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

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

Assessment Report

Difethialone

Product-type 14 (Rodenticides)

21 June 2007

Annex I - Norway

Difethialone (PT 14)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on 21 June 2007

in view of its inclusion in Annex I to Directive 98/8/EC

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE 4

1.1. Procedure followed 4

1.2. Purpose of the assessment report 5

1.3. Overall conclusion in the context of Directive 98/8/EC 5

2. OVERALL SUMMARY AND CONCLUSIONS 7

2.1. Presentation of the Active Substance 7

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis 7

2.1.2. Intended Uses and Efficacy 8

2.1.2.1. Field of use envisaged / Function and organism(s) to be controlled... 8

2.1.2.2. Effects on target organisms 8

2.1.2.3. Humaneness 8

2.1.3. Classification and Labelling 9

2.1.3.1. Proposal for the classification and labelling of the active substance .. 9

2.1.3.2. Proposals for the classification and labelling of the products Difethialone Blocks, Difethialone Paste and Difethialone Pellets 10

2.2. Summary of the Risk Assessment 11

2.2.1. Human Health Risk Assessment 11

2.2.1.1. Hazard identification and effect assessment 11

2.2.1.2. Exposure assessment and risk characterisation 16

2.2.2. Environmental Risk Assessment 21

2.2.2.1. Fate and distribution in the environment 21

2.2.2.2. Effects assessment 22

2.2.2.3. PBT and POP assessment 24

2.2.2.4. Exposure assessment 26

2.2.2.5. Risk characterisation 27

2.2.3. List of endpoints 32

3. DECISION 32

3.1. Background to the Decision 32

3.2. Decision regarding Inclusion in Annex I 33

3.3. Elements to be taken into account by Member States when authorising products 34

3.4. Requirement for further information 36

3.5. Updating this Assessment Report 36

APPENDIX I: LIST OF ENDPOINTS 37

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling 37

Chapter 2: Methods of Analysis 40

Chapter 3: Impact on Human Health 42

Chapter 4: Fate and Behaviour in the Environment 48

Chapter 5: Effects on Non-target Species 51

Chapter 6: Other End Points 52

APPENDIX II: LIST OF INTENDED USES 53

APPENDIX III: LIST OF STUDIES 55

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of difethialone 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.

Difethialone (CAS no. 104653-34-1) was notified as an existing active substance, by LiphaTech S.A.S, hereafter referred to as the applicant, 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 5(2) of that Regulation, Norway was designated as Rapporteur to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for difethialone as an active substance in Product Type 14 was 28 March 2004, in accordance with Annex V of Regulation (EC) No 2032/2003.

On 23 March 2004, the Norwegian competent authorities received a dossier from the applicant. The Rapporteur accepted the dossier as complete for the purpose of the evaluation on 28 September 2004.

On 30 September 2005 the Rapporteur submitted, in accordance with the provisions of Article 10(5) and (7) of Regulation (EC) No 2032/2003, 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 11 October 2005. The competent authority report included a recommendation for the inclusion of difethialone in Annex I to the Directive for product-type 14.

In accordance with Article 12 of Regulation (EC) No 2032/2003, the Commission made the competent authority report publicly available by electronic means on 19 January 2006. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

---

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

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

On the basis of the final competent authority report, the Commission proposed the inclusion of difethialone in Annex I to Directive 98/8/EC and consulted the Standing Committee on Biocidal Product on 21 June 2007.

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 21 June 2007.

1.2. Purpose of the assessment report

This assessment report has been developed and finalised in support of the decision to include difethialone in Annex I to Directive 98/8/EC for product-type 14. The aim of the assessment report is to facilitate the authorisation in Member States of individual biocidal products in product-type 14 that contain difethialone. 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

It appears from the examinations made that biocidal products used as rodenticides and containing difethialone 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 difethialone 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 difethialone 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,

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

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

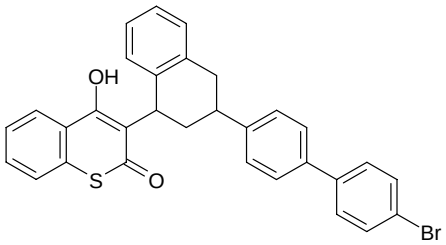
iii. the common principles laid down in Annex VI to Directive 98/8/EC.

