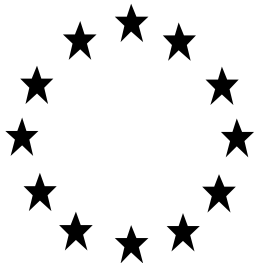
Directive 98/8/EC concerning the placing of biocidal products on the market

Inclusion of active substances in Annex I or IA to Directive 98/8/EC

Assessment Report



Bromadiolone

Product-type 14 (Rodenticides)

30 May 2008, revised 16 December 2010

Annex I - Sweden

Bromadiolone (PT14)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on 30 May 2008 in view of its inclusion in Annex I to Directive 98/8/EC, revised 16 December 2010 to take into account data from the second notifier.

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 bromadiolone as product-type 14 (Rodenticides), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I or IA to the Directive.

Bromadiolone (CAS no. 28772-56-7) was notified as an existing active substance, by the first applicant LiphaTech S.A.S, hereafter referred to as LiphaTech, and by the second applicant Bromadiolone Task Force, hereafter referred to as Task Force, in product-type 14.

Commission Regulation (EC) No 2032/2003 of 4 November 2003[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, Sweden was designated as Rapporteur Member State to carry out the assessment on the basis of the dossiers submitted by the two applicants. The deadline for submission of a complete dossier for bromadiolone as an active substance in Product Type 14 was 28 March 2004, in accordance with Annex V of Regulation (EC) No 1451/2007.

On 26 March 2004 the Swedish competent authority received dossiers from both applicants. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 29 September 2004 for LiphaTech and on 30 September 2004 as if it were complete for Task Force. The dossier of Task Force was not complete and this applicant agreed to submit further data in order to complete the dossier. During the process, there have been several complications, the most significant being the sudden death of the applicant's consultant in October 2004, and a new consultant had to be appointed to take over the management of the dossier. The Rapporteur Member State has had an extended dialogue with Task Force and has required further information in several steps until June 2008.

For LiphaTech, the Rapporteur Member State submitted on 30 June 2006, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 4 July 2006. For Task Force, the Rapporteur Member State submitted a competent authority report on 2 July 2009, and the Commission made the report available to

1 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

2 Commission Regulation (EC) No 2032/2003 of 4 November 2003 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market and amending Regulation (EC) No 1896/2000. OJ L 307, 24.11.2003, p. 1

all Member States on 3 July 2009. The competent authority reports included a recommendation for the inclusion of bromadiolone in Annex I to the Directive for product-type 14.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report for LiphaTech publicly available by electronic means on 20 December 2006, and for Task Force this was done on 2 September 2009. These reports did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority reports and the comments received on them, consultations of technical experts from all Member States (peer reviews) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority reports were amended accordingly. The merged conclusions of the risk assessment are presented in this assessment report.

On the basis of the final competent authority report for LiphaTech, the Commission proposed the inclusion of bromadiolone in Annex I to Directive 98/8/EC and consulted the Standing Committee on Biocidal Product on 30 May 2008.

In accordance with Article 11(4) of Regulation (EC) No 2032/2003, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 30 May 2008.

The addition of the Bromadiolone Task Force data to the bromadiolone assessment report was agreed upon at the 39th Competent Authority Meeting on 16 December 2010.

1.2. Purpose of the assessment report

This assessment report has been developed and finalised in support of the decision to include bromadiolone in Annex I to Directive 98/8/EC for product-type 14. The aim of the assessment report is to facilitate the authorisation and registration in Member States of individual biocidal products in product-type 14 that contain bromadiolone. In their evaluation, Member States shall apply the provisions of Directive 98/8/EC, in particular the provisions of Article 5 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 at the Commission website[3], shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Directive 98/8/EC, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

1.3. Overall conclusion in the context of Directive 98/8/EC

3 http://ec.europa.eu/comm/environment/biocides/index.htm

It appears from the examinations made that biocidal products used as rodenticides and containing bromadiolone may be expected not to present a risk to humans except for accidental incidents with children. Regarding non-target animals and the environment a risk has been identified. However, rodenticides like bromadiolone are considered necessary for reasons of public health and hygiene. If sufficient risk reduction measures, such as those detailed in sections 3.2 and 3.3 of this assessment report, are implemented, products containing bromadiolone are expected to satisfy the requirements laid down in Article 5 of Directive 98/8/EC. This conclusion is, therefore, subject to:

i. compliance with the particular requirements in the following sections of this assessment report,

ii. the implementation of the provisions of Article 5(1) of Directive 98/8/EC, and

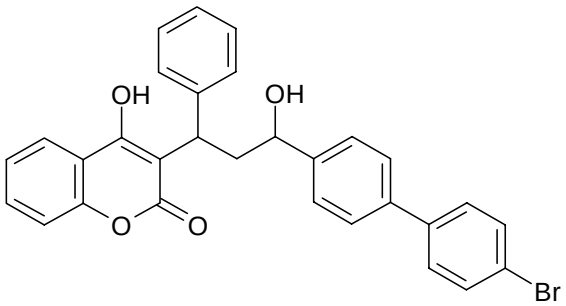
iii. the common principles laid down in Annex VI to Directive 98/8/EC.

Furthermore, these conclusions were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Article 5(1) and of the common principles laid down in Annex VI to Directive 98/8/EC.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

CAS-No.	28772-56-7
EINECS-No.	249-205-9
Other No. (CIPAC, ELINCS	CIPAC No. 371
IUPAC Name *	3-[(1*RS*,3*RS*;1*RS*,3*SR*)-3-(4′-bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin
Common name, synonym	Bromadiolone
Molecular formula	$C_{30}H_{23}BrO_4$
Structural formula	
Molecular weight (g/mol)	527.40
Purity of the active substance as manufactured	Min. 96.9%
Isomers	Isomeric mixture of the two racemic diastereomers (1*RS*,3*RS*) and (1*RS*,3*SR*). The range for the *syn*-isomer (1*RS*,3*RS*) is 70-90%. Both diasteromers are toxicologically active. More detailed information on the isomers is given in the respective Confidential Annex for the two applicants.
Impurities	None of the impurities present in technical bromadiolone are considered relevant. The information on impurities is found in the respective Confidential Annex for the two applicants.
Additives	Technical bromadiolone contains no additives

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

The minimum purity of 96.9% is based on the supporting analytical data (5-batch analysis) from LiphaTech. A minimum purity of 98% was set based on the supporting analytical data (5-batch analysis) of Task Force.

In conclusion the technical bromadiolone from the two applicants are considered technically equivalent (see Equivalence report for bromadiolone) and therefore the minimum purity of

96.9% shall apply for bromadiolone referring to a mixture of diastereomers (70-90% *syn*-isomer). For other specifications and isomeric contents at least bridging studies are needed.

Bromadiolone does not exhibit hazardous physical-chemical properties. Bromadiolone is a white odourless powder. It has low vapour pressure; Henry's law constant (8.99 x 10^{-7} $Pa.m^3.mol^{-1}$ or 4.25 x 10^{-4} $Pa.m^3.mol^{-1}$) was calculated based on an experimentally derived (extrapolated) value of 2.13 x 10^{-8} Pa at 25 °C or on a published vapour pressure of 2 x 10^{-6} Pa at 20 °C. The solubility of bromadiolone in water is pH dependant with the highest solubility of 0.18-1.2 g/l at pH 9-10 and 20°C (~0.1 mg/l at pH 4-5 and 2.48-18.4 mg/l at pH 7 and 20°C). Correspondingly, the log P_{ow} ranges between 2.5-3.2 at pH 9-10 to >5 at pH 4-5 (3.8-4.1 at pH 7). The pH dependency is thought to be due to the dissociation of the hydroxyl-group in the coumarin moiety of bromadiolone with predicted relevant pKa's of 4.5 and 9.0 for the enolic and ketalic forms respectively (i.e. technically not feasible to experimentally determine the pKa). The solubility in organic solvents tested ranged from 3 mg/l in n-heptane to 15 g/l in methanol at 20°C. The melting point was determined as a broad range of 172.4-201.7°C (98.8%) or as 198.3-199.8°C (~100%). Given that bromadiolone is a mixture of two diasteromers, which can have different physical and chemical properties, the broad range is not considered atypical. Bromadiolone decomposes before boiling. Bromadiolone is not highly flammable, explosive or oxidizing.

Acceptable methods for determination of bromadiolone and associated impurities present at quantities >0.1% w/w in the technical grade material as manufactured are available. It should be noted that the method provided by LiphaTech for determining bromadiolone in the technical material is based on a primary qualitative step (spectroscopy, isomeric distribution, melting point) and a subsequent quantitative step by an unspecific method (titration). This time-consuming approach is followed as the applicant states that no certified reference standards are available for bromadiolone which means that a routine chromatographic procedure (e.g. HPLC) cannot be used. On the other hand, the Task Force has provided and used a HPLC-UV method for the active ingredient assay in the supporting batch data. However, in that analysis a technical material from one of the manufacturers has been used as an external standard and the purity for that standard was determined by AOAC Official Method 983.11 which is a HPLC-method for brodifacoum technical. Hereby, it seems correct that no certified reference standards are available for bromadiolone. Nevertheless, as the Task Force method was sufficiently validated and deemed acceptable it is also presented in LoEP as it may be necessary to compare results from both analytical procedures to achieve an accurate result.

Acceptable analytical methods are provided by both applicants for soil, water, body fluids and tissues and food and feeding stuffs of animal and plant origin. An acceptable method for air was provided by LiphaTech, whereas a waiver was provided by Task Force, which was accepted due to the low vapour pressure of bromadiolone. In soil bromadiolone is determined by HPLC-MS (LOQ 0.22 µg/kg) or LC-MS/MS (0.01 mg/kg). The provided method for air is based on HPLC-UV (LOQ 0.5 $\mu g/m^3$). Water (drinking and surface) is determined by HPLC-FD (fluorescence detector) or HPLC-MS with LC-MS/MS for confirmation (LOQ 0.05 µg/l for both methods). Body fluids and tissues (blood and liver) are determined by two acceptable LC-MS/MS methods with LOQs of 0.05 mg/l (blood) and 0.05 mg/kg (liver) and 0.01 mg/l (blood) and 0.01 mg/kg (liver) respectively. A multi residue method for rodenticides, among them

bromadiolone, was provided for food and feeding stuffs of animal and plant origin in case of suspected contamination. It is based on LC-MS/MS but it is deemed only partially acceptable (cucumber and wheat, LOQ 0.01 mg/kg). Supplementary single methods were provided from the two applicants for acidic and oily matrices (lemon and oilseed rape) and for matrices of animal origin (meat). These two methods are based on LC-MS/MS and both have a LOQ of 0.01 mg/kg.

2.1.2. Intended Uses and Efficacy

Bromadiolone is used in products for pest control (Main Group 03, Product type 14, rodenticides).

Bromadiolone is used to control:

Rattus spp.	(rat)
Mus musculus	(house mouse)

In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

Bromadiolone is a second-generation single-dose anticoagulant rodenticide. It disrupts the normal blood clotting mechanisms resulting in increased bleeding tendency and, eventually, profuse haemorrhage and death. Effectiveness of bromadiolone depends on exposure (i.e. consumption of the bait by the target organism). The evaluation of the data provided in support of the efficacy of the accompanying product, establishes that the product is expected to be efficacious. Studies have been performed which demonstrate that bromadiolone has single-dose efficacy. Efficacy has been shown in laboratory tests for *Mus musculus* and *Rattus norvegicus* but not for *Rattus rattus*. Generally, effects can be observed using bait concentrations of 5 mg/kg or more. However, for effective and comprehensive control of rats and mice, a bait concentration of 50 mg/kg is proposed. The type of formulation of the product has no significant influence on the effects of bromadiolone on the target organisms. It should be noted that the assessment of LiphaTech covers wax blocks with intended uses in sewers, in and around buildings, in open areas and in waste dumps, and grains with intended uses in and around buildings, in open areas and in waste dumps.he assessment of Task Force covers wax blocks with intended uses in sewers and in and around buildings.

The use of bromadiolone as a rodenticide could cause suffering of vertebrate target organisms. The use of anticoagulant rodenticides is necessary as there are at present no other equally effective measures available to control the rodent population in the European Union. Rodent control is needed to prevent disease transmission, contamination of food and feeding stuffs and structural damage. It is recognised that such substances do cause pain in rodents but it is considered that this is not in conflict with the requirements of Article 5.1 of Directive 98/8/EC ‘to avoid unnecessary pain and suffering of vertebrates’, as long as effective, but comparable less painful alternative biocidal substances or biocidal products or even non-biocidal alternatives are not available.

Repeated use of coumarin-like anticoagulant rodenticides such as bromadiolone may lead to development of resistance. LiphaTech has provided information which says that resistance against bromadiolone is not widespread but has been observed in France, Germany and the UK, and concerned a few isolated sites in 2004 of less than 500 individuals each which remained in the site where they live. Bromadiolone resistance does not display the same pattern as the more widespread and better known warfarin resistance.

2.1.3. Classification and Labelling

Bromadiolone is not currently classified according to Annex VI of Regulation (EC) no 1907/2006 (REACH). The following classification and labelling is proposed on the basis of available data and according to the criteria in Directive 67/548/EEC and to the Commission Regulation (EC) No 1272/2008 (CLP). A classification proposal has been submitted to ECHA in August 2010.

Proposed classification according to the criteria in directive 67/548/EEC:
T+; R26/27/28
T; R48/23/24/25
Repr. Cat. 1; R61
N; R50-53

C≥0.5% T+;R61-26/27/28 - T; R48/23/24/25
0.25%≤C<0.5% T+; R26/27/28 – T; R48/23/24/25
0.025%≤C<0.25% T; R23/24/25 – T; R48/23/24/25
0.0025%≤C<0.025% Xn; R20/21/22 – R48/20/21/22

Proposed labelling according to the criteria in directive 67/548/EEC:
T+, N
R: 61-26/27/28-48/23/24/25-50/53
S: 53-45-60-61

Proposed classification according to the CLP Regulation 1272/2008:
Acute tox. 1; H300, H310, H330
Repr. 1A; H360D
STOT RE 1; H372
Aquatic Acute 1; H400
Aquatic Chronic 1; H410

C≥0.01% STOT RE 1; H372
0.001%≤C<0.01% STOT RE 2; H373
M-factor 1

Proposed labelling according to the CLP Regulation 1272/2008:
Signal word: Danger
Hazard statements: H360D, H330, H310, H300, H372, H400, H410

Bromadiolone is thermally stable below 200°C, its melting point. It is not classified as highly flammable and does not undergo self ignition below its melting point. It is not considered to be explosive or to have oxidising properties. There is no record that it has reacted with any storage container during many years of industrial production. It is concluded therefore, that there are no hazards associated with its physico-chemical properties under normal conditions of use.

The safety phrases proposed are based on the classification and risk phrases. The classification is based on toxicological studies summarised in III-A section 6 which indicate that bromadiolone is very toxic by inhalation, when swallowed or in contact with skin in acute accidental or intentional exposure and harmful by repeat exposure. Based on the structural similarities to and the same mechanism as warfarin, read-across from this substance is proposed, which would lead to classification for developmental toxicity. Regarding human health effects a provisional classification with R61 was decided in November 2006 by the TC C&L, but without a final decision on the category to be used (Repr.Cat 1 or Repr.Cat 2). The proposed classification for bromadiolone for acute and repeated dose toxicity was agreed upon. However, the classification for human health effects is still under discussion. Specific concentration limits are also required for the teratogenicity according to the CLP Regulation 1272/2008 but were not included in the classification dossier sent to ECHA in August, 2010 since the discussion on how to base specific concentration limits on reproductive effects was still ongoing at that time.

A proposal for the classification and labelling of the preparations Super Caid Bloc, Super Caid AS Appat and Protect-B wax block according to the Commission Directive 2004/73/EC (adapting to technical progress for the twenty-ninth time Council Directive 67/548/EEC) updating Annex I to Directive 67/548/EEC is presented below.

Proposed classification according to the criteria in directive 67/548/EEC:
Xn; R48/20/21/22

Proposed labelling according to the criteria in directive 67/548/EEC:
Xn
R: 48/20/21/22
S: 2-13-20/21-35-37-46-49.

No classification is required according to criteria detailed in Directive 67/548/EEC and 1999/45/EC based on the study results for the products (studies on acute toxicity, irritation, corrosivity and sensitisation). The concentration of bromadiolone in the products is well below the general concentration limits for classification given in Directive 1999/45/EC. However, due to the high toxicity of bromadiolone specific concentration limits have been agreed for human health effects.

