lab} (20°C, anaerobic):	No study available
degradation in the saturated zone:	Not applicable
Field studies (state location, range or median with number of measurements)	No study available
DT_{50f}:	No data
DT_{90f}:	No data

Anaerobic degradation	No study available
Soil photolysis	No study available
Non-extractable residues	Under aerobic conditions the bound residues exceeding 10% were 10.9% at day 208 day (final day) in the first aerobic biodegradation study and 11-24% during the second aerobic biodegradation study. The NER results in the second aerobic biodegradation study may be due to the extraction technique used, which is not as efficient as the technique use in the first aerobic biodegradation study. As the risk associated with bound residues is assumed to be less than for the active compound and the exposure to soil is restricted to only small areas there seems to be no need for further testing in order to identify bound residues at present.
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	In the first aerobic biodegradation study degradation of difethialone led to the formation of four unidentified metabolites which were present in quantities exceeding 5 % applied radioactivity. Four metabolites[15] detected are classified as relevant metabolites. The metabolites M2,M3, M4 and M7 which were observed at maximum levels of 8.3%, 13.5%,10.2% and 9.6 % applied radioactivity after 378, 189, 140 and 189 days, respectively. As the risk associated with bound residues is assumed to be less than for the active compound and the exposure to soil is restricted to only small areas there seems to be no need for further testing in order to identify metabolites at present.
Soil accumulation and plateau concentration	Not applicable.

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Soil distribution (partition) coefficient, Kd: Not determined. Freundlich soil adsorption coefficient, K_f: 2.3×10^5 to 2.4×10^7 ml/g (adsorption) 1.6×10^5 to 1.8×10^6 ml/g (desorption). Freundlich soil adsorption coefficient normalised for organic carbon content, K_fOC: 1.0×10^8 to 5.3×10^9 ml/g (adsorption) 5.4×10^7 to 3.9×10^8 ml/g (desorption). No pH effects observed/expected. Difethialone is considered immobile in soil.

[15] Adjusted text according to the new Guidance on the BPR (Volume IV. Part A, Section I: Introduction Version 1.1, November 2014, p. 26)

Fate and behaviour in air

Direct photolysis in air	No study available.
Quantum yield of direct photolysis	Not determined.
Photo-oxidative degradation in air	The estimated half-lives for the hydroxyl and ozone reactions in air are 2.2 and 2.0 hours, respectively (calculated with AOPWIN, v1.90)
Volatilization	Vapour pressure < 1.3 x 10^{-5} Pa. Henry's law constant < 1.8 x 10^{-2} Pa.m^3.mol^{-1} (based on a water solubility of 0.39 mg/l) Difethialone is not expected to volatilise to air in significant quantities.

Reference value for groundwater[16]

According to BPR Annex VI, point 68	0.07 µg/L

Monitoring data, if available

Soil (indicate location and type of study)	No data available.
Surface water (indicate location and type of study)	No data available.
Ground water (indicate location and type of study)	No data available.
Air (indicate location and type of study)	No 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 = 51 µg/l
Invertebrates			
Daphnia magna	48 hours	Immobilisation	EC50 = 4.4 µg/l
Algae			
Selenastrum capricornutum	72 hours	Growth rate	ErC50 > 180 µg/l
Microorganisms			

[16] Agreed at the Technical meeting on Biocides in November 2013

Activated sludge	3 hours	Respiration inhibition	EC50 > 100 mg/l

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia foetida*	14-day LC_{50} > 1000 mg/kg dry 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} = 0.4 to 0.8 mg/kg bw (rat)
Acute toxicity to birds	30-day LD_{50} (single dose) = 0.264 mg a.i./kg bw (bobwhite quail)
Dietary toxicity to birds	30-day LC_{50}/short term dietary (5 days feeding) = 0.560 mg a.i./kg food (bobwhite quail)
Reproductive toxicity to birds	Waived. NOEC = 0.01 mg/kg food (read across from an avian reproduction NOEC for difenacoum)

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 logKow of 6.29 according to the TGD and resulted in BCF_{fish} of about 40,000 l/kg. The $BCF_{earthworm}$ was calculated from the logKow of 6.29 according to the TGD and resulted in $BCF_{earthworm}$ of 23,943 l/kg.
Depration time (DT_{50})	Waived.

Depration time (DT_{90})	Waived.
Level of metabolites (%) in organisms accounting for > 10 % of residues	No data.

Chapter 6: Other End Points

Not applicable

Appendix II: List of new information used in the renewal process

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
AR	Berny P et al.	2014	Risk mitigation measures for anticoagulant rodenticides as biocidal products. Final Report. *ISBN 978-92-79-44992-5*	No	Public
AR	Buckle, A.	2012	Anticoagulant resistance in the United Kingdom and a new guideline for the management of resistant infestations of Norway rats (Rattus norvegicus Berk.). Pest Management Science, n/a–n/a. doi:10.1002/ps.3309	No	Public
AR	Elmeros M, Topping CJ, Christensen TK, Lassen P and Bossi R.	2015	Spredning af antikoagulante rodenticider med mus og eksponeringsrisiko for rovdyr. Bekæmpelsesmiddelforskning nr. 159. Miljøministeriet (In Danish with English summary).	No	Public
AR	European Commission	2015	62nd meeting of Representatives of Members States Competent Authorities for the implementation of Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products. Revised version of the summary of the workshop on the RMM report held in Brussels on 26/02/2015. CA-Nov15-Doc. 5.4.	No	Public
AR	Geduhn A, Jacob J, Schenke D, Keller B, Kleinschmidt, Esther A	2015	Relation between intensity of biocide practise and residues of anticoagulant rodenticides in red foxes (*Vulpes vulpes*). PLOS ONE DOI:10.1371/journal.pone.0	No	Public

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			139191.		
AR	López-Perea JJ, Camarero PR, Molina-López RA, Parpal L, Obón E, Sola J, Mateo R.	2015	Interspecific and geographical differences in anticoagulant rodenticide residues of predatory wildlife from the Mediterranean region of Spain. – Science of the Total Environment 511: 259–267.	No	Public
AR	Walker LA, Chaplow JS, Llewellyn NR, Pereira MG, Potter ED, Sainsbury AW, Shore RF.	2013	Anticoagulant rodenticides in predatory birds 2011: a Predatory Bird Monitoring Scheme (PBMS) report. Centre for Ecology & Hydrology, Lancaster, UK. 29pp.	No	Public