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

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

The purity of the active substance (> 97.6%) is the minimum degree of purity as specified from the applicant for the active substance production process. Specification of purity is based on the combined concentration of both diastereoisomers (cis and trans). Both diastereomers are considered as active substance. The exact ratio is considered confidential and can be found in Document V of the Competent Authority Report. The specification of the active substance after change of production site in 2005 is considered to be the same as before 2005.

Difethialone is a yellow powder with no discernible odour and with a melting point in the range of 233-236°C. It has a low vapour pressure (< 1.33 x 10^{-5} Pa at 22.6º C) and a low Henry's Law constant. Therefore, volatilisation is not expected to significantly contribute to the dissipation of difethialone in the environment. The compound has a water solubility of 0.39 mg/l at 25°C and is readily soluble in organic solvents (14,000 mg/l in dichloromethane). It has a high log octanol/water partition coefficient (log Kow = 6.29), indicating it is highly lipophilic and has a tendency to bioaccumulate. No reactivity towards container material known.

Adequate methodology exists for the determination of the active substance in the technical active substance, in the individual products and in soil, water, air, blood and liver tissues. Analytical methods have been developed to determine residues of difethialone in food and feeding stuff.

2.1.2. Intended Uses and Efficacy

2.1.2.1. Field of use envisaged / Function and organism(s) to be controlled

Difethialone is used as a rodenticide pest control substance (Main group 03, Product type 14).

Difethialone is used to control:

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

In addition, 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.

2.1.2.2. Effects on target organisms

Difethialone 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 the active substance depends on exposure (i.e. consumption of the bait by the target organism). 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 25 mg/kg is proposed. The formulated product type has no significant difference on the effects of the active substance on the target organisms.

2.1.2.3. Humaneness

The use of difethialone as a rodenticide could cause suffering of vertebrate target organisms. The use of anti-coagulant rodenticides is necessary as there are at present no other valuable 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. Such a comparative assessment is not under the scope of this report, but should be preformed when possible alternatives have been evaluated and all data are available.

2.1.3. Classification and Labelling

2.1.3.1. Proposal for the classification and labelling of the active substance

Hazard symbol:	Symbol letter: T+, N Indication of danger: Very toxic Dangerous to the environment	
Risk phrases	R26/27/28 R48/23/24/25 R61 R50/53	Very toxic by inhalation, in contact with skin and if swallowed. Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed May cause harm to the unborn child Very toxic to aquatic organisms, may cause long-term adverse effects in aquatic environments.
Safety phrases	 S45 S53 S60 S61	Chemicals classified with Repr. Cat. 1 are prohibited for general public use. In case of accident or if you feel unwell, seek medical advice immediately (show label where possible). Avoid exposure - obtain special instructions before use This material and its container must be disposed of as hazardous waste Avoid release to the environment. Refer to special instructions/safety data sheets.
Specific concentration limits	C ≥ 0.5% 0.25 ≤ C <0,5% 0.025% ≤ C< 0.25% 0.0025% ≤ C <0.025%	T+, N; R61 - 26/27/28 - 48/23/24/25 - 50/53 T+, N; R26/27/28 - 48/23/24/25 - 50/53 T, N; R23/24/25 - 48/23/24/25 - 51/53 Xn; R20/21/22 - 48/20/21/22 - 52/53

Justification for the proposal

On basis of study results from studies presented in the dossier classification of difethialone was proposed according to principles detailed in Annex VI of Council Directive 67/548/EEC (with amendments and adaptations).

The proposed classification for environment was agreed in April 2006 by the Technical Committee on Classification and Labelling (TC C&L) of Dangerous Substances.

The classification for human health effects is in May 2007 still under discussion. 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

difethialone for acute and repeated dose toxicity was agreed upon. In May 2007 the provisionally classification for reprotoxicity was not confirmed as the TC C&L decided to await further results from studies on anticoagulant rodenticides before finalising the discussion on reprotoxicity. Specific concentration limits for difethialone were agreed upon as proposed.

2.1.3.2. Proposals for the classification and labelling of the products Difethialone Blocks, Difethialone Paste and Difethialone Pellets

Hazard symbol:	Symbol letter: Xn Indication of danger: Harmful	
Risk phrases	R48/20/21/22 R 52/53	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases	S2: S13: S20/21: S37 S46: S61	Keep out of reach of children. Keep away from food, drink and animal feeding stuffs. When using do not eat, drink or smoke. Wear suitable gloves If swallowed, seek medical advice immediately and show this container or label. Avoid release to the environment. Refer to special instructions/safety data sheets.