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification

Bromadiolone is a second-generation single-dose anticoagulant rodenticide. It disrupts the normal blood clotting mechanisms resulting in increased bleeding tendency and, eventually, profuse haemorrhage and death. Like all anticoagulant rodenticides, bromadiolone is structurally similar to vitamin K. Blood forms a clot at the site of injury by virtue of a complicated 'clotting cascade', involving numerous clotting factors. The clotting factors are made in the liver as inactive precursors, converted to active form and allowed to circulate in the bloodstream. Vitamin K is employed in the liver in the activation process, and is used in a continuous cyclic process involving several enzymes. The anticoagulant rodenticides block these enzymes, preventing regeneration of the vitamin K and preventing activation of the clotting factors.

Bromadiolone requires labelling with the symbol T+ and the risk phrases R 28 'Very toxic if swallowed'; R27 'Very toxic in contact with the skin' and R26 'Very toxic by inhalation'. Bromadiolone is not classified as a skin irritant, eye irritant or a skin sensitiser.

Repeated dosing studies show effects on blood coagulation and death at low doses (µg/kg bw/day), and therefore labelling with R48/23/24/25 is warranted.

The Commission Working Group of Specialised Experts on Reproductive Toxicity has unanimously recommended that all AVK rodenticides should collectively be regarded as human teratogens due to the structural similarity to and the same mode of action as the known developmental toxicant warfarin (meeting in Ispra, 19-20 September 2006). Therefore based on read across data from warfarin, bromadiolone is considered to be a possible developmental toxicant and requires the classification as Reprotoxic with the labelling R61, may cause harm to the unborn child.

2.2.1.2. Effects assessment

No oral absorption value could be set on the LiphaTech study, but the absorption was > 70 % of the administered dose, based on (carcass, bile- and urinary excretion, Task Force study). The major route of excretion was via the faeces accounting for ca 50-60 % of the dose, whilst approximately 1-5 % was excreted via urine. Bile investigations showed that biliary elimination plays a major role in the excretion. No parent bromadiolone was excreted in bile or urine. The main retention site was the liver. A non-guideline study in three cows was completed (LiphaTech). According to this study bromadiolone does not seem to accumulate into milk. The information from the ADME studies was not enough to propose a full metabolism pathway for any of the applicants but the study provided by LiphaTech identified one major metabolite in faeces as a hydroxylated analogue of bromadiolone; hydroxylation was proposed on the benzylic carbon atom. No dermal absorption study were performed on the

active substance alone (it was only provided for the formulated product or mixed with bait), but a default value of 10% could be used if considered necessary.

Dermal penetration in humans was estimated as < 1.6% for a powdered product. Based on data from in vitro human skin studies with two representative products containing bromadiolone, the dermal absorption was less than 0.3% for the wax block formulations.

In acute oral toxicity studies, bromadiolone was very toxic to rats with a LD50 to the rat of between 0.56 and 1.31 mg/kg bw. Bromadiolone is slightly less toxic to dogs with a LD50 value of 8.1 mg/kg bw. The symptoms were observed 1-2 days prior to death and included signs of internal haemorrhage, which were confirmed at necropsy. Bromadiolone was also acutely toxic by dermal administration, with an LD50 of 1.71 mg/kg bw in rabbits (LiphaTech) and with a combined sexes dermal LD50 value of 23.3 mg/kg in rats (Task Force). The LC50 by inhalation, in rats was 0.43 µg/L (LiphaTech). Waiving of inhalation studies has been accepted for Task Force, since operator exposure through inhalation is unlikely to occur based in the information presented concerning production procedures and based on the physical-chemistry data showing low vapour pressure. However, a classification as R26 ‘Very toxic by inhalation’ is warranted based on the other applicant’s data (LiphaTech).

Bromadiolone is not considered to be a skin or eye irritant or a skin sensitiser.

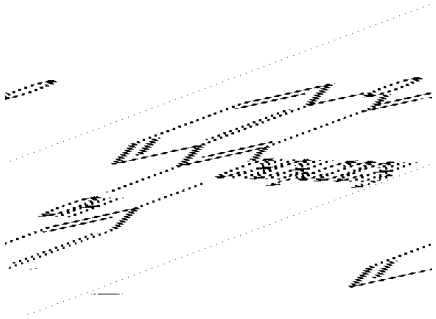
Repeated dose oral studies showed that at doses as low as 20 µg/kg/day in the dog, lethal effects developed after 64 to 85 days administration. The clinical signs, haematological and post mortem data were consistent with the known pharmacological action of the active substance; impairment of the clotting cascade and increased prevalence of haemorrhage leading to death. There were no indications of other secondary toxicities: histopathology revealed no hypertrophy or hyperplasia of the target organ, the liver. In the 90-day oral exposure study in rabbits (data provided by Task Force), a significant increase in prothrombin time was seen in the 1 µg/kg dose group. The overall NOAEL for repeat dose effects for both applicants is 0.5 µg/kg/day based on the absence of adverse effects in this dose group. The dermal exposure is expected to be low as the use of gloves when handling the baits is expected, and route-to-route extrapolation based on data from the acute oral and dermal studies does not indicate that dermal exposure constitutes a greater risk than oral exposure. Therefore, waiving of a repeat dose dermal toxicity study has been accepted. Also, due to that bromadiolone has a low vapour pressure and exposure via inhalation is expected to be negligible both during production and during the use of bait blocks, waiving of the repeat dose inhalation study has been accepted. The subchronic dermal toxicity study is also waived. A subchronic oral study has been performed for bromadiolone using the rabbit as test species, which may be used in route-to-route extrapolation. The highly cumulative nature of the material means that lower doses, administered over several days, can also be predicted to cause death. In all cases death was caused by the specific pharmacological action of the molecule, inducing fatal haemorrhage. The mechanism of clotting inhibition caused by hydroxy coumarin type anticoagulant rodenticides is dependent on inhibition of vitamin K epoxide or vitamin K reductases and is unaffected by route of application. Therefore specific repeat dose dermal or inhalation studies would not provide any additional useful information to that obtained in various species in repeat dose and subchronic studies by the oral route.

A non-guideline study in the dog submitted by LiphaTech demonstrated that after ingestion of a single lethal dose or repeated administration of sublethal doses of bromadiolone on five occasions at 48 hour intervals, antidotal therapy consisting of slow intravenous injection of vitamin K followed by 7 days of oral administration of vitamin K resulted in rapid and complete recovery.

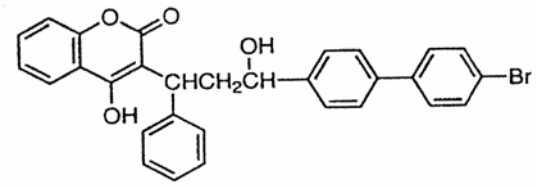
A study in rat with bromadiolone pellets (50 ppm end use product) submitted by LiphaTech also showed that vitamin K can reverse the effects. However, the effectiveness varied with the duration of exposure to bromadiolone.

Bromadiolone was not mutagenic in a standard range of in vitro and in vivo tests. The carcinogenicity study and the chronic toxicity study were waived. Performing long-term exposure studies is technically difficult when studying highly toxic substances such as bromadiolone, since dose levels, at which toxicity is identifiable but without rendering high levels of lethality, are hard to predict. The waiving is accepted, also considering the lack of genotoxicity.

The molecules both have significant structural similarity to vitamin K. This structural similarity is responsible for the ability to interfere with i.e. block the enzymes used to regenerate vitamin K. The major differences in the active substances lie in their 'tails', which have varying degree of lipophilicity. There is long term experience with warfarin, widely used in anti-clotting therapy in humans for over forty years, with no association with increased incidence of cancer. The absence of adverse effects in millions of humans following four decades of long term warfarin therapy is considered sufficient evidence that warfarin is not carcinogenic. The structural similarity of bromadiolone to warfarin (see below), together with the negative results in the guideline mutagenicity tests, indicates that bromadiolone is not carcinogenic.



Warfarin



Bromadiolone

In addition, evidence is presented to show that it would not be possible to perform a meaningful long-term study in any species because of the accumulative nature and high toxicity of the active substance.

Reproductive effects of bromadiolone can not be excluded by the submitted two-generation reproduction toxicity study (Task Force), but since long term exposure studies are technically hard to perform for such highly toxic substances as bromadiolone, no new study will be required. As with carcinogenicity, the primary reason for not requiring such a study is the long-

term use of the structurally similar molecule warfarin in humans without association with adverse effects on fertility. The 2-generation study is therefore accepted as waived for both applicants. A teratogenicity study on rabbit showed severe fetal malformations following exposure to maternally toxic levels of bromadiolone (Task Force). However, the possibility that the effects seen may have been due to non-specific influences such as generalised toxicity cannot be excluded. Bromadiolone was not embryotoxic or teratogenic in guideline studies in rat and rabbit (LiphaTech). However, based on the structural similarity to and the same mode of action as warfarin, bromadiolone is considered as a possible developmental toxicant. The Commission Working Group of Specialised Experts on Reproductive Toxicity has unanimously recommended that all AVK rodenticides should collectively be regarded as human teratogens due to the structural similarity to and the same mode of action as the known developmental toxicant warfarin (meeting in Ispra, 19-20 September 2006). Therefore based on read across data from warfarin, bromadiolone is considered to be a possible developmental toxicant and requires the classification as Reprotoxic with the labelling R61, may cause harm to the unborn child.

The toxicological studies do not indicate any neurotoxic effects. A neurotoxicity study would be scientifically unjustified and would not provide any new data. Based on this and animal welfare grounds it is deemed unnecessary to conduct a neurotoxicity study and applicant's justification is accepted. Also, the mechanism for bromadiolone as an anticoagulant is well known and no mechanistic studies were considered necessary.

There are no case reports from the manufacturer concerning adverse effects in users applying the products. The Task Force submitted data on poisoning cases with bromadiolone. During the time period 1996–1999 a total of 115 calls concerning bromadiolone were received by the Milan Poisons Center, 98 of which involved clinical cases among humans or animals. The most common route of exposure was through ingestion and in 55% of the cases children under the age of four years were exposed. The symptoms were reported in eleven human cases and included vomiting, gastric pyrosis and itching. Only one case was reported with haematological problems. Vitamin K1 is the antidote, and it is important to monitor the clotting ability of the blood (prothrombin time) to continue the treatment long enough. If diagnosis is made quickly and appropriate therapy is instituted the prognosis is good.

The derivation of an acceptable level of exposure value for single use (AELacute) is based on the teratogenicity study in rabbits submitted by Task Force. It is based on the LOAEL of 2 µg/kg bw, using a safety factor of 600 (10 for interspecies and 10 for intraspecies variability, 2 for using LOAEL instead of NOAEL and an extra factor of 3 for severity of effects) and with correction of 70% oral absorption, resulting in an AELacute of 0.0023 µg/kg bw. It was decided at TM III, 2006 that an extra AF of 3 will be used for all AVKs, while it was recognised that this factor is not scientifically derived. At TM I, 2007 it was further decided that a factor of 3 is considered sufficient to provide safe margins to cover for the use of subchronic studies for chronic exposure scenarios. To derive an AELmedium, for repeated exposure, the subchronic study in rabbit submitted by Task Force is used, since it was performed in the most sensitive species. The NOAEL in this study is 0.5 µg/kg bw based on the prolonged prothrombin time seen at 1 µg/kg bw. With a safety factor of 300 and with correction of of 70% oral absorption, this would lead to an AELmedium of 0.0013 µg/kg bw. To set an AELchronic the same NOAEL as for AELmedium will be used as no chronic studies

have been performed. An extra safety factor of 3 will cover for the differences in exposure time.

2.2.1.3. Exposure assessment

In the final CAR for bromadiolone, LiphaTech a worst case dermal absorption of 1.6% was used for the products Super Caid Bloc and Super Caid AS Appat. However, the dermal absorption is lower for wax bloc products, which has also been shown for Task Force. Therefore the exposure to wax block products are recalculated for a dermal absorption of 0.32% which is similar to what was used for Task Force (i.e. 0.36% even though data for this applicant suggest that the dermal absorption of Protect-B as a wax block is even lower).

Human health risk for professional users

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

SUPER CAID AS APPAT is supplied loose and in protective LDPE sachets for use by professional users.

For Protect-B and Super Caid Bloc, SUPER CAID AS APPAT which is placed in position by hand, dermal exposure of users is likely to be limited to the hands during application and exposure of other parts of the body is negligible. For non-users, the risk of dermal exposure to residues during application is considered to be small and after application, they are not likely to come into contact with products used in sewers or around buildings. Children could potentially be the group most at risk as they may play inside or around buildings where baits have been placed. It is important that product labels and good practice advice users to prevent access to bait by children.

Protect-B, Super Caid Bloc and SUPER CAID AS APPAT is not likely to directly reach the mouth of professional or amateur users, and thus the risk during use is considered to be low. It is possible however that dermal contamination may lead to oral exposure, if the hands are not washed properly after handling. Also for non-users, risk of oral exposure to residues during or after application is considered to be low. Children or infants may play close to the floor where baits have been placed indoors and could be incidentally exposed by touching unprotected blocks. However, product labels and good practice advise users to prevent access to bait by children. For products applied in tamper resistant bait boxes this risk for exposure will be very limited. Protect-B, Super Caid Bloc and SUPER CAID AS APPAT also contains a bittering agent to prevent infants from chewing and ingesting baits and blocks.

The exposure during production of the active ingredient and formulation of the products has not been assessed. Where appropriate, exposure assessments are based on default values in EU Guidance documents, namely Technical Notes for Guidance (TNsG) on Human Exposure to

Biocidal Products, Part 3, Section 7.2 (June 2002). In addition, exposure assessments are also done using values derived from the submitted operator exposure studies. Total systemic exposures of bromadiolone to professional operators applying Protect-B and Super Caid Bloc are summarised in the table below.

Product and use	**Gloves used**	**Total Systemic Exposure (µg/kg bw/day)**			
		Default	% of $AEL_{medium, chronic}$ (0.0012µg/kg bw/day)	Measured	% of $AEL_{medium, chronic}$ (0.0012µg/kg bw/day)
SUPER CAID BLOC, in sewers, against rats	YES	0.0187	1558	0.00186	155
	NO	0.187	15583	0.0186	1550
Protect-B, in sewers, against rats	YES	0.0028	233	0.000418	35
	NO	0.028	2333	0.00418	348
SUPER CAID BLOC , in and around buildings, against rats	YES	0.00675	563	0.00196	163
	NO	0.0675	5625	0.0196	1633
Protect-B, in and around buildings, against rats	YES	0.00169	141	0.000358	30
	NO	0.0169	1408	0.00358	298
SUPER CAID BLOC, in and around buildings, against mice	YES	0.00448	373	0.00196	163
	NO	0.0448	3733	0.0196	1633
Protect-B, in and around buildings, against mice	YES	0.000675	56	0.000358	30
	NO	0.00675	563	0.00358	298

SUPER CAID BLOC, in open areas, against rats and mice	YES	0.0056	467	0.00187	156
	NO	0.056	4667	0.0187	1558
SUPER CAID AS APPAT, in and around buildings, against rats	YES	0.000475	40	0.000686	57
	NO	0.00475	396	0.00456	380
SUPER CAID AS APPAT, in and around buildings, against mice	YES	0.000475	40	0.000400	33
	NO	0.00475	396	0.00298	248
SUPER CAID AS APPAT, in open areas, against rats and mice	YES	0.000395	33	0.000558	47
	NO	0.00395	329	0.00462	385

Human health risk for non-professional users

Non professional users are untrained and cannot be expected to wear protective clothing. Use is occasional for a short time in a single day and unlikely to be repeated more than once a week. After use the product is likely to be collected and disposed of in a controlled way (as directed by product labels). The products are used by non professionals in and around buildings against rats and mice. Total systemic exposures to bromadiolone of non-professional operators applying Protect-B, Super Caid Bloc and Super Caid AS Appat are summarised in the table below. The use of sachets reduces exposure, but the risk assessment is performed without sachets.

Product and use	**Total Systemic Exposure (µg/kg bw/day)**			
	Default	% of AEL_{acute} (0.0023 µg/kg bw/day)	Measured	% of AEL_{acute} (0.0023 µg/kg bw/day)
SUPER CAID BLOC, in and around buildings, against rats	0.0075	326	0.00176	23
SUPER CAID BLOC, in and around buildings, against mice	0.0050	217	0.00176	23
Protect-B, in and around buildings, against rats	0.00187	81	0.000396	17
Protect-B, in and around buildings, against mice	0.00075	33	0.000396	17
SUPER CAID AS APPAT, in and around buildings, against rats	0.0005	22	0.000156	7
SUPER CAID AS APPAT, in and around buildings, against mice	0.0005	22	0.000104	5

Human health risk from indirect exposure as a result of use.

Adults or children may be present following application and may theoretically be incidentally exposed by touching unprotected Protect-B, Super Caid Bloc and Super Caid AS Appat baits. For products applied in bait stations or outdoors, incidental exposure will be very limited. Children are potentially the group most at risk as they may play inside or around buildings where baits have been placed. However, product labels and good practice advise users to prevent access to bait by children. In theory, infants could be exposed orally by chewing bait or touching their mouths with contaminated fingers.

Product	% of AEL_{acute} (0.0023 mg/kg bw/day)		
	adults (60 kg)	Children (15 kg)	infants (10 kg)
Super Caid Bloc	NA	793130	2170
Protect-B	NA	793130	2170
Super Caid AS Appat	NA	793130	2170

2.2.1.4. Risk characterisation

Acceptable exposure is estimated for professional operators applying Protect-B, SUPER CAID BLOC and SUPER CAID AS APPAT on a daily basis, wearing gloves. The exposure is considered acceptable also for SUPER CAID BLOC even though the exposure exceeds 100%. The reason for this is that the worst case dermal absorption of 1.6% for dermal absorption was used in the calculations when it is according to the study much lower for the wax block (around 0.3%). Furthermore, the operator exposure assessment used 75 manipulations plus 15 manipulations for clean up, whereas it was decided at TM III, 2010 that 60 manipulations plus 15 manipulations for clean up should generally be used for the risk assessment of the rodenticides. When based on these values the exposure would be acceptable. In the worst case scenario, wax blocs in sewers for control of rats, the exposure was 1558% and 233% of AEL for SUPER CAID BLOC and Protect-B respectively when based on default values. These values were changed to 155 and 35% of AEL for SUPER CAID BLOC and Protect-B respectively when based on more realistic measured values. The corresponding values for use in and around buildings for control of rats are exposure 563, 141 and 40% of AEL for SUPER CAID BLOC, Protect-B and SUPER CAID AS APPAT respectively when based on default values, which were changed to 163, 30, 57% of AEL respectively when based on measured values. For use against rats and mice in open areas, the exposure were 467 and 33% of AEL for SUPER CAID BLOC and SUPER CAID AS APPAT respectively when based on default values and 163 and 47% of AEL when based on measured values.

Acceptable exposure is estimated also for non-professional operators applying Protect-B, SUPER CAID BLOC and SUPER CAID AS APPAT respectively on a single occasion. For use in and around buildings to control rats the exposure was 81, 321, 22% of AEL respectively when based on default values. When the estimations were based on measured values the margins were even higher i.e. 17, 23, 7% of AEL respectively. Since non-professionals can not be expected to wear protective clothing, the estimations are for use without gloves. Non-professional operators are not expected to apply the products on a daily basis and therefore comparisons with a repeated dose AEL are not considered appropriate.

Children are potentially the group most at risk as they may play inside or around buildings where baits have been placed. Infants could be exposed orally by chewing bait or touching their mouth with contaminated fingers. The exposure was 2170% of AEL_{acute} based on a default exposure value which assumes that infants will ingest 10 mg of poison bait and 793130% of AEL_{acute} when assuming that children will ingest 5 g bait. These values show that infants and children ingesting bait will be at risk. However, Protect-B, SUPER CAID BLOC and SUPER CAID AS APPAT contains a bittering agent which would prevent ingestion of the baits. Therefore, in practice the margins of safety are expected to be higher than those calculated. It is also, as mentioned above, important that product labels and good practice advise users to prevent access to bait by children.

Approximately <5% of the radioactivity is excreted into urine of rats after oral exposure. However, no parent compound was detected in the urine. Therefore the amount bromadiolone present on the fur is expected to be negligible and consequently it will not be transferred to the hands to any significant extent. Exposure of adults and children handling dead rodents is therefore assumed to be negligible. In addition infants playing with dead rodents are considered an unlikely scenario.

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and distribution in the environment

Bromadiolone is not readily biodegradable under environmentally relevant conditions or during sewage treatment processes. It is also not inherently biodegradable. No hydrolysis was found at the investigated pH 7, and 9, so hydrolysis of bromadiolone is not expected to be a significant process in the environment. Photolysis of bromadiolone in aqueous solution is rapid with a half-life of 12 hours or less. Photolytic degradation was studied by LiphaTech and led to the formation of carbon dioxide and significant levels of six unidentified degradation products which had either reached plateau levels or were declining at the end of the study (15 days). Bromadiolone is quickly degraded in soil under aerobic conditions with an estimated DT_{50} value between 4 and 53 days (at 12°C, extrapolated from 20 and 25°C, LiphaTech), however degradation led to the formation of unidentified soil metabolites which persisted in significant quantities for > 1570 days. Degradation studies in soil have not been performed by Task Force and their justification stating that the release of bromadiolone is only local has been accepted. Bromadiolone is strongly adsorbed to soil and K_{OC} values range between 1563 and 41600 mL/g, which corresponds to ‘slightly mobile’ to “non-mobile” according to the SSLRC classification index. Laboratory soil column leaching and aged leaching studies performed by LiphaTech indicate that bromadiolone and any potential degradation products, even if released indirectly to soil in small quantities, are not likely to move through the soil profile and are unlikely to reach groundwater in significant quantities. To clarify the distribution properties of bromadiolone a soil degradation study including degradation rates and formation of major metabolites may be required by Task Force at the product authorisation stage. The rapid photolysis rate in air ($t_{½}$ ca 2 hours), the low vapour pressure of bromadiolone and the low Henry’s law constant together show that bromadiolone is not expected to volatilise to or persist in air in significant quantities.

A strong tendency to adsorb to sediment combined with a high degree of photo-instability means that bromadiolone is unlikely to remain in the water column of surface waters. Nevertheless two studies have been conducted by LiphaTech of bioconcentration in the tissues of fish under artificial conditions in the laboratory. In a study with bluegill sunfish the maximum bioconcentration factor for bromadiolone was 460 for whole fish. In non-edible tissues the maximum BCF was 1,658 and in edible tissues 161. In a second study with channel catfish, the bioconcentration factors in whole fish ranged from 24 (day 1) to 74 (day 14). In edible and non-edible tissues the maximum bioconcentration factors were 59 and 641, respectively. Two fish bioconcentration studies were performed by Task Force, but both failed. Taken together, the fish studies are of low reliability, and therefore BCF was derived by calculation from log K_{ow}, resulting in BCF values of 339 to 575. It can be concluded that bromadiolone has potential to bioaccumulate.

2.2.2.2. Effects assessment

Based on the results of acute toxicity studies, bromadiolone is toxic to fish (*Oncorhynchus mykiss*). According to the study performed by Task Force the 96 h LC_{50} was 2.86 mg/L (nominal concentration, the measured concentrations of bromadiolone were all within the range 95-102 % of nominal). The LiphaTech study resulted in a 96 h LC_{50} that exceeded 8.0 mg/L, the single concentration applied and confirmed by analysis. No fish died at the limit concentration.

Daphnia magna was similar in sensitivity to fish, with a 48 h LC_{50} of 5.79 mg/L (Task Force) and 2.0 mg/L (LiphaTech) recorded under flow-through conditions. The LiphaTech endpoint was based on lethality rather than immobilisation and on mean measured concentrations of bromadiolone in the test media. It is possible that the value would be somewhat lower if the endpoint were based on immobility.

Algae represented the most sensitive of the three aquatic trophic levels tested, in spite of the fact that the conditions necessary in algal growth inhibition tests are the ones most likely of all the aquatic acute toxicity tests to result in lowering of exposure concentrations, based on the photo-instability of bromadiolone in aqueous solution. Concentrations of bromadiolone were reduced to below the limit of quantification under the conditions of the four-day test. The 96 h E_bC_{50} for *Scenedesmus subspicatus* was 0.17 mg/L and the NOEC with respect to biomass yield was 0.037 mg/L (LiphaTech). Levels of growth inhibition recalculated to specific growth rates were included by LiphaTech at a later stage, and the resulting 72 h E_rC_{50} of >1 mg/l is presented for comparison. The E_bC_{50} for *S. subspicatus* serves as the key endpoint for the aquatic risk assessment for LiphaTech. Due to several shortcomings of this study and consequently large uncertainty and likely underestimation of toxicity an assessment factor of 10 has been added. The Task Force study was done on *Pseudokirchneriella subcapitata* resulting in an E_rC_{50} of 1.14 mg/L. Due to the rapid photolysis of the test substance, the test concentrations used to express the results were calculated by the Task Force according to the OECD Guidance document on aquatic toxicity testing of difficult substances and mixtures. However, it is likely that the degradation is much faster than what can be seen as a disappearance in 72 h, so, although this study is better performed than the LiphaTech study the RMS still considers that the resulting effect value (E_rC_{50}) is most probably an underestimation

of toxicity. Therefore, RMS applies an extra assessment factor of 3 to the E_rC_{50} to compensate for this uncertainty.

The effect of bromadiolone on aerobic biological sewage treatment processes was assessed by determining inhibition of respiration of the micro-organisms present in activated sludge following 3 h contact and the resulting calculated EC_{50} was 31.6 mg/L (nominal, LiphaTech). Concentrations causing 20% and 80% respiration suppression were not calculated, but 23.5% inhibition occurred at 10 mg/L (the lowest concentration tested), indicating that the EC_{20} was approximately 10 mg/L. The corresponding result from Task Force is an EC_{50} of 132.8 mg/L.

Justifications for not submitting studies on sediment dwelling organisms, being that there will be only limited exposure for organisms in the aquatic compartment, have been accepted. Instead, the PNEC for sediment dwelling organisms was calculated with the equilibrium partitioning method (EPM) according to TGD II, resulting in 0.83 mg/kg ww (Task Force).

The effect of bromadiolone on earthworms was assessed in an acute toxicity test in which *Eisenia fetida* were exposed in artificial soil to a liquid formulation containing 10.34 g bromadiolone/L. The 14-day LC_{50} of bromadiolone was greater than 9.48 mg/kg dry soil, the highest concentration applied. If this value is normalised with respect to moisture content of the soil, the resulting LC_{50} is 8.4 mg/kg soil (LiphaTech). In the study performed by Task Force no effects of bromadiolone were found on earthworms at 1331 mg/kg dw, the highest concentration tested. This effect concentration was adjusted due to soil moisture content, giving a NOEC of 918 mg/ kg ww. Using an assessment factor of 1000, this would give a $PNEC_{soil}$ of 0.918 mg/kg ww. PNEC was also calculated from the aquatic toxicity data using equilibrium partitioning calculations, which resulted in a $PNEC_{soil}$ of 0.099 mg/kg ww. The difference between these figures is notable, especially when taking into account the data of LiphaTech. Due to that only one soil organism was tested and also considering the uncertainties arising from the data of the two applicants, the $PNEC_{soil}$ value derived from the equilibrium partitioning calculations may be considered as the more realistic value and is used in the risk assessment for Task Force.

The resulting PNEC values for the aquatic and soil compartments are listed in the table below. (LT = LiphaTech; TF = Task Force)

Compartment	Organism/test	Results	Assess-ment factor	PNEC
Freshwater	Alga/ growth inhibition	E_rC_{50} = 1.14 mg/L E_bC_{50} = 0.17 mg/L	1000x3 1000x10	3.8 10^{-4} mg/L (TF) 1.7 10^{-5} mg/L (LT)
STP microorganisms	Sewage sludge/ respiration inhibition	EC_{50} = 132.8 mg/L EC_{50} = 31.6 mg/L	100 100	1.33 mg/L (TF) 0.32 mg/L (LT)
Sediment	Calculated/ EPM	-	-	0.83 mg/kg ww (TF)
Soil	Calculated/ EPM Earthworm acute toxicity	- LC_{50} >8.4 mg/kg soil	- 1000	0.099 mg/kg (TF) >0.0084 mg /kg (LT)

Bromadiolone is toxic to birds, with an acute LD_{50} value of 138 mg/kg bw for bobwhite quail (LiphaTech). In the acute toxicity study presented by Task Force Japanese quail were exposed to bromadiolone once and then observed for 14 days. This study was conducted to determine the lethal dose, but it also made it possible to determine effect concentrations at which birds did cower, which was found to be a dose dependent effect. The LD_{50} was, on average for both sexes, 134 mg/kg bw. In total, five short-term dietary tests with 5 days exposure time were conducted by LiphaTech with observation periods ranging from three to 35 days. The lowest LC_{50} value observed was 62 mg bromadiolone/kg food with bobwhite quail. The higher LC_{50} values obtained in the four other dietary studies are rendered unreliable since the diets included sources of vitamin K that would have counteracted the effects of bromadiolone. Despite this fact, in one of those tests the LC_{50} was 110 mg/kg food and the NOEC < 19 mg/kg food and at this lowest tested concentration the mortality was still 40 %. Taken together, the real NOEC value would quite possibly be much lower than 19 mg/kg food. The NOEC values of those four dietary tests are also based on that mortalities occurred at all concentrations and may therefore underestimate toxicity. For Task Force, a second acute study with partridge which resulted in an LC_{50} of 28.9 mg/kg food has been considered by RMS as supportive as short term toxicity data. Lethal effects were found at bromadiolone levels from 18.2 mg/kg bw, i.e. at much lower dosage than in the acute toxicity study above. The test concentration is expressed as dose, but this is not dose in its correct meaning since in practice it was continuous feeding during 10 days.

LiphaTech presented a 20 weeks avian reproduction study with Japanese quail on the related substance difenacoum. This study did not result in any substance-related effects and the resulting NOEC was >0.1 mg/kg diet, which was the highest tested concentration. As agreed at the Technical Meeting (TMII-07), readacross is accepted and this serves as the key study in the long-term avian risk assessment for LiphaTech. The Task Force presented a six weeks bird reproduction test in which bromadiolone was supplied via drinking water. It was difficult to

determine any clear effects on reproduction in this study, but it showed effects on liver weight, spleen weight and testes weight. Effects on 14 day survival of the hatchlings were also found and there were indications on a decreased body weight gain of the adult birds. The NOEC was determined to 39 µg/kg bw/day or 0.26 mg/L drinking water (measured concentration).

Three studies have been presented by LiphaTech that were conducted to simulate the secondary poisoning of non-target predatory birds and mammals that may potentially occur following intake of poisoned target rodents containing bromadiolone residues. In the first, rats were first fed with bromadiolone bait pellets for three days, followed by uncontaminated feed for a fourth day, before being euthanised and fed to five great-horned owls (*Bubo virginianus*) at the rate of one carcass per bird per day for seven days. Four of the owls died during the course of the subsequent 30-day observation phase, with inactivity noted in the period immediately prior to death and with widespread and massive haemorrhaging identified at the cause of death post mortem. The sole survivor generally avoided the livers and only partially consumed the intestines of the poisoned rats during the exposure period, but evidence of earlier internal haemorrhaging was also found in this bird following termination at the end of the study. The bromadiolone intake of the owls that died was estimated to between 0.034 and 0.076 mg/kg bw/d with a mean value of 0.056 mg/kg bw/d. This value has been used to assign a PNECoral for secondary poisoning. An assessment factor of 3000 (TGD, table 23) shall be used if the available data is a short term effect value (LC_{50}). The suggested assessment factor takes into account interspecies variation, lab to field extrapolation and acute to chronic extrapolation. However, it may be argued that since the tested species is an owl, the interspecies factor can be omitted and the assessment factor can thus be lowered to 300. Further reduction of the assessment factor is not considered possible, due to the uncertainty caused by that the available effect data is LC_{100} and not LC_{50}. The remaining two studies were done on barn owls and stone martens and are described in published scientific literature. In conclusion, the intake of poisoned rats may cause severe effects including death to predatory birds. The effect on wild mammals seems to be less severe, but the submitted study comprised a limited number of animals and the concentration of bromadiolone in the mice fed to the martens was not known. There are several reports on bromadiolone content in and bromadiolone related effects on non-target species and predators. Studies indicate that bromadiolone is distributed among many species in the environment. Three studies were submitted by Task Force on secondary poisoning of birds by anticoagulant rodenticides. From the studies it may be concluded that the investigated rodenticides posed a high risk of secondary poisoning to owls and that consumption of 3 mice that were poisoned with the related substance brodifacoum caused lethality to barn owls. Lethal liver concentrations were found between 0.63 and 1.7 mg brodifacoum/kg fw. This correlates well with a submitted field report where liver concentrations of dead hawks after a field trial were investigated and found to be on average 0.23 mg brodifacoum/kg fw.

Bromadiolone is acutely toxic to mammals with acute oral rat LD_{50} of 1.31 mg/kg (Task Force) and slightly lower, 0.56-0.84 mg/kg bw, for LiphaTech. The long-term study that is used in the risk assessment for Task Force was the NOAEL from the 90 day subchronic test with rabbit of $5\ 10^{-4}$ mg/kg bw/day, and the corresponding data from LiphaTech is a NOAEL of $2\ 10^{-3}$ mg/kg bw/day from a subchronic test with rat done on the related substance difethialone. No extra assessment factor is used, since difethialone is at least as toxic as bromadiolone. For LiphaTech, there is also a subchronic test with dog. The assessment factor for long-term effects

on dogs is set to 30, which accounts for laboratory to field and subchronic to chronic extrapolation, since the PNEC value for dog is used only for the long-term risk assessment of primary poisoning of this species.