Justification for the proposals

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 difethialone 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 difethialone, specific concentration limits for the environment have been agreed. Specific concentration limits for human health effects are still under discussion. If the proposed specific concentration limits (see table in chapter 2.1.3.1) are accepted, the three difethialone containing products (Blocks, Paste and Pellets) will be classified for environmental effects as well as for repeated dose toxicity. As for acute toxicity, the concentration of the active substance in the products is equal to the proposed specific concentration limit for classification of the products with Xn; R20/21/22. However, no classification for acute oral and dermal toxicity is needed as the study results on the products do not meet the classification criteria. No acute inhalation studies on the products are presented, but the physical nature of these products is such that classification for acute inhalational toxicity is not considered needed.

Additional labelling:

Directive 1999/45/EEC may not allow a sufficient description of the special risks which may arise during the use of biocidal products, anticoagulant rodenticides in particular. Thus, in addition to the phrases listed above, labelling, as specified in Article 20(3) of Directive 98/8/EC, as well as additional labelling for rodenticides, might become necessary (see chapter 3.3).

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

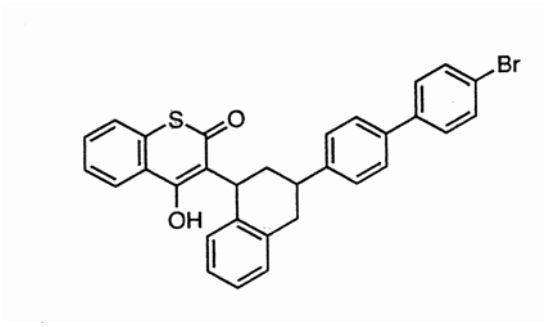
2.2.1.1. Hazard identification and effect assessment

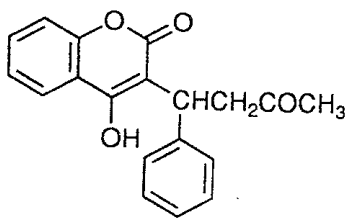
Human health effects of active substance

Difethialone 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, difethialone 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.

Difethialone is present as two diastereoisomers, with similar kinetics. Both diastereomers are active. Difethialone is structurally and functionally almost similar to the first generation rodenticide active ingredient warfarin at the functional coumarin (left-hand) end of the molecule.

Figure.1. The chemical structure of difethialone and warfarin





Difethialone Warfarin

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 the 'tail', which has varying degrees of lipophilicity.

Warfarin, has been used for many years for treatment of thromboembolic diseases in humans. Treatment is associated with increased risk of bleeding episodes as the most common reported

side effect as well as e.g. skin necrosis and haematomas in various organs .Bone protein depletion is observed in female humans after long-term anticoagulant treatment. Warfarin is associated with the induction of developmental malformations when taken as a therapeutic agent during pregnancy. Use during pregnancy is contraindicated.

Absorption, distribution, metabolism and excretion

The key metabolism study in rats with radiolabelled difethialone showed that difethialone is rapidly absorbed with a short plasma half-life (2.3 days), but a longer liver half-life (approximately 18 weeks) following an exposure to 0.5 mg difethialone/kg bw. The liver was the organ of accumulation, with 23 to 43% of administered dose in males and females present in the liver at 24 hours, and approximately 10% still present after 6 months. Elimination was exclusively in the faeces as unchanged parent material, with 37% excreted in the first 3 days, 57% within 14 days. There was no excretion via expired air or urine. The high dose level of 5 mg/kg was fatal, but the plasma half-life and the accumulation of difethialone in the liver, was similar to that seen at the lower dose level.

A clear estimate of the percentage of oral absorption can not be given based on the toxicokinetic studies, because of the long half-life in the liver. Biliary excretion studies (normally used to assess absorption) are too short to give a meaningful result. However, absorption of difethialone seems to be extensive. An assumption of 100% absorption is used in the risk assessment.

A human dermal absorption value of difethialone to be used in the risk assessment of the products was calculated at 4% based on in vivo and in vitro absorption studies on a glycol formulation of difethialone.

Acute toxicity

In acute oral toxicity studies, difethialone was very toxic to rats and mice with the lowest LD_{50} to the male rat of 0.55 mg/kg bw and to the mouse 1.29 mg/kg bw. Difethialone is less toxic to dogs (11.8 mg/kg bw) and cats (≥ 16 mg/kg bw, study of low reliability) with pigs showing a greater sensitivity (LD_{50} of 2.0 to 3.0 mg/kg bw).