The long-term PNECs for birds and mammals are presented in the table below. (LT = LiphaTech; TF = Task Force)

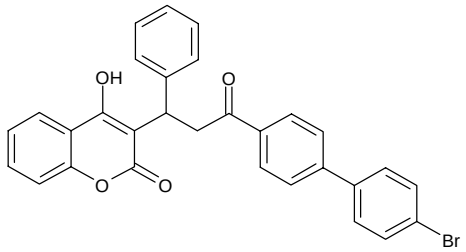
Organism group	Species/test	Results	Assess-ment factor	PNEC (conc. in food)	PNEC (dose)
Birds	TF: Japanese quail (*Coturnix coturnix japonica*) reproduction test 42 days	NOEC = 0.039 mg/kg bw/day 0.26 mg/L drinking water	30	0.0087 mg/L (TF)	0.0013 mg/kg bw/day (TF)
	LT: Japanese quail/ reproduction test 140 days (20 weeks)	NOEC = 0.1 mg/kg food NOEL = 0.01138 mg/kg bw/day	30	0.0033 mg/kg (LT)	0.00038 mg/kg bw/day (LT)
	LT: Great horned owl/ secondary poisoning dietary 7 days	LD_{100} = 0.056 mg/kg bw/d	300	0.00075 mg/kg[2] (LT)	0.00019 mg/kg bw/d (LT)
Mammals	TF: Rabbit 90 days	NOAEL = 5 10^{-4} mg/kg bw/day	90	0.00019 mg/kg[1] (TF)	0.0000056 mg/kg bw/day (TF)
	LT: Rat 90 days	NOAEL = 2 10^{-3} mg/kg bw/day	90	0.00044 mg/kg[1] (LT)	0.000022 mg/kg bw/day (LT)
	LT: Dog 90 days	NOAEL = 8 10^{-3} mg/kg bw/day	30	0.011 mg/kg[1] (LT)	0.00027 mg/kg bw/day (LT)

[1] calculated using conversion factor from Table 22 in the TGD.
[2] calculated using a conversion factor bw/dfi = 4 (EUBEES mean value for owls).

2.2.2.3. PBT assessment

Bromadiolone is not readily biodegradable, has a relatively high bioconcentration factor and is toxic to both aquatic organisms and mammals. Thus, a PBT assessment was performed. The PBT assessment is similar to the one submitted to the TCNES Subgroup on Identification of PBT and vPvB Substances to their meeting in March 2008. It is based on data from both applicants of bromadiolone.

The P screening criterion is fulfilled for bromadiolone since it is “not readily biodegradable” in water, which is further supported by that it is “not inherently biodegradable”. Bromadiolone is also stable to hydrolysis. The degradation rates in the soil studies show primary degradation with DT_{50} < 120 days in soil. Five metabolites are formed in quantities exceeding 10 % of AR and non-extractable residues are formed at maximum 21 % of AR. Although the TGD part II should be followed there is an additional P criterion in REACH Annex XIII, namely DT_{50} > 120 days in soil. One of the relevant metabolites, bromadiolone ketone, with a max formation of 39.6 % of AR, has a half-life in soil exceeding 120 days and a log K_{ow} of 6.8 (as predicted using the software ECOSAR Kowwin v.1.67) which is higher than for bromadiolone itself. Also, it is evident from the structure of bromadiolone ketone that it has a similar level of toxicity as bromadiolone itself, which should be taken into account when the P criterion is evaluated. In conclusion, the P screening criterion for water is fulfilled and in addition, bromadiolone fulfils the soil P criterion of REACH taking the toxic and persistent metabolites into consideration.



Structure of the metabolite bromadiolone ketone.

The laboratory studies on bioconcentration in fish are both of low reliability and they are not used to assess the B criterion. BCF studies are technically difficult to conduct as bromadiolone including its metabolite bromadiolone ketone is highly toxic to fish. The calculation method uses log K_{ow} as input value, and the BCF values, based on log K_{ow} measured at pH 6 and pH 7, are both below the trigger value for fulfilment of the screening B criterion. Despite this, some uncertainty regarding the fulfilment of the B criterion remains since there are monitoring studies available that show residues of bromadiolone in wildlife in which most of the incidents of contamination are believed to be due to feeding of contaminated prey. However, it is not possible to draw any conclusions in relation to the B/vB criteria as the exposure situation is not known. The metabolite bromadiolone ketone has a predicted log K_{ow} of 6.8 and thus fulfils the screening B criterion. In conclusion, there is a possibility that the screening criterion for B is fulfilled for bromadiolone.

Bromadiolone is very toxic and is classified as T+, R26/27/28 and R48/23/24/25. The substance should therefore be considered as fulfilling the T criterion. Based on structural similarities, there is reason to assume that some of the metabolites (particularly bromadiolone ketone) are as toxic as the mother substance. Regarding the T-criterion for environment bromadiolone is potentially toxic based on results from short-term toxicity data on aquatic organisms. In conclusion, the T criterion is fulfilled for bromadiolone.

To summarise, the uncertainties with regard to the B-criterion can not be clarified at the moment and bromadiolone should be considered as a potential PBT substance.

2.2.2.4. Exposure assessment and Risk characterisation

The representative products all contain 0.005 % bromadiolone. For use in sewers there are two wax block formulations, Super Caid Bloc and Protect-B, whilst for use in and around buildings there are these two and a third product Super Caid AS Appat, formulated as grains. LiphaTech has also identified uses in open areas and waste dumps for their products Super Caid Bloc and Super Caid AS Appat.

Environmental risk in the aquatic compartment (incl. sediment)

Exposure of surface water to bromadiolone following typical usage, except the use in sewers, is considered negligible. Following use in sewers, potential residues including metabolites of bromadiolone could remain in treated STP effluent which might be received by surface waters, taking into account a dilution of 10 x in the recipient. Based on worst case assumptions the maximum predicted environmental concentration (PEC) of bromadiolone in surface water following such use is expected to be $5.2\ 10^{-6}$ mg/L (LiphaTech) and $6.2\ 10^{-6}$ mg/L (Task Force). The respective PNEC values for the aquatic environment are $1.7\ 10^{-5}$ mg/L (LiphaTech) and $3.8\ 10^{-4}$ (Task Force). Risk characterisation is therefore based on PEC/PNEC ratios of 0.31 (LiphaTech) and 0.016 (Task Force), which indicates that there are no unacceptable risks to aquatic biota. According to TGD II the risk for sediment can be calculated by increasing the PEC/PNEC ratio for the aquatic compartment by a factor of 10. This is supposed to take into consideration the possibility of ingestion of contaminated sediment particles by sediment dwelling organisms. The corresponding PEC/PNEC ratios are then 3.1 (LiphaTech) and 0.16 (Task Force). For LiphaTech this indicates a small unacceptable risk but an acceptable risk for Task Force, which illustrates that there are uncertainties in the assessment and also, they are based on true worst case assumptions.

The PEC/PNEC ratio for STP microorganisms was determined to $6.2\ 10^{-5}/1.33 = 4.7\ 10^{-5}$ (Task Force) and $1.7\ 10^{-4}/0.32 = 5.3\ 10^{-4}$ (LiphaTech) and it is concluded that the risk for STP microorganisms caused by bromadiolone used for control of rodents in sewers is acceptable.

For the risk assessment of bromadiolone in groundwater the highest concentration, as calculated according to TGD II, was found in the in and around buildings scenario with a soil pore water concentration of $1.8\ 10^{-4}$ mg/L (Task Force). The general maximum permissible concentration according to directive 80/778/EEC is 10^{-4} mg/L. This comparison indicates a slight unacceptable risk of groundwater contamination. However, the in and around buildings scenario is strictly worst case which describes the situation in much localised spots of soil. Also, groundwater concentrations are assumed to be the same as the concentrations in pore water, i.e. no consideration is given to dilution when bromadiolone migrates through soil layers. Further, risk mitigation measures including good management practices in rodenticide use as described in section 3 are likely to substantially reduce bromadiolone contamination to soil relative to the worst case exposure scenario, and it is considered that bromadiolone will not move to groundwater in significant quantities.

Environmental risk in the atmosphere

Since bromadiolone will be used only locally and since it has a low vapour pressure and low Henrys law constant the concentration of bromadiolone in the atmosphere will be negligible. Therefore no risk assessment is performed for the atmosphere.

Environmental risk in the terrestrial compartment

Exposure of soil to bromadiolone following typical usage could potentially occur via residues present in sewage sludge after use in sewers and via direct release (spillages) and disperse release (deposition by urine and faeces) mechanisms. Based on some worst case assumptions, potential residues in soil (PEC) are not expected to exceed 0.00002 mg/kg (the 10-year cumulative PEC consequently becomes 0.0002 mg/kg) for sewage sludge application on soil (LiphaTech). The corresponding PEC value from Task Force is 0.00072 mg/kg based on sludge application to agricultural soil. Predicted exposure through a combination of transfer (direct release) and deposition via urine and faeces (disperse release) onto soil is results in a PEC of maximum 0.0166 mg/kg (LiphaTech) and 0.046 mg/kg (Task Force). Risk characterisation based on the LiphaTech soil PNEC value of >0.0084 mg/kg results in a PEC/PNEC ratio of <2.0, which indicates a small unacceptable risk due to the effect of bromadiolone on soil invertebrates. However, the effect value is uncertain being a “greater than” value based on the highest tested concentration. The risk assessment of Task Force using an EPM derived PNEC of 0.099 mg/kg results in a PEC/PNEC ratio of 0.46, indicating acceptable risk in the terrestrial compartment.

Non compartment specific effects relevant to the food chain (primary and secondary poisoning)

Non-target vertebrates may be exposed to bromadiolone either directly by ingestion of exposed product (primary poisoning) or indirectly by ingestion of the carcasses of target rodents that contain residues of bromadiolone (secondary poisoning).

Assessment of secondary poisoning through the aquatic food chain is not performed for the following reasons: the risk assessment for the aquatic compartment indicates that there will be very low concentrations of bromadiolone in the aquatic compartment, and there was no risk identified of bromadiolone for surface water or sediment dwelling organisms. The justification for not performing an assessment of secondary poisoning via the terrestrial food chain is that secondary poisoning will be limited due to the small area that potentially is contaminated by bromadiolone around buildings and the limited number of earthworms inhabiting this area.

Primary and secondary poisoning of non target mammals and birds following use of products containing bromadiolone in sewers is considered negligible. Non-target mammals and birds are unlikely to enter sewers and feed on bait blocks in sewage systems. Rats that live underground in sewers are also unlikely to take bait and deposit significant quantities in accessible places above ground, thus preventing exposure to non-target animals living above sewers. There is a possibility of secondary exposure if bromadiolone poisoned cockroaches or rats from sewers

appear on the ground, but this is more of a concern and the issue is further considered in the in and around building scenario.

Due to the highly toxic nature of bromadiolone, primary and secondary poisoning presents a hazard to non target mammals and birds following use in and around buildings. The risk assessment of bromadiolone used in and around buildings is summarised by presenting PEC/PNEC ratios for long-term primary and secondary poisoning. The risks posed by use in open areas and on waste dumps can be considered as adequately covered by the same assessment.

For the acute situation, as was agreed at TMIII-06, PNEC derivation for birds and mammals will only apply to long-term effects and acute effects will only be evaluated on a qualitative basis. It is important to stress that this qualitative assessment is not intended to be used for the risk characterisation of primary and secondary poisoning of rodenticides and shall not be used for a comparative assessment. This comparison should only give a first indication of the acute toxicity of the substance.

Primary poisoning

In the Tier 1 assessment of primary poisoning it is assumed that the whole day's food requirement is satisfied by consumption of wax blocks, and therefore the concentration in food will be the same as the concentration of a.s. in the bait, 50 mg/kg. This is then compared to the long-term PNECs for birds and mammals. The resulting PEC/PNEC ratios in the table below reveal a high risk for both birds and mammals of long-term primary poisoning (LT = LiphaTech; TF = Task Force).

	PEC (conc. in food, mg/kg)	**PNEC (conc. in food)**	**PEC/PNEC**
Birds	50	0.021 mg/kg 0.0087 mg/L	2380 (LT) 5750 (TF)
Mammals	50	0.00044 mg/kg 0.00019 mg/kg	114000 (LT) 263000 (TF)
Dog	50	0.011 mg/kg	4550 (LT)

Tier 2 acute qualitative risk assessment for bait containing bromadiolone in and around buildings, step 2 (realistic worst case).

Non-target animal	**PECoral = ETE, conc. of bromadiolone after one meal (mg/kg)**	**LD_{50} dose (mg/kg bw/d)**	**PECoral higher than LD_{50} (y/n)**
Dog	1.64	11.8 1.3	n (LT) y (TF)
Pig	0.27	0.56-0.84 1.3	n (LT) n (TF)

Pig, young	0.86	0.56-0.84 1.3	y (LT) n (TF)
Tree sparrow	12.44	138 134	n (LT) n (TF)
Chaffinch	10.80	138 134	n (LT) n (TF)
Wood pigeon	3.90	138 134	n (LT) n (TF)
Pheasant	3.88	138 134	n (LT) n (TF)

This comparison indicates that birds are not at risk for acute primary poisoning; while the situation for mammals is more uncertain. Dogs and pigs are at risk or very close to being at risk.

Tier 2 long-term risk assessment for bait containing bromadiolone in and around buildings. Very high risks for long-term primary poisoning of both mammals and birds are identified. However, long-term consumption of these quantities of bromadiolone bait is generally not realistic and should be regarded strictly as worst case.

Non-target animal	**PEC = EC, concentration of bromadiolone after one day of elimination (mg/kg)**	**PNEC dose (mg/kg bw/day)**	**PEC/PNEC**
Dog	1.10 1.15	0.00027 0.0000056	4074 (LT) 205000 (TF)
Pig	0.18 0.19	0.000022 0.0000056	8223 (LT) 33900 (TF)
Pig, young	0.58 0.60	0.000022 0.0000056	26313 (LT) 107000 (TF)
Tree sparrow	8.71	0.00038 0.0013	22909 (LT) 6700 (TF)
Chaffinch	7.56	0.00038 0.0013	19895 (LT) 5800 (TF)
Wood pigeon	2.73	0.00038 0.0013	7186 (LT) 2100 (TF)
Pheasant	2.72	0.00038 0.0013	7147 (LT) 2100 (TF)

Secondary poisoning

The tier 1 qualitative acute risk assessment of secondary poisoning based on measured residue levels (presented by the applicant) in target rodents indicates no risk for birds or mammals. However, this qualitative assessment is only an indication and is not intended to be used for the risk characterisation of secondary poisoning of rodenticides.

The tier 1 long-term risk assessment based on measured (LiphaTech) or default (Task Force) residue levels in target rodents results in very high PEC/PNEC values for predatory birds and mammals.

	$PNEC_{oral}$ (conc. in food)	PEC_{oral} Bromadiolone conc. in target rodent (mg/kg bw), ESD default values	PEC/PNEC
Birds	0.00075 mg/kg 0.0087 mg/L	3.19 13.9	4250 (LT) 1600 (TF)
Mammals	0.00044 mg/kg 0.00019 mg/kg	3.19 13.9	7250 (LT) 73200 (TF)

In the tier 2 assessment it is assumed that 50% of the diet of each predator species on a single day consists of rodents containing bromadiolone and that they are caught on day 5 just after their last meal, on day 7 two days after their last meal or on day 14 (resistant rodents). It is also assumed that bromadiolone bait has contributed 100% of the daily food intake of the target rodents. The calculations are based on measured residue levels (LiphaTech) or default levels (Task Force) in target rodents. This assessment results in very high risks for birds and mammals. Since baiting campaigns involving the use of bromadiolone bait are not expected to extend beyond three weeks, the endpoint from a 90-day study in mammals may be regarded as being of less relevance. On the other hand, a comparison with monitoring data from the literature indicates that the very high risks of secondary poisoning emerging from the calculations according to the ESD are confirmed. This is notable and a more thorough investigation into monitoring data and comparison with modelled data should be carried out in conjunction with the future comparative assessment of second generation rodenticides.

Species	PEC conc. in food (mg/kg bw)			PNEC dose (mg/kg bw/day)	PEC/PNEC			applicant
	day 5	day 7	day 14		day 5	day 7	day 14	
Barn owl *(Tyto alba)*	0.395 1.7	0.194	 2.1	0.00019 0.0013	2081 1300	1020	 1600	LT TF
Little owl *(Athene noctua)*	0.451 2.0	0.221	 2.3	0.00019 0.0013	2374 1500	1164	 1800	LT TF
Tawny owl *(Strix aluco)*	0.363 1.6	0.178	 1.9	0.00019 0.0013	1913 1200	938	 1500	LT TF
Kestrel *(Falco tinnunculus)*	0.600 2.6	0.294	 3.1	0.00019 0.0013	3160 2000	1549	 2400	LT TF
Red kite *(Milvus milvus)*	0.273	0.134		0.00019	1438	705		LT
Fox *(Vulpes vulpes)*	0.146 0.6	0.071	 0.8	0.000022 0.0000056	6615 110000	3242	 140000	LT TF
Polecat	0.303	0.148		0.000022	13770	6749		LT

(Mustela putorius)	1.3		1.6	0.0000056	180000		290000	TF
Stoat *(Mustela erminea)*	0.433 1.9	0.212	 2.3	0.000022 0.0000056	19693 340000	9652	 410000	LT TF
Weasel *(Mustela nivalis)*	0.625 2.7	0.306	 3.3	0.000022 0.0000056	28416 480000	13927	 590000	LT TF

Conclusion

The conclusion of the quantitative risk assessments is that there are, in some cases very high, unacceptable risks to non-target vertebrates via primary and secondary poisoning. Therefore, it would seem more appropriate to develop and validate risk management procedures than to refine the risk assessment procedures.

To minimise the likelihood of target rodents developing resistance to second-generation anticoagulant rodenticides, long-term deployment of baits as a preventative control measure is not recommended. Product labels additionally instruct users to retrieve and securely dispose of all unconsumed baits at the end of control programmes. Both these factors limit the opportunity for exposure and reduce the primary poisoning risk to small non-target animals. Provided that baits are deployed in accordance with the product labelling and other approved guidance on good practice, the primary poisoning risk to non-target mammals may be considered to be negligible.

The risk of secondary poisoning of bromadiolone to birds and small mammals is expected to be significantly reduced by restricting its use to treatment campaigns of limited duration, limiting access of non-target animals to the blocks and removing dead and moribund rodents during a baiting campaign to minimise the opportunity secondary exposure. These mitigation measures are described in good practice guidance documents, in training material for pest control professionals and on the labels of the products. Also, with the aim of harmonising the assessments of second generation anticoagulant rodenticides, a common approach to the use of risk mitigation measures has been agreed at the CA meeting in March 2007, and these measures are listed in section 3 below.

2.2.3. List of endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

3. DECISION

3.1. Background to the Decision

Bromadiolone has been evaluated as a rodenticide against rats and mice for the following use patterns: in and around buildings[4] (professional and non-professional use), sewers (professional use only), open areas (professional use only) and waste dump (landfill) perimeters (professional use only).

Assessed from the documentation for the active substance bromadiolone and the representative products Super Caid Bloc, Super Caid AS Appat and Protect-B, biocidal products intended to control rats and mice, are sufficiently effective. Health risks for the users of the biocidal products are at an acceptable level if principles of good working practice are applied and use instructions on the label are respected. The accidental ingestion of baits poses a risk to infants. Adequate measures for protection and risk mitigation have to be applied during use. High risks to the environment have been identified, primarily to non-target animals. In order to make it possible to include bromadiolone in Annex I of Directive 98/8/EC, it is of paramount importance that exposure to non-target animals is minimised by relevant risk mitigation measures and special precautions must be taken in order to avoid the development of resistance to bromadiolone.

It is recognised that anticoagulants like bromadiolone do cause pain in rodents but it is considered that this is not in conflict with the requirements of Article 5.1 of Directive 98/8/EC "to avoid unnecessary pain and suffering of vertebrates", as long as effective, but comparably less painful alternative biocidal substances or biocidal products or even non-biocidal alternatives are not available.

Bromadiolone is a candidate for a comparative risk assessment due to its risk for secondary poisoning of non-target vertebrates and risk for secondary exposure of humans. Such a comparative assessment, with a risk benefit analysis, can only be performed when possible alternative rodenticides have all been evaluated.

According to a preliminary evaluation of the persistence, bioaccumulating and toxic (PBT) properties of bromadiolone, a definite conclusion on the PBT assessment can not be drawn at the moment. Bromadiolone has been evaluated by the TC NES subgroup on Identification of PBT and vPvB Substances, and has been appointed as a potential PBT substance. This will be taken into account in a future comparative risk assessment.

As several anticoagulants have been assessed for possible Annex I entry at the same time, being quite similar regarding the hazardous properties and associated risks, the Commission initiated work on possible risk mitigation measures for all anticoagulant rodenticides. A

[4] This area of use is defined as: "the building itself and the area around the building that needs to be treated in order to deal with the infestation of the building"

document describing possible risk mitigation measures for all anticoagulant rodenticides has been agreed at the 24th CA-meeting (CA-March07-Doc.6.3-final). The document distinguishes between measures to be taken into account at community level through restrictions in the Annex I entry decision, and measures that can be taken into account at national level when products are to be authorised. The proposal for Annex I decision in chapter 3.2 and the elements to be taken into account by Member States when authorising products, as described in chapter 3.3, are based on this assessment report and on the Commission document on risk mitigation measures for anticoagulants used as rodenticides.

3.2. Decision regarding Inclusion in Annex I

Bromadiolone shall be included in Annex I to Directive 98/8/EC as an active substance for use in product-type 14 (Rodenticides), subject to the following specific provisions:

The active substance bromadiolone, as manufactured, shall have a minimum purity of 969 g/kg (with reference to the mixture of two racemic diastereomers; 70-90% *syn*-isomer (1*RS*,3*RS)* 10-30% *anti*-isomers (1*RS*,3*SR*)).

Member States shall ensure that authorisations are subject to the following conditions:

The nominal concentration of bromadiolone in the products shall not exceed 50 mg/kg and only ready-for-use baits shall be authorised

Products shall contain an aversive agent and, where appropriate, a dye.

Products shall not be used as tracking powder.

Primary as well as secondary exposure of humans, non-target animals and the environment are minimised, by considering and applying all appropriate and available risk mitigation measures. These include, amongst others, the restriction to professional use only, setting an upper limit to the package size and laying down obligations to use tamper resistant and secured bait boxes.

3.3. Elements to be taken into account by Member States when authorising products

- Efficacy has been shown in laboratory tests for *Mus musculus* and *Rattus norvegicus* but not for *Rattus rattus*, so therefore, in case of product applications for use against roof rat (*Rattus rattus*), efficacy tests on this species should be provided.

- Bromadiolone baits should not be placed so that food, feeding stuffs or drinking water could be contaminated.

- The size of the package placed on the market should be proportionate to the duration of the treatment and appropriate to the pattern of use of particular user groups.

- Product design and use restrictions should be optimised in order to ensure sufficient and efficient rodent control while at the same time minimizing the risk for primary poisoning. This could include the use of tamper resistant bait boxes and the need to secure the baits so that rodents cannot remove the bait from the bait box. It could also

include regular check of the bait points for damage and to repair or replace, as appropriate.

- When tamper-resistant bait stations are used, they should be clearly marked to show that they contain rodenticides and that they should not be disturbed.

- The restriction of products to specific areas and manners of use and also restrictions of products to professionals or trained professionals only, should be considered.

- In addition to the elements already listed in Article 20(3) of Directive 98/8/EC, all packaging of anticoagulant rodenticides should be marked with the following standard phrases to protect humans, animals and the environment:

    - Baits must be securely deposited in a way so as to minimise the risk of consumption by non-target animals or children. Where possible, secure baits so that they cannot be dragged away.

    - Search for and remove dead rodents at frequent intervals during treatment (unless used in sewers), at least as often as when baits are checked and/or replenished. Dispose of dead rodents in accordance with local requirements.

    - Unless under supervision of a pest control operator or other competent persons, do not use anticoagulant rodenticides as permanent baits.

    - Remove all baits after treatment and dispose of them in accordance with local requirements.

    - Keep out of the reach of children. (This last safety precaution should always be carried on the label of the products, if not already legally required by 1999/45/EC. The others could be stated elsewhere on the packaging or on the accompanying leaflet together with the other directions for use and disposal of the product required by article 20(3) of Directive 98/8/EC.)

- Adequate safety instructions (including use of appropriate personal protective equipment) should be provided in the use instructions.

- Member states should encourage the application of Codes of Good Practices in rodent control. These measures could include (but should not be restricted to) the following factors:

    - The population size of the target rodent should be evaluated before a control campaign. The number of baits and the timing of the control campaign should be in proportion to the size of infestation.

    - A complete elimination of rodents in the infested area should be achieved.

    - The use instruction of products should contain guidance on resistance management for rodenticides.

- Resistant management strategies should be developed, and bromadiolone should not be used in an area where resistance to this substance is suspected.

- The authorisation holder shall report any observed resistance incidents to the Competent Authorities or other appointed bodies involved in resistance management.

- When the product is being used in public areas, the areas treated must be marked during the treatment period and a notice explaining the risk of primary or secondary poisoning by the anticoagulants as well as indicating the first measures to be taken in case of poisoning must be made available alongside the baits.

3.4. Requirement for further information

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions, and permit the proposal for the inclusion of bromadiolone in Annex I to Directive 98/8/EC.

However, a valid study showing the efficacy of the product in damp conditions is required by Task Force and it is recommended that such study is performed at the product authorisation stage before approval for use in sewers could be granted. Also, to clarify the soil distribution properties of bromadiolone including the possibility that bromadiolone may reach groundwater a soil degradation study including degradation rates and formation of major metabolites may be required by Task Force at the product authorisation stage.

3.5. Updating this Assessment Report

This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information referred to in Articles 7, 10.4 and 14 of Directive 98/8/EC. Such adaptations will be examined and finalised in connection with any amendment of the conditions for the inclusion of bromadiolone in Annex I to the Directive.

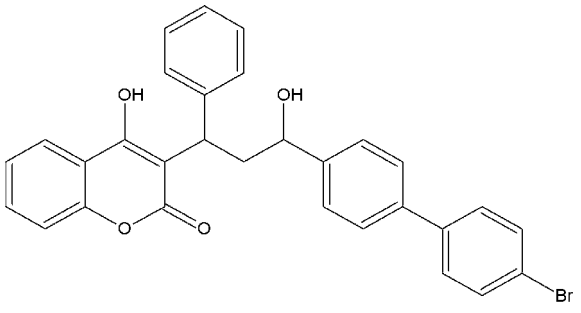
Appendix I: List of endpoints

Where relevant, separate results are reported for the two applicants. LT = LiphaTech; TF = Task Force

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

Active substance (ISO Common Name)	bromadiolone
Product-type	PT 14

Identity

Chemical name (IUPAC) *	3-[(1*RS*,3*RS*;1*RS*,3*SR*)-3-(4′-bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin
Chemical name (CA)	3-[3-(4'-bromo[1,1'-biphenyl]-4-yl-)-3-hydroxy-1-phenylpropyl]-4-hydrox-2H-1-benzopyran-2-one
CAS No	28772-56-7
EC No	249-205-9
Other substance No.	CIPAC: 371 RTECS: GN493470
Minimum purity of the active substance as manufactured (g/kg or g/l)	969 g/kg (relates to the mixture of two racemic diastereomers; 70-90% *syn*-isomer (1*RS*,3*RS)* 10-30% *anti*-isomers (1*RS*,3*SR*))
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None of the impurities included in the technical material are considered relevant.
Molecular formula	$C_{30}H_{23}BrO$
Molecular mass	527.4 g/kg
Structural formula	

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

Physical and chemical properties

Melting point (state purity)	172.4-201.7°C (98.8%) 198.3-199.8°C (~100%)
Boiling point (state purity)	Decomposition before boiling
Temperature of decomposition	Decomposition before boiling
Appearance (state purity)	White powder (98-100%) Odourless (99-100%)
Relative density (state purity)	1.45-1.46 g/cm^3 at 20-21°C (98.7-98.8%)
Surface tension	71.3-72.1 mN/m at 20-21°C and a concentration of 1.47-17.4 mg/l (98.8-98.9%)
Vapour pressure (in Pa, state temperature)	2.13 x 10^{-8} Pa at 25°C (extrapolated; 100%) < 0.05 x 10^{-3} Pa at 45°C (99.9%)
Henry's law constant (Pa m^3 mol $^{-1}$)	4.25 x 10^{-4} Pa.m^3 mol^{-1} (using a published vapour pressure of 2.0 x 10^{-6} Pa at 20°C and a water solubility of 2.48 mg/l at pH 7) 8.99 x 10^{-7} Pa m^3.mol^{-1} (using a vapour pressure of 2.13 x 10^{-8} Pa at 25°C and a water solubility of 12.5 mg/L at 25°C in purified water)
Solubility in water (g/l or mg/l, state temperature)	In buffered solutions at 20°C: pH 4-5: 0.10-0.11 mg/l (98.7-98.8%) pH 7: 18.4 mg/l (98.7%) pH 9: 0.18 g/l (98.8%) pH 10: 1.23 g/l (98.7%) In purified water: 12.5 mg/l at 25°C (98.7%; pH not stated) 2.48 mg/l at 20°C (98.8%; pH 7)
Solubility in organic solvents (in g/l or mg/l, state temperature)	n-heptane: 3.1-3.4 mg/l at 15-25°C (98.8%) n-hexane: 7.15 mg/l at 25°C (100%) methanol: 6.93-15.0 g/l at 25°C (98.8-100%)
Stability in organic solvents used in biocidal products including relevant breakdown products	Not applicable. Neither technical bromadiolone as manufactured nor the representative products contain any organic solvents.
Partition coefficient (log P_{OW}) (state temperature)	In buffered solutions: pH 4-5: log P_{ow} = >5 (20-25°C; 98.7-98.8%) pH 6-7: log P_{ow} = 3.8-4.1 (20-25°C; 98.7-99.1%) pH 9-10: log P_{ow} = 2.5-3.2 (20-25°C; 98.7-98.8%) In purified water: log P_{ow} = 4.3 at 23°C (100%; pH not stated)

Hydrolytic stability (DT_{50}) (state pH and temperature)	See Chapter 4 below
Dissociation constant	Technically not feasible to experimentally determine the dissociation constant, due to low water solubility. Predicted pKa (ACD/PhysChem Suite): pKa_1=4.5 (deprotonation of the hydroxyl-group in the coumarine moiety of the enolic form of bromadiolone) pKa_2=9.06 (deprotonation of the carbon between the ketone and the lactone in the coumarine moiety of the keto form of bromadiolone)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	In buffered 96% ethanolic solution (98.4-99.5%): maxima: 259 nm (ε = 29637 $L.mol^{-1}.cm^{-1}$), 313 nm (ε = 13949 L $mol^{-1}.cm^{-1}$) In methanol (98%): maxima: 263 nm (ε = 32325 $L.mol^{-1}.cm^{-1}$), 310 nm (ε = 11095 L $mol^{-1}.cm^{-1}$)
Photostability (DT_{50}) (aqueous, sunlight, state pH)	See Chapter 4 below
Quantum yield of direct phototransformation in water at Σ > 290 nm	See Chapter 4 below
Flammability	Not highly flammable (technical material, purity not stated)
Explosive properties	Not explosive (theoretical consideration)

Classification and proposed labelling

with regard to physical/chemical data	None	
with regard to toxicological data	T+; R26/27/28, T; R48/23/24/25, Repr.Cat. 1 or 2; R61	
with regard to fate and behaviour data	None.	
with regard to ecotoxicological data	N, R50/53	
Specific concentration limits for human health	C ≥ 0.5% 0.25% ≤ C < 0.5% 0.025% ≤ C < 0.25% 0.0025% ≤ C < 0.025%	T+; R61-26/27/28 – T;R48/23/24/25 T+; R26/27/28 – T; R48/23/24/25 T; R23/24/25 – T; R48/23/24/25 Xn; R20/21/22 – R48/20/21/22

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	Method provided by LiphaTech (see further the Confidential Annex): 1. Qualitative step (spectroscopy, isomeric distribution, melting point) 2. Quantitative step (titration)

	Method provided by Task Force: HPLC-UV
Impurities in technical active substance (principle of method)	See the confidential Annex for the respective applicant

Analytical methods for residues

Soil (principle of method and LOQ)	HPLC-MS (LOQ 0.22 µg/kg) LC-MS/MS (LOQ 0.01 mg/kg)
Air (principle of method and LOQ)	HPLC-UV (LOQ 0.5 µg/m^3) No confirmatory method available-not considered needed due to the low vapour pressure
Water (principle of method and LOQ)	HPLC-FD (LOQ 0.05 µg/l), HPLC-MS (LOQ 0.05 µg/l) confirmation: LC-MS/MS
Body fluids and tissues (principle of method and LOQ)	LC-MS/MS (LOQs 0.05 mg/l blood, 0.05 mg/kg liver) LC-MS/MS (LOQs 0.01 mg/l blood, 0.01 mg/kg liver)
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Multi residue method: LC-MS/MS (LOQ 0.01 mg/kg cucumber and wheat) Single method: LC-MS/MS (LOQ 0.01 mg/kg lemon and oilseed rape)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	LC-MS/MS (LOQ 0.01 mg/kg meat)

Chapter 3: Impact on Human Health

(The critical values for risk assessment of both applicants are highlighted in bold)