Difethialone was also acutely toxic by dermal administration (LD_{50} of 6.5 mg/kg bw) and by inhalation (nose only: $LC_{50} \geq 5.0$ µg/l/4h but <19.3 µg/l/4h) in rats.

Based on these data classification with T+;R26/27/28: Very toxic by inhalation, in contact with skin and if swallowed' is warranted.

None of the rat or mice acute oral studies investigated sublethal effects. In the acute oral study in dogs effects on coagulation were measured, and it was possible to derive a $LOAEL_{acute}$ of 5 mg/kg bw. At 5 mg/kg bw, the lowest dose used, only a minor increase in coagulation time was observed. The plasma prothrombin level, was reduced by up to 50% indicating a certain effect of difethialone on vitamin K. At higher doses a dose dependent increase in coagulation time was noted that seemed to reflect the severity of haemorrhage.

Irritation, corrosivity and sensitisation

Difethialone is not classified as a skin irritant, eye irritant or a skin sensitiser.

Repeated dose toxicity

Repeat-dose oral studies show that even at doses as low as 4 µg/kg bw/day in the rat and 20 µg/kg bw/day in the dog, hemorrhagic effects begin to be seen after around 90 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.

The $LOAEL_{RDT}$ established in the 90 day repeat dose oral studies was 4 µg/kg bw/day based on haemorrhagic changes seen at necropsy. Classification with T; R48/23/24/25 :'Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed' is warranted based on the data from the repeated dose oral studies plus extrapolation from the acute data for the dermal and inhalation route of exposure.

The $NOAEL_{RDT}$ established in the 90 day repeated dose oral studies were 2 µg/kg bw/day in the rat study and 10 µg/kg bw/day in the dog study.

Repeated dose dermal or inhalation studies (28 and 90 days) are waived.

Genotoxicity

Difethialone was not mutagenic in a standard range of in vitro and in vivo tests.

Chronic toxicitiy/ carcinogenicity

Carcinogenicity and long-term toxicity studies are waived.

Reproductive toxicity

Difethialone was not embryotoxic or teratogenic in guideline studies in rat and rabbit. However, the conventional OECD Guideline 414 may have limitations in the detection of possible teratogenic effects of coumarin related compounds. Warfarin, a well documented human teratogen is classified as a reproductive toxicant (Repr. Cat. 1; R61). Since difethialone has the same chemically active group and the same well-known mode of action by which warfarin causes teratogenicity in humans, it is proposed to classify difethialone for developmental toxicity with Repr. Cat. 1; R61 in the same way as warfarin.

A two generation study in the rat is waived.

Neurotoxicity

Difethialone was investigated, in various screening tests for potential pharmacological activity other than its known anticoagulant properties. Specifically, the following endpoints were investigated: antianginal activity *in vivo* or *in vitro*; antihypertensive activity; sedative activity; anticonvulsant activity; antidepressant activity; antispasmodic activity in a variety of *in vitro* tests; analgesic, anti-inflammatory or gastric antiacid activity. The absence of sedative activity, anticonvulsant activity, antidepressant activity and the absence of any clinical signs in rodent and dog toxicity tests support the conclusion that difethialone shows no neurotoxic effects.

Other toxicological studies

Two non-guideline studies in the dog demonstrated that Vitamin K_1 was an effective antidote following single lethal doses of difethialone when administered in conjunction with monitoring of prothrombin time and signs of haemorrhage. There are indications that intravenous administration of vitamin K may cause anaphylactic shock if administered too quickly.

In a rat study where difethialone pellets (25 ppm end use product) were given to rats as sole food for 24, 48 or 72 hours, half of the rats in each group were given antidotal vitamin K administration by subcutaneous injection followed by 13 days oral administration. The other rats were not given vitamin K. All of the rats that were not given vitamin K died. Observations prior to death and post mortem findings were consistent with death by haemorrhage. All of the rats treated with vitamin K after 24 hours exposure to difethialone survived, but only one rat treated with vitamin K after respectively 48 and 72 hours survived.

Medical data

Many incidents of human poisoning, both accidental and intentional, of anticoagulant rodenticides have been reported in literature. These substances have longer retention time in the body and consequently a more prolonged effect than warfarin. Difethialone is manufactured in small quantities worldwide and only one published case report of difethialone intoxication has been found. A few cases of intoxications from occupational exposure to anticoagulants have been reported.