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Bromadiolone was rapidly and extensively absorbed by rats. An exact oral absorption value could not be set based on LiphaTech data but maximum levels in the plasma were attained after 9 hours. **The oral absorption was >70% (71-77% based on carcass, urinary- and biliary excretion, Task Force data)** Absorption fairly slow with peak plasma levels of total radioactivity not being seen until 4-8 h post dose. Peak tissue concentrations of radioactivity were observed at 4 and 24 h post dose.
Rate and extent of dermal absorption:	Based on in vitro studies on products a value of 1.6% was obtained that was used for the risk assessment. However, data for both applicants suggest low absorption of wax block formulations i.e. approx 0.3% for SUPER CAID BLOC (LiphaTech). Based on an in vitro study of formulated active (bait:saline incorporated bromadiolone 0.00255 w/w) and a representative wax block formulation (0.005 %

	w/w) a worst case value of 0.36% was obtained that was used for this risk assessment (Task Force). No study on the pure active substance for LiphaTech or Task Force. **Based on MW (>500) and log Pow (>4) a default value of 10% can be estimated for the active substance if no other studies are available.**
Distribution:	Extensively bound to plasma proteins (>98.8%). Liver and GI tract were only tissues investigated. Radioactivity in the G.I tract at 48 hours accounted for a mean of 18.0% of the dose. The majority of the dose is eliminated unchanged in faeces via bile and no other tissues show evidence of any molecule retention (LiphaTech). Tissue levels above plasma levels, low dose: liver, adrenal glands, kidney, and spleen (1h post dose and 24h post dose) and thyroid (1h post dose) lungs (24h post dose). High dose: liver and kidney (1h post dose) and liver, kidney, adrenal glands and lungs. (24h post dose) (Task Force)
Potential for accumulation:	Bromadiolone has the potential for bioaccumulation in the liver. The liver half life is approximately 318 days (LiphaTech). 33-48% of dose was retained in the animal 7 days post dose, mainly in liver (Task Force).
Rate and extent of excretion:	Bromadiolone is excreted relatively slowly and almost entirely via the bile and faeces. As a maximum around 5% of radioactivity was excreted into urine (Task Force, but contained no parent bromadiolone). Around 20% of the bromadiolone dose was excreted unchanged into faeces.(Task Force)
Toxicologically significant metabolite(s)	The sole major metabolite was identified as a hydroxylated analogue of bromadiolone (hydroxlation proposed as occurring on the benzylic carbon atom). None of the metabolites identified for hydroxy coumarin derivatives used as rodenticides have been shown to be toxicologically significant (LiphaTech). Investigation of metabolites was not performed (Task Force)

Acute toxicity

Rat LD_{50} oral	1.31 mg/kg bw (male and female rats combined) 95% confidence limits 1.17 to 1.49 mg/kg bw/day (Task Force) Between 0.56 and 0.84 mg/kg bw (female rat) (LiphaTech) **R28**
Rat LD_{50} dermal	23.31 mg/kg bw (male and female rabbits combined) (Task Force) 1.71 mg/kg bw (male and female rats combined) (LiphaTech) **R27**

Rat LC_{50} inhalation	No data no study (Task Force) 0.43 µg/L (males and females combined) (LiphaTech) **R26**
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization (test method used and result)	Not a skin sensitizer

Repeated dose toxicity

Species/ target / critical effect	Anticoagulant effects (dog, rat, rabbit)
Lowest relevant oral NOAEL / LOAEL	Task Force: NOAEL 2.5 µg/ kg bw/day (rat) **NOAEL 0.5 µg/kg bw/day (rabbit)** LiphaTech: NOAEL 8 µg/ kg bw/day (dog) **R48/23/24/25**
Lowest relevant dermal NOAEL / LOAEL	No studies, not required
Lowest relevant inhalation NOAEL / LOAEL	No studies, not required

Genotoxicity	No genotoxic effects

Carcinogenicity

Species/type of tumour	Study waived
lowest dose with tumours	Study waived

Reproductive toxicity

Species/ Reproduction target / critical effect	Study waived
Lowest relevant reproductive NOAEL / LOAEL	Study waived
Species/Developmental target / critical effect	Rabbit, rat
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	Task Force: **Maternal toxicity (rabbit):** **LOAEL 2 µg/kg bw/day/ NOAEL < 2 µg/kg bw/day** **Developmental toxicity (rabbit):** **LOAEL 2 µg/kg bw/day/NOAEL 4 µg/kg bw/day** LiphaTech: Maternal toxicity (rabbit): LOAEL 4 µg/kg bw/day/ NOAEL 8 µg/kg bw/day Developmental toxicity: LOAEL >8 µg/kg bw/day/ NOAEL ≥8 µg/kg bw/day Maternal toxicity (rat): LOAEL 70 µg/kg bw/day/ NOAEL 35 µg/kg bw/day Developmental toxicity:

	LOAEL >70 µg/kg bw/day/ NOAEL ≥70 µg/kg bw/day **R61** (read across from warfarin)

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	No studies, not required
Lowest relevant developmental NOAEL / LOAEL.	No studies, not required

Other toxicological studies

.....	Studies in rats and dogs demonstrated the effectiveness of vitamin K as an antidote to anticoagulant intoxication. The effectiveness varied with duration of exposure to bromadiolone (LiphaTech).

Medical data

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

Summary	Value	Study	Safety factor
ADI (acceptable daily intake, external long-term reference dose)	Not required	Not required	Not required
ARfD (acute reference dose)	Not required	Not required	Not required
AEL-acute	**0.0023 µg/kg bw/day**	90-day rabbit (Task Force)	300*
AEL-medium, chronic	**0.0012 µg/kg bw/day**	Developmental toxicity study rabbit (Task Force)	600*

*Adjusted for 70% oral absorption in rat (Task Force)

Acceptable exposure scenarios (including method of calculation)

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

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 5; 25°C: not possible to calculate due to poor linear correlation. Assumed very little degradation at environmentally relevant conditions. (LT)
	pH 7; 25°C: not possible to calculate due to poor linear correlation. Assumed no significant degradation at environmentally relevant conditions. (LT) pH 7, 50°C: no hydrolysis of bromadiolone during the 120 days test. (TF)

	pH 9; 25°C: not possible to calculate due to poor linear correlation. Assumed no significant degradation at environmentally relevant conditions. (LT) pH 9, 50°C: no hydrolysis of bromadiolone during the 120 days test. (TF)
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	LiphaTech: Under artificial sunlight: DT_{50} = 11.5 minutes in buffer solution, pH 7 (corresponding to 29.4 minutes in "natural summer sunlight" at latitude 50°N). DT_{50} = 14.0 minutes in sterile pond water, pH 8.4 (corresponding to 36.0 minutes in "natural summer sunlight" at latitude 50°N). Task Force: Natural sunlight at latitude 52° N, aqueous solution: DT_{50} = 2.98 minutes (summer) and 30.4 minutes (winter) at a quantum yield of 0.25. DT_{50} = 74.5 minutes (summer) and 768 minutes (winter) at a quantum yield of 0.01. Photolysis was biphasic with a combination of the two above rates. Metabolites not identified by any of the applicants.
Readily biodegradable (yes/no)	No (both applicants)
Biodegradation in seawater	Not applicable (exposure to seawater unlikely).
Non-extractable residues	Not applicable (exposure to aquatic systems unlikely).
Distribution in water / sediment systems (active substance)	Not applicable (exposure to aquatic systems unlikely).
Distribution in water / sediment systems (metabolites)	Not applicable (exposure to aquatic systems unlikely).

Route and rate of degradation in soil

Mineralization (aerobic)	1.7 to 22.9% after *ca* 100 days. (LT) Study waived (TF)
Laboratory studies (range or median, with number of measurements, with regression coefficient)	LiphaTech: DT_{50lab} (20°C, aerobic): At 20°C DT_{50} value 2 to 7days (4 soils, 40% MWHC). At 25°C DT_{50} value 19 days (1 soil, 75% 1/3 bar moisture). At 12°C (calculated from the above values) DT_{50} value 4 to 53 days (5 soils). Task Force: Study waived
	LiphaTech DT_{90lab} (20°C, aerobic): At 20°C DT_{90} value 14 to 49 days (4 soils, 40% MWHC). At 25°C DT_{90} value 585 days (1 soil, 75% 1/3 bar moisture). At 12°C (calculated from the above values) DT_{90} value

	26 to 1630 days (5 soils) Task Force: Study waived
	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	No degradation (TF) Study waived (LT)
Soil photolysis	Not applicable
Non-extractable residues	8.8 to 21% after *ca* 100 days. (LT) Study waived (TF)
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	LiphaTech: Degradation of bromadiolone led to the formation of five unidentified metabolites which were present in significant quantities: Ketone/M2 21.1 % of AR (14 d, 25°C) 39.6 % of AR (28 d, 20°C) M4 15.9 % of AR (56 d, 20°C) M5 14.3 % of AR (56 d, 20°C) Unk 1 19.2 % of AR (120 d, 25°C) Unk 3/M9 24.8 % of AR (270 d, 25°C) 24.8 % of AR (154 d, 20°C) Task Force: Study waived, metabolites not identified.
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)	LiphaTech: Soil distribution (partition) coefficient (K_D): 5.3 to 10.4 mL/g (adsorption) 13.2 to 22.3 mL/g (desorption). Freundlich soil adsorption coefficient (K_F): 5.3 to 10.4 mL/g (adsorption) 13.2 to 22.3 mL/g (desorption). Freundlich soil adsorption coefficient normalised for organic carbon content (K_{OC}): 1563 to 1709 mL/g (adsorption) 2157 to 6651 (desorption). No pH dependence observed. Task Force: Soil distribution (partition) coefficient (K_D): 71.2-1250 mL/g (adsorption) Soil adsorption coefficient normalised for organic carbon content (K_{OC}): 3530 to 41600 mL/g (adsorption), average value 14770 mL/g used for calculations.

	No pH dependence observed. Bromadiolone is considered slightly mobile to non-mobile in soil.

Fate and behaviour in air

Direct photolysis in air	The photochemical oxidative degradation half-life of bromadiolone in air was estimated using the EPIWIN v 3.12, which is based on the structure activity relationship (QSAR's). The half-lives for the hydroxyl and ozone reactions in air are estimated to be 2.09 and 2.015 hours respectively, indicating that if present in air, bromadiolone would not be expected to persist. (both applicants)
Quantum yield of direct photolysis	Not determined.
Photo-oxidative degradation in air	Latitude: n.a Season: n.a DT_{50} n.a
Volatilization	Vapour pressure at ambient temperature is 2.13×10^{-8} Pa (OECD 104) (LT); 2.0×10^{-6} Pa (TF) Henry's law constant = 8.99×10^{-7} $Pa.m^3$ mol^{-1} (based on a water solubility of 12.5 mg/L) (LT); . 4.25×10^{-4} $Pa.m^3$ mol^{-1} (TF) Bromadiolone is therefore not considered volatile and is not expected to volatilise to air in significant quantities.

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} = >8.0 mg/L (nominal) (LT) LC_{50} = 2.86 mg/L (nominal) (TF)
Invertebrates			
Daphnia magna	48 hours	lethality immobilisation	LC_{50} = 2.0 mg/L (LT) EC_{50} = 5.79 mg/L (nominal) (TF)
Algae			

Scenedesmus subspicatus *Pseudokirchneriella subcapitata*	96 hours (72 hours) 72 hours	growth inhibition (b) growth inhibition (gr) growth inhibition (gr)	E_bC_{50} = 0.17 mg/L (LT) (E_rC_{50} = 1.0 mg/L) E_rC_{50} = 1.14 mg/L (TF) (geometric mean of the initial measured conc. and half the LOQ)
Microorganisms			
Activated sludge	3 hours	respiration inhibition	EC_{50} = 31.6 mg/L (nominal) (LT) EC_{50} = 132.8 mg/L (extrapolated) (TF)

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia fetida*	14-day LC_{50} > 8.4 mg/kg wet soil (synthetic OECD substrate) (LT) 13 days LC_{50} = 918 mg/L wet soil (TF)
Reproductive toxicity to ……	Waived

Effects on soil micro-organisms

Nitrogen mineralization	Waived
Carbon mineralization	Waived

Effects on terrestrial vertebrates

Acute toxicity to mammals	LD_{50} between 0.56 and 0.84 mg/kg bw (rat) (LT) LD_{50} = 1.31 mg/kg bw (rat) (TF)
Acute toxicity to birds	LD_{50} = 138 mg/kg bw (bobwhite quail) (LT) LD_{50} = 134 mg/kg bw (Japanese quail) (TF)
Dietary toxicity to birds	5-day LC_{50} = 62 mg/kg food (bobwhite quail) (LT) 10-day LC_{50} = 28.9 mg/kg food (partridge, study presented as acute study) (TF)
Dietary toxicity (secondary poisoning) to birds	7-day LD_{100} = 0.056 mg/kg bw/d (great horned owl) (LT)
Reproductive toxicity to birds	NOEC = 0.1 mg/kg food (Japanese quail, tested substance difenacoum) (LT) NOEC = 0.26 mg/L drinking water (Japanese quail) (TF)

Effects on honeybees

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

Effects on other beneficial arthropods

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

Acute toxicity to ……..	Not applicable.

Bioconcentration

Bioconcentration factor (BCF)	LiphaTech: Whole fish: 460 (*Lepomis macrochirus*). BCF (calculated from a log K_{ow} of 4.07) = 575 Task Force: Bioconcentration tests failed due to high mortalities. BCF (calculated from a log K_{ow} of 3.8) = 339
Depuration time (DT_{50}) (DT_{90})	> 14 days (LT)
Level of metabolites (%) in organisms accounting for > 10 % of residues	Metabolites not quantified.

Chapter 6: Other End Points

Appendix II: List of Intended Uses

Product/ Site of use	Field of use/ Product type	Organisms controlled	Application type	Number and timing of application	Re-marks
Super Caid Bloc, wax blocks Sewers	MG03: Pest control. Product type 14.	Rats (*Rattus* spp.)	User category – Professional only, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	90 g of product every 3 to 6 m over area of infestation. The bait points are visited on a regular basis (for example 1, 3, 7, 14, 21 days) and any consumed or spoilt rodenticide is replenished or replaced. Once consumed the product is effective over a period of 3 to 6 days.	--
Super Caid Bloc, wax blocks In and around buildings	As above	Rats (*Rattus* spp.) and mice (*Mus* spp.)	User category – Professional and Non-professional, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	As above	--
Super Caid Bloc, wax blocks Open areas	As above	Rats (*Rattus* spp.) and mice (*Mus* spp.)	User category – Professional only, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	100 g of product applied to each burrow, burrows treated on typically two occasions. Once consumed the product is effective over a period of 3 to 6 days.	--
Super Caid Bloc, wax blocks Waste dumps	As above	Rats (*Rattus* spp.) and mice (*Mus* spp.)	User category – Professional only, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use), in sachets only	90 g of product every 3 to 6 m over area of infestation. The bait points are visited on a regular basis (for example 1, 3, 7, 14, 21 days) and any consumed or spoilt rodenticide is replenished or replaced. Once consumed the product is effective over a period of 3 to 6 days.	--
Super Caid AS Appat, grains In and around	As above	Rats (*Rattus* spp.) and mice (*Mus*	User category – Professional and Non-professional, Method - Manual application, Application aim – Control,	As above	--

Product/ Site of use	Field of use/ Product type	Organisms controlled	Application type	Number and timing of application	Re-marks
buildings		spp.)	Type of formulation – bait (ready for use).		
Super Caid AS Appat, grains Open areas	As above	Rats (*Rattus* spp.) and mice (*Mus* spp.)	User category – Professional only, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	100 g of product applied to each burrow, burrows treated on typically two occasions. Once consumed the product is effective over a period of 3 to 6 days.	--
Super Caid AS Appat, grains Waste dumps	As above	Rats (*Rattus* spp.) and mice (*Mus* spp.)	User category – Professional only, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use), in sachets only	90 g of product every 3 to 6 m over area of infestation. The bait points are visited on a regular basis (for example 1, 3, 7, 14, 21 days) and any consumed or spoilt rodenticide is replenished or replaced. Once consumed the product is effective over a period of 3 to 6 days.	--
Protect-B, wax blocks Sewers	As above	Rats (*Rattus* spp.)	User category – Professional only, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	20-200 g block/cesspool, Maximum 100 bait points treated (max 60/day). 21-day campaign, most of the bait is applied during the first week	--
Protect-B, wax blocks In and around buildings	As above	Rats (*Rattus* spp.)	User category – Professional and Non-professional, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	10 x 20 g blocks/bait point; bait points 5-10 m apart. 21-day campaign, repeated 2-3 times a year. Professionals: maximum 60 bait points treated/day plus remains of 15 bait points collected. Non-professionals: maximum 5 bait points treated/day plus remains of 5 bait points collected.	--
Protect-B, wax blocks In and around buildings	As above	Mice (*Mus* spp.)	User category – Professional and Non-professional, Method - Manual application, Application aim – Control, Type of formulation – bait (ready for use).	2 x 20 g blocks/bait point; bait points 5-10 m apart. 21-day campaign, repeated 2-3 times a year. Professionals: maximum 60 bait points treated/day plus remains of 15 bait points collected. Non-professionals: maximum 5 bait points treated/day plus remains of 5 bait points collected.	--