The anticoagulant effect can be recognized by simple tests such as clotting time, Quick test or prothrombin rate determinations. The antidotal treatment regimen is well characterized – parenteral administration of vitamin K_1 (phytomenadione) followed by long term oral administration of the antidote to stabilize prothrombin times. Oral administration of the antidote can be sufficient in minor poisoning cases.

AOEL (Acceptable Operator Exposure Level)

The derivation of an Acceptable Operator Exposure Level for acute exposure ($AOEL_{acute}$) was based on the $LOAEL_{acute}$ of 5 mg/kg bw established in an acute oral study in dogs. Applying a safety factor of 1800 (normal inter- and intraspecies safety factor of 100, a factor of 2 for LOAEL to NOAEL extrapolation, a factor of 3 for use of a moderate sensitive species and a factor of 3

due to the severity of the potential developmental effect) an $AOEL_{acute}$ value of 2.8 µg/kg bw can be derived4.

The derivation of an Acceptable Operator Exposure Level for repeated exposure ($AOEL_{RDT}$) was based on the $NOAEL_{RDT}$ established in the 90 day rat study. Applying the normal safety factor of 100 (inter- and intraspecies factor) and an additionally safety factor of 3 due to the severity of the potential developmental effect an $AOEL_{RDT}$ value of 0.007 µg/kg bw/day can be derived.

Human health effects of products

The products Difethialone Blocks (a cereal grain wax block), Difethialone Paste (a cereal based paste) and Difethialone Pellets (a cereal/wax pellet) are all ready to use formulations containing difethialone at 25ppm. In standard acute oral and dermal toxicity tests, the LD_{50} values are above 2000 mg/kg bw. The products are not irritating to skin or eyes and are not sensitisers.

The absorption of difethialone from the end use products has not been tested directly, but absorption of difethialone from liquid (glycol solvent) and dry (wheat flour) concentrates of the active substance has been measured.

An *in vivo* rat dermal absorption study showed that the dermal delivery (absorbed dose and amounts retained in the epidermis and dermis layers of the skin) following topical application of difethialone in glycol solvent (1.25 g/l) was approximately 12% 24 hours post dosing.

The dermal delivery was lower following application of difethialone in wheat flour (0.5% w/w) diluted 1:1 in water by volume (varied between 0.72 and 3.63) than following application of difethialone in glycol solvent.

Strateum corneum contained more difethialone following application of the glycol solvent formulation (approximately 21% of difethialone 24 hours post dosing) than after application of difethialone in wheat flour - water formulation (varied between 7.42 and 11.62%).

Tape stripping was performed in the study, but the strips were pooled; hence no information on the concentration gradient of test substance across the stratum corneum could be established. While test substance retained within the upper layer of stratum corneum would be expected to be shed (sloughed) and not be available for dermal absorption, amounts of test substance from the "deep" stratum corneum could be considered as available for dermal absorption.

Due to the lipophilicity and low water solubility of difethialone and the fact that the products (wax and paste) contain a non-polar phase of fats and waxes, the values derived from the glycol formulation is used to estimate absorption from use of products.

---

4 At the Technical Meeting on Biocides, May 2007 it has been decided to derive the acute AOEL from the maternal NOAEL established in a teratogenicity study with the most sensitive species, applying a safety factor of 300. This decision has been taken after finalisation of the assessment of difethialone but should be taken into account if performing a comparative assessment and in future revisions of the risk assessment of difethialone.

In vivo human dermal absorption may be calculated by combining rat *in vivo* data and rat:human *in vitro* data, 12 % ÷ 3 = 4 %. This represents a reasonable worst case value for the absorption of difethialone from all products and is used in absence of actual data on the end use formulations of difethialone. The value is derived from the dermal delivery of difethialone in glycol solvent 24 h after application, i.e. excluding test material in the tape strips (stratum corneum).

There are some unresolved uncertainties related to the dermal absorption of difethialone from the end use products. On one hand the exclusion of the considerable amount of difethialone retained in the stratum corneum may lead to an underestimation of the actual absorption. On the other hand dermal penetration is influenced by the vehicle. Including test material in the stratum corneum from the glycol solvent formulation in the calculations of dermal absorption to be used in the exposure calculation for the end use products might overestimate the dermal absorption from these bait matrixes.

In vivo and in vitro studies have demonstrated that there is an inverse relation between concentration (area dose) and percentage of absorption. At low concentrations the absorbed test substance expressed as percentage of applied dose per time interval is in general higher than the percentage absorption at high concentrations (Guidance document on Dermal Absorption, Sanco/222/2000 rev. 7).

Based on these considerations (the dependency of dermal absorption on the vehicle and the dermal area dose), actual test data on the end use formulations should be provided and taken into account when products are to be authorised. The studies should preferentially include information from sequential tape stripping to estimate what percentage of the test material is retained within the deep stratum corneum; hence being potentially available for absorption.

Back calculations to determine the percentage of dermal absorption of difethialone from a product that would give an estimated exposure equal to the AOEL for repeated exposure have been carried out for all exposure scenarios for professionals (see 2.2.1.2).

2.2.1.2. Exposure assessment and risk characterisation

Human health risk for professional users

Exposure assessments are based on:

1) default values from the Technical Notes for Guidance (TNsG) on Human exposure to Biocidal Products

2) values derived from operator exposure studies where exposure of non-professional operators carrying out a range of tasks (decanting of loose grain baits, filling of bait boxes and cleaning up and disposal of bait) was measured using two end-use products, wax and loose grain bait, containing the surrogate active substances coumatetralyl and flocoumafen.

Adjustments of the calculations are done in both cases using worst case assumptions of daily usage e.g. daily number of manipulations/handlings (including both application and post application tasks) and product specific information on amount of bait to be used per bait point.

A human dermal absorption of 4% is used in the assessment (for a discussion of the uncertainties of the chosen value and the need for further data when the products are to be authorised see 2.2.1.1). A 90 % reduction of dermal exposure from use of protective gloves is assumed. For calculations with default values from TNsG, a calculation is also presented for the assumption that gloves are not used.

The skin is the main exposure route. Inhalation exposure (100% absorption is assumed) mainly to dust from decanting of loose grain bait/pellet bait, makes an additional contribution to the estimated total systemic exposure.

The maximum estimated systemic exposure for professionals using Difethialone Blocks, Difethialone Paste and Difethialone Pellets on a single occasion accounted for 0.84 % of $AOEL_{acute}$ (Difethialone Block used for control of rats in sewers) if based on EU default values and assuming the use of protective gloves. Without gloves the corresponding value was 8.4 % of $AOEL_{acute.}$ Based on more realistic measured values taken from the operator exposure study, the exposure for the three products accounted for 0.015 to 0.088 % of the $AOEL_{acute}$.

For professional operators using the products on a repetitive or daily basis, the worst case systemic exposure was estimated for Difethialone Block used for control of rats in sewers. The exposure exceeded the $AOEL_{RDT}$ (336 % of $AOEL_{RDT)}$ if based on EU default values and assuming the use of protective gloves. When assuming that gloves were not used, the exposure accounted for as much as 3360 % of $AOEL_{RDT}$. However, based on more realistic measured values taken from the operator exposure study, the exposure was lower than the $AOEL_{RDT}$ for all three products and all use areas (5.9 to 35 % of $AOEL_{RDT}$).

For Difethialone Blocks, Difethialone Paste and Difethialone Pellets the estimated systemic exposure was in almost all cases lower when based on more realistic extrapolated measurements from the operator exposure studies than on default values. Furthermore, the measured values for Difethialone Pellets represent a worst-case scenario as the measured exposure was based on handling loose grain bait whereas Difethialone Pellets are waxy non-dusty pellets and exposure is likely to be lower. Paste products were not used in the operator study. In the assessment the product concentrations measured when handling wax blocks were related to Difethialone Paste. Difethialone Paste is supplied in sachets. The results represent very much an overestimation when loading Difethialone Paste. However, when cleaning used traps, the dermal exposure is likely to be underestimated.

A summary of the risk assessment for professional operators is presented in the table below.

Table 2.1. Summary of risk assessment for professional operators

Product (pest controlled)	% of AOEL					
	Acute toxicity ($AOEL_{acute}$ = 2.8 µg/kg bw)			Repeated dose toxicity ($AOEL_{RDT}$ = 0.007 µg/kg bw/day)		
	Based on default values		Based on measured values	Based on default values		Based on measured values
Difethialone Blocks (rats in sewers)	With gloves	**0.84**	**0.083**	With gloves	**336**	**33**
	Without gloves	**8.4**		Without gloves	**3360**	
Difethialone Blocks (rats in/around buildings)	With gloves	**0.30**	**0.088**	With gloves	**121**	**35**
	Without gloves	**3.0**		Without gloves	**1210**	
Difethialone Block (mice in/around buildings)	With gloves	**0.20**	**0.088**	With gloves	**80**	**35**
	Without gloves	**2.0**		Without gloves	**800**	
Difethialone Paste (rats and mice)	With gloves	**0.13**	**0.088**	With gloves	**54**	**35**
	Without gloves	**1.3**		Without gloves	**540**	
Difethialone Pellets (rats)	With gloves	**0.021**	**0.024**	With gloves	**8.5**	**9.5**
	Without gloves	**0.21**		Without gloves	**85**	
Difethialone Pellets (mice)	With gloves	**0.021**	**0.015**	With gloves	**8.5**	**5.9**
	Without gloves	**0.21**		Without gloves	**85**	