Appendix III: List of studies

Data protection is claimed by the applicants in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. For studies marked Yes(i) data protection is claimed under Article 12.1(c) (i), for studies marked Yes(ii) data protection is claimed under Article 12.1(c) (ii). These claims are based on information from the applicants. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

LiphaTech S.A.S

Section No. in Doc III A	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 2/ A2.7/01	Schmit, T.J.	2003	Analysis of Maki technical Liphatech Inc. laboratory report no. None GLP/Unpublished *This report contains confidential information.*	Y	Lipha
Section 2/ A2.7/02	Caruel, H	2005	Bromadiolone active ingredient 5 batch analysis. Lipha SA, Report No. BRO0510B. GLP, Unpublished. *This report contains confidential information.*	Y	Lipha
Section 2/ A2.8.9/01	Schmit, T.J.	2003	Analysis of Maki technical Liphatech Inc. laboratory report no. None GLP/Unpublished *This report contains confidential information.*	Y	Lipha
Section 2/ A2.8.9/02	Caruel, H	2005	Bromadiolone active ingredient 5 batch analysis. Lipha SA, Report No. BRO0510B. GLP, Unpublished. *This report contains confidential information.*	Y	Lipha
Section 3/ A3.1.1/01	Sarff, P	2002a	Determination of melting point/melting range for bromadiolone. ABC Laboratories America, Inc., laboratory report no. 47069. GLP/Unpublished.	Y	Lipha
Section 3/ A3.1.1/02	Pesselman, R.	1990a	Melting point/melting range determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-607. GLP/Unpublished.	Y	Lipha
Section 3/ A3.1.2/01	Jackson, W.	2002	Boiling point – bromadiolone. Syngenta technology and projects, laboratory report no. HT02/291. GLP/Unpublished.	Y	Lipha

Section No. in Doc III A	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 3/ A3.1.3/01	Sarff, P., Locke, J.	2002	Determination of density for bromadiolone. ABC Laboratories America, Inc., laboratory report no. 47070. GLP/Unpublished.	Y	Lipha
Section 3/ A3.1.3/02	Pesselman, R.	1990b	Density determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-608. GLP/Unpublished.	Y	Lipha
Section 3/ A3.2/01	Pesselman, R.	1991a	Vapor pressure determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-659. GLP/Unpublished.	Y	Lipha
Section 3/ A3.2.1/01	Curl, M	2003	The Calculation of Henry's Law Constant for Bromadiolone. TSGE laboratory report no. 12-1-11.HL Not GLP/Unpublished	Y	Lipha
Section 3/ A3.3.1/01	Farrell, M	2002	Physical state determination of bromadiolone technical. LiphaTech, Inc., laboratory report no. 02117. GLP/Unpublished.	Y	Lipha
Section 3/ A3.3.1/02	Pesselman, R.	1990c	Physical state determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-605. GLP/Unpublished.	Y	Lipha
Section 3/ A3.3.2/01	Farrell, M	2002	Color determination of bromadiolone technical. LiphaTech, Inc., laboratory report no. 02116. GLP/Unpublished.	Y	Lipha
Section 3/ A3.3.2/02	Pesselman, R.	1990d	Munsell color determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-604. GLP/Unpublished.	Y	Lipha
Section 3/ A3.3.3/01	Pesselman, R.	1990e	Odor determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-606. GLP/Unpublished.	Y	Lipha
Section 3/ A3.4/01	Queche, P.	1999	NMR, MS, IR, UV/vis spectra. bromadiolone active ingredient. Lipha s.a., laboratory report no. ASBROR200-99. Not GLP/Unpublished.	Y	Lipha

Section No. in Doc III A	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 3/ A3.5/01	Hahn, J	2002a	Determination of water solubility (column elution method – pH4 and 7 / shake flask method – pH10) for bromadiolone. ABC Laboratories America, Inc., laboratory report no. 47071. GLP/Unpublished.	Y	Lipha
Section 3/ A3.5/02	Pesselman, R.	1992	Solubility determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-658. GLP/Unpublished.	Y	Lipha
Section 3/ A3.6/01	Hahn, J	2002b	Determination of dissociation constant for bromadiolone. ABC Laboratories America, Inc., laboratory report no. 47075. GLP/Unpublished.	Y	Lipha
Section 3/ A3.7/01	Pesselman, R.	1992	Solubility determination of bromadiolone (BDN). Hazleton Laboratories America, Inc., laboratory report no. HLA 6001-658. GLP/Unpublished.	Y	Lipha
Section 3/ A3.9/01	Sarff, P	2002b	Determination of n-octanol/water partition coefficient (shake flask method) for bromadiolone. ABC Laboratories America, Inc., laboratory report no. 47074. GLP/Unpublished.	Y	Lipha
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Section 3/ B1 3.4-01	Tremain, S.	2003	Supercaid Bloc: determination of hazardous physico-chemical properties. SafePharm Laboratories Limited, laboratory report no. 1840/007. GLP/Unpublished.	Y	Lipha
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Section 3/ B1 3.7-02	Carter, R.	1993	Storage stability determination of Maki MiniBlocks. LiphaTech Inc. report no. 92028. GLP/Unpublished.	Y	Lipha
Section 3/ B1 3.7-03	Evans, A	2003	Protocol: Supercaid Bloc: Determination of long term stability and physico-chemical characteristics. SafePharm Laboratories Limited, laboratory report no. 1840/005. GLP/Unpublished.	Y	Lipha
Section 3/ B1 3.7-04	Wooley, A., Mullee, D.	2003	Supercaid Bloc: determination of accelerated storage stability and physico-chemical characteristics. SafePharm Laboratories Limited, laboratory report no. 1840/004. GLP/Unpublished.	Y	Lipha
Section 4/ B1 4.1-01	Woolley, A.J. and Mullee, D.M.	2003	Supercaid Bloc: Determination of method validation. SafePharm Laboratories, Report No. 1840/006. GLP, Unpublished.	Y	Lipha
Section 5/ B1 5.10-01	Lorgue, G.	1998a	Study on the efficacy of bromadiolone blocks in the rat, wild strain, rattus Norvegicus. Laboratoire de Toxicologie, ENVL, laboratory report no.P98.01 Non GLP/Unpublished	Y	Lipha
Section 5/ B1 5.10-02	Lorgue, G.	1998b	Study on the efficacy of bromadiolone blocks in the mouse, wild strain, mus musculus. Laboratoire de Toxicologie, ENVL, laboratory report no. P98.02 Non GLP/Unpublished	Y	Lipha
Section 5/ B1 5.10-03	Orth, M.S.	1991	Miniblock product comparison in albino mice. LiphaTech Inc. laboratory report no. 91039. GLP/Unpublished	Y	Lipha
Section 5/ B1 5.10-04	Orth, M.S.	1990a	Bromadiolone: Maki Miniblock in albino mice. LiphaTech Inc. laboratory report no. 90068 GLP/Unpublished	Y	Lipha
Section 5/ B1 5.10-05	Orth, M.S.	1990b	Bromadiolone: Maki Miniblock in Swiss Webster mice. LiphaTech Inc. laboratory report no. 90201. GLP/Unpublished.	Y	Lipha
Section 5/ B1 5.10-06	Orth, M.S.	1990c	Bromadiolone: Maki Miniblocks in Swiss Webster mice. LiphaTech Inc. laboratory report no. 90199. GLP/Unpublished.	Y	Lipha

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Section 5/ B1 5.10-07	Orth, M.S.	1990d	Bromadiolone: Maki Miniblocks in Wistar rats. LiphaTech Inc. laboratory report no. 90206. GLP/Unpublished.	Y	Lipha
Section 5/ B1 5.10-08	Orth, M.S.	1990e	Bromadiolone: Maki Miniblocks in Wistar rats. LiphaTech Inc. laboratory report no. 90200. GLP/Unpublished.	Y	Lipha
Section 5/ B1 5.10-09	Orth, M.S.	1990f	Bromadiolone: Maki Miniblocks in Wistar rats. LiphaTech Inc. laboratory report no. 90067. GLP/Unpublished.	Y	Lipha
Section 6/ B1 6.1.1-01	Glaza, S.M.	1993	Acute oral toxicity study (Limit test) of Maki paraffin block with bitrex in rats. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 41200808 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.1.1-02	Myers, R.C. and Christopher, S.M	1993	Maki mini blocks: Acute peroral Toxicity study in the rat (limit test). Bushy Run Research Center, Export, PA, USA. Laboratory report no. 93N1259 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.1.2-01	Glaza, S.M.	1993	Acute Dermal Toxicity Study (Limit test) of Maki paraffin block with bitrex in Rabbits. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 41200809 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.1.2-02	Parker, R.M.	1992	Dermal limit study of maki mini blocks administered to New Zealand White rabbits. TSI Redfield Laboratories, Redfield, AR, USA. Laboratory report no. 008-0006 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.2-01	Glaza, S.M.	1993a	Primary Dermal Irritation Study of Maki paraffin block with bitrex in Rabbits. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 41200810 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.2-02	Glaza, S.M.	1993b	Primary Dermal Irritation Study of Maki Mini blocks in rabbits. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 30702257 GLP/Unpublished	Y	Lipha

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Section 6/ B1 6.2-03	Glaza, S.M.	1993c	Primary Eye Irritation Study of Maki paraffin block with bitrex in Rabbits. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 41200811 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.2-04	Shapiro, R.	1977	Eye Irritation in the rabbit. Product Safety Labs, East Brunswick, NJ, USA. Laboratory report no. PSL T-215 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.3-01	Glaza, S.M.	1993	Dermal sensitisation study of MAKI paraffin block with bitrex in Guinea pigs – closed patch technique. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 41200812 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.3-02	Glaza, S.M.	1994	Dermal sensitisation study of MAKI mini blocks in Guinea pigs – Closed Patch technique. Hazleton Wisconsin, Madison, Wisconsin, USA. Laboratory report no. HWI 30702259 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.6-01	Snowdon, P.J.	2003	Pilot study to determine primary sources of exposure to operators during simulated use of anticoagulant rodenticide baits. Synergy Laboratories Limited laboratory report no. SYN/1301 GLP/Unpublished	Y	Lipha
Section 6/ B1 6.6-02	Chambers, J.G., Snowdon, P.J.	2004	Study to determine potential exposure to operators during simulated use of anticoagulant rodenticide baits. Synergy Laboratories Limited laboratory report no. SYN/1302 GLP/Unpublished	Y	Lipha

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	World Health Organisation	1995	Environmental Health Criteria For Anticoagulant Rodenticides, ISBN: 92-4-157175-6	N	Public domain
A2.7	Garofani, S	2004	Draft Report: Bromadiolone technical analysis of five batch samples, Chem Service S.r.l., CH-039/2004, GLP, (Un)	Y	Task Force
A2.8	Garofani, S	2004	Draft Report: Bromadiolone technical analysis of five batch samples, Chem Service S.r.l., CH-039/2004, GLP, (Un)	Y	Task Force

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A3.1	Anderson W	1999	Product Chemistry: Technical Grade Product Stillmeadow Incorporated report 4745-98GLP, Unpublished	Y	Task Force
A3.1	Mullee B.J., O'Connor D.M.	2006	Bromadiolone Technical: Determination of general physico-chemical properties SPL Project Number: 2073/002 GLP, Unpublished	Y	Task Force
A3.2	Fabbrini Dr R	1997	BROMADIOLONE Determination of the Vapour Pressure. ChemService report CH-14/96-C-BDL GLP, Unpublished	Y	Task Force
A3.2.1	SafePharm Laboratories	2004	US EPA, EPIWIN v3.12, EPI Suite Software, 2004	Y	Task Force
A3.3	Anderson W	1999	Product Chemistry: Technical Grade Product Stillmeadow Incorporated report 4745-98 GLP, Unpublished	Y	Task Force
A3.3	Drake R.M.	2005	Determination of the Direct Photolysis Rate in Water by Sunlight of Bromadiolone, Chemex Environmental International Limited, Cambridge, UK Chemex reference: ENV6766/080319 GLP, Unpublished	Y	Task Force
A3.4	Anderson W	1999	Product Chemistry: Technical Grade Product Stillmeadow Incorporated report 4745-98GLP, Unpublished	Y	Task Force
A3.4	Drake R.M.	2005	Determination of the Direct Photolysis Rate in Water by Sunlight of Bromadiolone, Chemex Environmental International Limited, Cambridge, UK Chemex reference: ENV6766/080319 GLP, Unpublished	Y	Task Force
A3.4	Novak L	2005	IR, MS, ^{1}H- and ^{13}C-NMR Spectra of Bromadiolone, Budapest University of Technology and Economics, Institute for Organic Chemistry	Y	Task Force
A3.5	Anderson W	1999	Product Chemistry: Technical Grade Product Stillmeadow Incorporated report 4745-98GLP, Unpublished	Y	Task Force
A3.5	Mullee B.J., O'Connor D.M.	2006	Bromadiolone Technical: Determination of general physico-chemical properties SPL Project Number: 2073/002 GLP, Unpublished	Y	Task Force

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A3.7	Mullee B.J., O'Connor D.M.	2005	Bromadiolone Technical: Determination of solubility in organic solvents and surface tension. SPL Project Number : 2073/001 GLP, Unpublished	Y	Task Force
A3.9	Anderson W	1999	Product Chemistry: Technical Grade Product Stillmeadow Incorporated report 4745-98GLP, Unpublished	Y	Task Force
A3.9	Mullee B.J., O'Connor D.M.	2005	Bromadiolone Technical: Determination of partition coefficient SPL Project Number: 2073/003 GLP, Unpublished	Y	Task Force
A3.10	Anderson W	1999	Product Chemistry: Technical Grade Product Stillmeadow Incorporated report 4745-98GLP, Unpublished	Y	Task Force
A3.10	Mullee B.J., O'Connor D.M.	2006	Bromadiolone Technical: Determination of general physico-chemical properties SPL Project Number: 2073/002 GLP, Unpublished	Y	Task Force
A3.13	Mullee B.J., O'Connor D.M.	2005	Bromadiolone Technical: Determination of solubility in organic solvents and surface tension. SPL Project Number : 2073/001 GLP, Unpublished	Y	Task Force
A4.1 (1)	Garofani, S	2004	Draft Report: Bromadiolone technical validation of the analytical method for the impurities determination, Chem Service S.r.l., CH-038/2004, GLP, (Un)	Y	Task Force
A4.1 (2)	Garofani, S	2004	Draft Report: Bromadiolone technical validation of the analytical method for the active ingredient determination, Chem Service S.r.l., CH-037/2004, GLP, (Un)	Y	Task Force
A4.2 (a)/01	Morlacchini, M.	2006	Residues Determination of Brodificoum, Difenacoum and Bromadiolone in Soil: Final Report for Bromadiolone Residue Determination. CERZOO. Project Code: CZ/05/002/ACTIVA/SOIL GLP, Unpublished	Y	Task Force
A4.2 (a)/02	Morlacchini, M.	2009	Residues determination of Brodifacoum, Difenacoum and Bromadiolone in soil. Supplement n.2 to the Final Report: Bromadiolone residue determination. CERZOO (Italy), Study CZ/05/002/Activa/Soil GLP, Unpublished	Y	Task Force

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A4.2 (b)	Martinez, M. P.	2005	Bromadiolone Technical: Validation of the Analytical Method for the Determination of the Residues in Drinking, Ground and Surface Waters. ChemService S.r.l. ChemService Study No. CH-290/2005 GLP, Unpublished	Y	Task Force
A4.2 (d)/01	Papa Dr P, Rocchi Dr L	2001	Methods of analysis of the rodenticide residues in human and animal body fluids and tissues, IRCCS Policlinico San Matteo of Pavia: Analytical Clinical Toxicology Laboratory. GLP, Unpublished	Y	Task Force
A4.2 (d)/02	Marshall, L.	2010a	Method validation for the determination of bromadiolone in animal matrices (liver and blood), CEM Analytical Services Limited (CEMAS), Report No.CEMS-4550. GLP, Unpublished	Y	Task Force
A4.3/01	Turnbull, G.	2005	Validation of Analytical Methodology to Determine Rodenticides in Food Matrices. Central Science Laboratory unpublished report number PGD-180, 16 June 2005. GLP, Unpublished	Y	CEFIC
A4.3/02	Marshall, L.	2010b	Method validation for the determination of Bromadiolone in crop matrices (oilseed rape seed and lemon), CEM Analytical Services Limited (CEMAS), Report No. CEMR-4559. GLP, Unpublished	Y	Task Force
A5	Brunton, C.F.A., Macdonald, D.W. and Buckle, A.P.	1993	Behavioural resistance towards poison baits in Brown rats. Applied Animal Behaviour Science.	N	Public Domain
A5	Gill, J.E., Kerins, G.M. and MacNicoll, A.D.	1992	Inheritance of low grade brodifacoum resistance in the Norway rat. Journal of Wildlife Management 56, 809-816.	N	Public Domain
A5	Greaves, J. H., Shepherd, D. S and Quy, R.	1982	Field trials of second-generation anticoagulants against difenacoum-resistant Norway rat populations. Journal of Hygiene, Cambridge 89, 295-301.	N	Public Domain
A5	Humphries, R.E., Meeham, A.P. and Sibly, R.M.	1992	The characteristics and history of behavioural resistance in inner-city house mice in the UK. In: Borrecco, J.E. and Marsh, R.E. (eds.) 15th Vertebrate Pest Conference. University of California, Davis, pp. 161-164.	N	Public Domain
A5	Lund, M.	1984	Resistance to the second-generation anticoagulant rodenticides. In: Clark, D. O. (ed.) 11th Vertebrate Pest Conference. University of California, Davis pp 89-94	N	Public Domain

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A5	MacNicoll, A. D. and Gill, J. E.	1987	The occurrence and significance of rodenticide resistance in the UK. In : Lawson, T. J. (ed.) Stored Products Pest Control. British Crop Protection Council Monograph No. 37. BCPC Publications, Thorton Heath, UK, pp. 89-95	N	Public Domain
A5	Misenheimer, T.M. and Suttie, J.W.	1990	Warfarin resistance in a Chicago strain of rats. Biochemical Pharmacology 40, 2079-2084.	N	Public Domain
A5	Quy, R. J. , Shepherd, D. S. and Inglis, I. R.	1992a	Bait avoidance and effectiveness of anticoagulant rodenticides against warfarin- and difenacoum-resistant populations of Norway rats. Crop Protection. 11, 14-20.	N	Public Domain
A5	Quy, R. J., Cowan, D. P., Haynes, P., Inglis, I. R. and Swinney, T.	1992b	The influence of stored food on the effectiveness of farm rat control. In: Pests and Diseases. British Crop Protection Council Monograph No. 42. BCPC Publications, Thornton Health, UK, pp. 291-300	N	Public Domain
A6.1.1	Sebestyen I	1996	Acute Oral Toxicity Study of Test Substance Technical Bromadiolone in Rats. Toxicological Research Centre Ltd. Report 96/299-001P GLP, Unpublished	Y	Task Force
A6.1.2	Sebestyen I	1996	Acute Dermal Toxicity Study of Test Substance Technical Bromadiolone in Rats. Toxicological Research Centre Ltd. Report 96/299-002P GLP, Unpublished	Y	Task Force
A6.1.4 (1)	Kuhn JO	1999	Technical Bromadiolone - Report: Primary Dermal Irritation Study in Rabbits. Stillmeadow Incorporated. Report 4743-98 GLP, Unpublished	Y	Task Force
A6.1.4 (2)	Kuhn JO	1999	Technical Bromadiolone - Report: Primary Eye Irritation Study in Rabbits. Stillmeadow Incorporated. Report 4742-98 GLP, Unpublished	Y	Task Force
A6.1.5(1)	Kuhn J	1999	Dermal Sensitization Study in Guinea Pigs. Stillmeadow Incorporated. Report 4770-98 GLP, Unpublished	Y	Task Force
A6.1.5(2)	Stahl, Janos	2004	Draft Report: Skin sensitisation of test item Bromadiolone Technical in Guinea pigs by Buehler method. LAB International Research Centre Hungary Ltd	Y	Task Force

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A6.2 (1)	Punler, MJ	2008	The Metabolism of [^{14}C]-Bromadiolone in the Rat. Charles River Laboratories. Report 29088 GLP, Unpublished	Y	Task Force
A6.2 (2)	Parmar G, Bratt H, Moore R & Batten PL	1987	Evidence for common binding site in vivo for the retention of anticoagulants in rat liver. Published Report Hum Toxicol, 6: 431-432.	N	Public Domain
A6.2 (3)	Allen C. Ray, Michael J. Murphy, Michael D. DuVall and John C. Reagor	1989	Determination of brodifacoum and bromadiolone residues in rodent and canine liver. Published Report Am J Vet Res, Vol 50, No. 4, April 1989, 546-550.	N	Public Domain
A6.2 (4)	Toner F	2008	The In Vitro Percutaneous Absorption of Radiolabelled Bromadiolone in Two Test Preparations Through Human Skin, Charles River Laboratories, Study No. 780513, Report No. 28712. GLP, Unpublished	Y	Task Force
A6.3.1	Szakonyi IP	2002	28-day Preliminary study of 90-day Repeated Dose Oral Toxicity Study of Test Item Bromadiolone Technical in Rats. GLP, Unpublished	Y	Task Force
A6.4.1	Béres E	2004	Draft Report: 90-day repeated dose oral toxicity study of bromadiolone technical in rabbit, LAB International Hungary Ltd, 03/735-101N, GLP, (Un)	Y	Task Force
A6.6.1	Hernadi D	2001	Draft report: Bromadiolone Technical: Testing of Bromadiolone Technical with Bacterial Reverse Mutation Assay. Toxicological Research Centre Ltd. report 01/617-007M GLP, Unpublished	Y	Task Force
A6.6.2	Béres E	2001	Draft report: BROMADIOLONE: In Vitro Mammalian Chromosomal Aberration study of Test item Bromadiolone Technical. Toxicological Research Centre Ltd. report 01/617-020C GLP, Unpublished	Y	Task Force
A6.6.3	Béres E	2001	Draft report: BROMADIOLONE: Mutagenic Evaluation of Test Item Bromadiolone Technical in CHO/HPRT Assay. Toxicological Research Centre Ltd. report 01/617-015C GLP, Unpublished	Y	Task Force

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A6.8.1	Druga A	2004	Draft report: Teratology Study with test item Bromadiolone Technical in Rabbits. Toxicological Research Centre Ltd. GLP, Unpublished	Y	Task Force
A6.8.2	Szakonyi IP	2004	Two generation reproduction toxicity study of test item bromadiolone technical in rats. Toxicological Research Centre Ltd. Report 03/735-202PR GLP, Unpublished	Y	Task Force
A6.12.3	Davanzo F, Faraoni L, Pirina A, Sesana F, Pannacciulli E	2001	Information about and toxicity of anticoagulant rat poisons: Case Histories from the Milan Poisons Centre 1996-1999 Unpublished	Y	Task Force
A7.1.1.1.1	Laky V	2001	Draft report: Hydrolysis of Bromadiolone as a function of pH. Toxicological Research Centre Ltd. Report 01/617-336AN GLP, Unpublished	Y	Task Force
A7.1.1.1.2	Drake, RM	2005	Determination of the Direct Photolysis Rate is Water by Sunlight of Bromadiolone, Chemex Environmental International Ltd, ENV6766/080319-REISSUE, GLP, Unpublished.	Y	Task Force
A7.1.1.2.1	Gaty S	2002	Draft report: Determination of Biodegradability of BROMADIOLONE TECHNICAL test item with Closed Bottle Test. Toxicological Research Centre Ltd. Report 01/617-322AN GLP, Unpublished	Y	Task Force
A7.1.1.2.2	Drake, R	2005	Determination of the inherent biodegradability of Bromadiolone, Chemex Environmental International Limited, Chemex Reference no: ENV6988/080319, GLP, Unpublished	Y	Task Force
A7.1.2.1.2	Drake, R	2005	Determination of the anaerobic biodegradability of Bromadiolone, Chemex Environmental International Ltd, Study report: ENV6989/110414, GLP, Unpublished	Y	Task Force
A7.1.3	O'Connor B.J and Woolley S.M.	2007	Bromadiolone: Determination of Adsorption Coefficient, SafePharm Laboratories Ltd., SPL Project Number: 2073/0005., GLP, Unpublished	Y	Task Force
A7.3.1	SafePharm Laboratories	2004	US EPA, EPIWIN v3.12, EPI Suite Software, 2004	Y	Task Force
A7.4.1.1	Scheerbaum D	2007	Bromadiolone Fish (rainbow trout), acute toxicity test, semi-static, 69h, Dr U. Noack-laboratorien, Study No FAR113101 GLP, Unpublished	Y	Task Force

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A7.4.1.2	Noack M	2007	Bromadialone Acute immobilization test (static, 48h) *Daphnia magna*, Dr U. Noack-Laboretorien, Study No DAI113101 GLP, Unpublished	Y	Task Force
A7.4.1.3	Scheerbaum D	2007	Bromadiolone Alga, Growth inhibition test with *Pseudokirchneriella subcapitata*, 75 h, Dr U.Noack-Laboratorien, Study No SPO113101 GLP, Unpublished	Y	Task Force
A7.4.1.4 (1)	Gaty S	2002	Draft Report: Activated Sludge, Respiration Inhibition Test with BROMADIOLONE TECHNICAL Test Item. Toxicological Research Centre Ltd. Report –01/617-027AS GLP, Unpublished	Y	Task Force
A7.4.1.4 (2)	Staniland, JD	2004	An evaluation of the effect of Bromadiolone on the respiration rate of actived sludge, Chemex Environmental International Ltd, ENV7144, GLP, Unpublished	Y	Task Force
A7.4.2	SafePharm Laboratories	2004	US EPA, EPIWIN v3.12, EPI Suite Software, 2004	Y	Task Force
A7.4.3.3.1	Stittle, D, & Sacker, DJ	2004	The Bioconcentration Potential of Bromadiolone in Rainbow Trout (Oncorhynchus mykiss) under flow-through conditions, Chemex Environmental International Ltd, ENV6552/080319, GLP, (Un)	Y	Task Force
A7.4.3.5.2	Vryenhoef,. H., Mullee, D.M	2007	*Lemna Minor* Growth Inhibition Test, Safepharm Laboratories, SPL Report No. 2073/0006	Y	Task Force
A7.5.1.2	Staniland, J	2005	The toxicity to *Eisenia foetida foetida* of Bromadiolone, Chemex Environmental International Limited, Chemex reference: ENV6987/110414, GLP, Unpublished	Y	Task Force
A7.5.3.1.1 (1)	Hegdal PL Blaskiewicz RW	1984	Evaluation of the potential hazard to barn owls of Talon (brodifacoum bait) used to control rat sand house mice. Published. Environmental Toxicology and Chemistry Vol 3. 167-179.	N	Public Domain
A7.5.3.1.1 (2)	Krambias A Hoppe AH	1987	The response of captive partridges to dosing with anticoagulant rodenticides. Published. Control of Mammal Pests 181-186.	N	Public Domain
A7.5.3.1.1 (3)	Gaty, S	2004	Draft Report: Acute oral toxicity of Bromadiolone technical on Japanese Quail (*Coturnix coturnix japonica*), LAB International Hungary Ltd, 04/916-115FU, GLP, Unpublished	Y	Task Force

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A7.5.3.1.3	Gaty Szabolcs	2004 2005	Avian Reproduction Toxicity Test of Bromadiolone Technical in the Japanese Quails (*Coturnix coturnix japonica*), LAB International Research Centre Hungary Ltd, 04/804-206FU, GLP, Unpublished Amendment to the final report: Avian reproduction toxicity test of Bromadiolone technical in Japanese quails. LAB International Research Centre Hungary Ltd. Study number: 04/804-206FU	Y	Task Force
A7.5.7.1.1	Rammell CG Hoogenboom JJL Cotter M Williams JM Bell J	1984	Brodifacoum residues in target and non-target animals following rabbit poising trials. Published. New Zealand Journal of Experimental Agriculture, 1984, Vol. 12: 107-111.	N	Public Domain
A7	Fournier-Chambrillon C, Berny PJ, Coiffier O, Berbedienne P, Dasse´B, Delas G, Galineau H, Mazet A, Pouzenc P, Rosoux R and Fournier P	2004	Evidence of secondary poisoning of free-ranging riparian mustelids by anticoagulant rodenticides in France: Implications for conservation of European mink (*Mustela lutreola*). Journal of wildlife diseases, 40 page 688-695.	N	Public Domain
A7	McDonald, RA, Harris, S, Turnbull, G, Brown, P and Fletcher, M.	1998	Anticoagulant rodenticides in stoats (*Mustela erminea*) and weasels (*Mustela nivalis*) in England. Environmental Pollution 103: 17-23.	N	Public Domain
A7	Newton I, Wyllie I, and Freestone P	1997	Mortality causes in British Barn owls (*Tyto alba*), based on 1101 carcasses examined during 1963-1996. In Duncan JR, Johnson DH, and Nicholls TH editors. Biology and conservation of owls in the northern hemisphere, Winnipeg, Canada. United States Department of Agriculture, p 299-307.	N	Public Domain
A7	Ramell CG, Hoogenboom JJL, Cotter M, Williams JM, and Bell J	1984	Brodifacoum residues in target and non-target animals following rabbit poisoning trials. New Zealand Journal of experimental agriculture 12, page 107-111.	N	Public Domain
A7	Shore RF, Birks JDS and Freestone P	1999	Exposure of non-target vertebrates to second-generation rodenticides in Britain, with particular reference to the polecat *Mustela putorius*. New Zealand Journal of ecology 23, page 199-206.	N	Public Domain

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A7	Gillies CA and Pierce RJ	1999	Secondary poisoning of mammalian predators during possum and rodent control operations at Trounson Kauri park, Northland, New Zealand. New Zealand Journal of Ecology, 23, 183-192.	N	Public Domain
A7	Eason CT and Spurr EB	1995	The toxicity and sub-lethal effects of Brodifacoum in birds and bats, a literature review, science for conservation. Department of conservation, P.O Box 10-420 Wellington, New Zealand.	N	Public Domain
A7	Barnett EA, Fletcher MR, Hunter, K and Sharp EA	2005	Pesticide poisoning of animals in 2004. Investigations of suspected incidents in the United Kingdom. A report of the Environmental Panel of the advisory Committee on pesticides.	N	Public Domain
A7	Broman E	2003	Environment and moose population dynamics. PhD thesis Department of Applied Environmental science, Göteborg University Gothenburg, Sweden	N	Public Domain
A7	Balcomb R	1986	Songbird carcasses disappear rapidly from agricultural fields. Auk 103:817-820	N	Public Domain
A9			Material Safety Data Sheets of Bromadiolone Unpublished	Y	Task Force

Protect-B wax block

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
B3.7 (1)	Major Aniko	1993	Accelerated Storage Stability Test of Protect-B Wax Block. Babolna Bioenvironmental Centre Ltd., Hungary. Unpublished	Y	Task Force
B4.1	-	2001	Determination of Bromadiolone active ingredient, HPLC-007a. Babolna Bioenvironmental Centre Ltd., Hungary. Unpublished	Y	Task Force

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
B5.10	Schmidt J.	2002 - 2004	2 Years' Appetiblity and acceptance trials of different rodenticide blocks and baits, Babolna Bioenvironmental Centre Ltd., Hungary. Unpublished	Y	Task Force
B6.4	Toner F	2008	The In Vitro Percutaneous Absorption of Radiolabelled Bromadiolone in Two Test Preparations Through Human Skin, Charles River Laboratories, Study No. 780513, Report No. 28712. GLP, Unpublished	Y	Task Force
B.6.6(i)	Chambers JG and Snowdon PJ	2004	Study to Determine Potential Exposure to Operators During Simulated Use of Anticoagulant Rodenticide Baits, Synergy Laboratories Ltd., Report No. SYN/1302	Y	CEFIC/ EBPF Rodenti-cides data develop-ment group
B7.8.7.1 (1)	Kaukeinen D E	1982	A review of the secondary poisoning hazard to Wildlife from the Use of Anticoagulant Rodenticides, Biological Research Centre, ICI Americas Inc., P.O Box 208, Goldsboro, NC 27530	N	Public Domain
B7.8.7.1 (2)	Newton I & Wyllie I	late 1980:s	Effects of New Rodenticides on Owls, Institute of Terresterial Ecology, Monks Wood Experimental Station, Abbots Ripton, Huntingdon, Camba PE17 2LS	N	Public Domain
B7.8.7.1 (3)	Gray A, Eadsforth C V, Dutton A J	1994	The toxicity of three second-generation rodenticides to Barn Owls. Published. Pestic. Sci. 42, 179-184	N	Public Domain
B7.8.7.1 (4)	Wyllie I, Newton I, Freestone P	early 1990:s	Rodenticide residues in British Barn owls, Institute of Terrestrial Ecology, Monks Wood, Abbots Ripton, Huntingdon, Cambs PE17 2LS	N	Public Doman