Because of uncertainties in the dermal absorption value used in the exposure assessment and the identified need for test results from the actual end use products, back calculations to determine the percentage of dermal absorption of difethialone from a product that would give an estimated exposure equal to the AOEL for repeated exposure are carried out for all exposure scenarios for professionals. The calculations provide cut off values to be used when products are to be authorised (See 3.3).

Table 2.2. Dermal absorption that gives an estimated systemic exposure equal to the AOEL for repeated exposure (calculations based on measurements from the operator exposure study)

Product (pest controlled)	Dermal absorption (%) that gives an estimated systemic exposure equal to the AOEL for repeated exposure (0.007 µg/kg bw/day)
Difethialone Block (rats in sewers)	12.0
Difethialone Block (rats in/around buildings)	11.4
Difethialone Block (mice in/around buildings)	11.4
Difethialone Paste (rats and mice)	11.4
Difethialone Pellets (rats)	50.9
Difethialone Pellets (mice)	77.5

Human health risk for non professional users

Exposure assessments are based on:

1) default values from the Technical Notes for Guidance on Human exposure to Biocidal Products

2) values derived from operator exposure studies (see description given for professional users)

Difethialone Blocks, Difethialone Paste and Difethialone Pellets are assumed to be used infrequently and not on a daily basis by non-professional. The skin is the main exposure route. Non professional users are assumed to not wear protective gloves (or other protective clothing).

The margins of exposure (MOE = LOAEL/Exposure) were high; 5.3 x10^5 to 8.0 x 10^6 based on default values and 2.3 x 10^6 to 3.8 x 10^7 based on more realistic measured values taken from the operator exposure study.

For Difethialone Blocks, Difethialone Paste and Difethialone Pellets, the estimated systemic exposure was lower when based on more realistic extrapolated measurements from the operator exposure studies. Furthermore, the measured values for Difethialone Pellets represent a worst-case scenario as the measured exposure was based on handling loose grain bait whereas Difethialone Pellets are waxy non-dusty pellets and exposure is likely to be lower. Paste products were not used in the operator study. In the assessment the product concentrations measured when handling wax blocks were related to Difethialone Paste. Difethialone Paste is supplied in sachets. The results represent very much an overestimation when loading Difethialone Paste. However, when cleaning used traps, the dermal exposure is likely to be underestimated.

A summary of the risk assessment for non-professional operators is presented in the table below.

Table 2.3 Summary of risk assessment for non-professional operators

Product (pest controlled)	**Margins of Exposure ($LOAEL_{acute}$ of 5 mg/kg bw (5000 µg/kg bw) /Exposure)**	
	Based on default values	**Based on measured values**
Difethialone Blocks (rats)	**5.3×10^5**	**2.3×10^6**
Difethialone Blocks (mice)	**8.0×10^5**	**2.3×10^6**
Difethialone Paste (rats and mice)	**1.5×10^6**	**2.8×10^6**
Difethialone Pellets (rats)	**8.0×10^6**	**2.6×10^7**
Difethialone Pellets (mice)	**8.0×10^6**	**3.8×10^7**

Human health risk from indirect exposure as a result of use

Adults or children may be present following application and may be incidentally exposed by touching unprotected Difethialone Blocks, Difethialone Paste and Difethialone Pellets baits. For products applied in locked, anchored and tamper resistant bait stations, incidental exposure will most likely be limited. However, rodents hoard food and will therefore translocate bait from bait stations, subsequently making bait accessible for animals, birds and humans. 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 mouths with contaminated fingers. However, Difethialone Blocks, Difethialone Paste and Difethialone Pellets contain a bittering agent (denatonium benzoate) to prevent oral consumption. The substance will probably reduce the possibility of oral exposure, but it will not eliminate the risk of poisoning.

The calculated margin of exposure ($LOAEL_{acute}$/Exposure) was 200000 for infants based on a default exposure value which assumes that infants will ingest 10 mg bait (default of bait treated with repellent). If the calculation was based on an ingestion of 5 gram, which is the amount Poison specialists generally estimate that a child could consume in one bite, the margin of exposure ($LOAEL_{acute}$/Exposure) would be 400. In the latter case, the MOE would be below the minimal acceptable MOE of 1800 (the normal inter and intraspecies safety factor of 100, a factor of 2 for LOAEL to NOAEL extrapolation, a factor of 3 for the use of a moderate sensitive species and a factor of 3 due to the severity of the potential developmental effect (which is also considered relevant for infants). Accidental intake of 5 gram poses a risk to infants.

Table2.4. Summary of risk assessment for non-users

Product (pest controlled)	Margins of Exposure based on default values ($LOAEL_{acute}$/Exposure)			
	adults (60 kg)	children (15 kg)	infants (10 kg) (10mg ingestion)	(5g ingestion)
Difethialone Blocks	NA[a]	NA[a]	200000	400
Difethialone Paste	NA[a]	NA[a]	200000	400
Difethialone Pellets	NA[a]	NA[a]	200000	400

[a] Not applicable.

Exposure of adults and children handling dead rodents is assumed to be low as products are oral baits, and only low amounts of difethialone will be present on rodent fur. Difethialone is excreted by the rat only in faeces and not in urine, and therefore urine will not contribute to the amount of difethialone on rodent fur.

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and distribution in the environment

Biodegradation

Biodegradation of difethialone in sewage treatment plants has been investigated under aerobic and anaerobic conditions. Difethialone is found to be neither aerobically nor anaerobically biodegradable. The active substance is slowly degraded in soil under aerobic conditions with half-lives between 417 and 976 days at 12°C (mean value 635 days). Degradation of difethialone lead to the formation of two unidentified metabolites, exceeding 10 % applied radioactivity and more than 10 % non-extractable residue (NER) was formed during biodegradation. However, further testing in order to identify metabolites and bound residues is not considered necessary due to the spatially restricted use pattern of difethialone.

Abiotic degradation

Hydrolysis of the active substance is not expected to be a significant process in the environment due to a half-life of 175 days at pH 7. In aqueous solutions, the active substance is rapidly and extensively photolysed with DT_{50} values between 23.4 and 62 minutes. Photolysis of the active substance led to the formation of significant levels of degradation products (> 10 %) which persist for > 48 hours. However, photolysis is not to be expected to be a significant degradation path in the environment as it only takes part in the upper layers of surface water. Moreover, the high adsorption tendency of difethialone to organic matter reduces difethialone concentrations in surface waters. The parent substance is highly toxic to aquatic organisms and it is anticipated that the unknown degradation products, which have higher water solubility than difethialone, are as toxic as difethialone. Therefore, no further testing was required.

Distribution/Mobility

Due to the low vapour pressure, difethialone is not expected to partition to the atmosphere to a relevant extent. Should it be present in air, it is expected to be quickly degraded be photo-oxidation.

The active substance is strongly and rapidly adsorbed to soil and is indicated as 'non mobile' in soil according to the SSLRC classification index.

Bioaccumulation

Measurements of aquatic and terrestrial bioaccumulation of difethialone have not been performed. Therefore the bioconcentration factors for fish and earthworm have been calculated according to the TGD, showing a high potential for bioaccumulation:

BCF_{fish} = 39,974 l/kg
$BCF_{earthworm}$ = 23,943 l/kg

2.2.2.2. Effects assessment

Effects on aquatic organisms

Based on the results of acute toxicity studies, difethialone is highly acute toxic to aquatic organisms. No long-term tests have been performed.

The lowest 96-hour LC50 for fish was 51 µg/l *(Salmo gairdneri)*. *Daphnia magna* was more sensitive than fish, with a 48-hour EC50 of 4.4 µg/l. The endpoint was based on immobilisation. Both tests were conducted under static conditions and exposure concentrations were not verified analytically. Due to the low water solubility of difethialone and possible adsorption to glassware, the real exposure concentrations are likely to have decreased over the test period. The toxicity of difethialone to fish and aquatic invertebrates might therefore be underestimated. The $PNEC_{aquatic}$ is based on the EC50 from the test with *Daphnia magna* and therefore the PNEC might be too high. However, the PEC/PNEC ratios for the aquatic compartment are very low (worst-case PEC/PNEC = 0.16) and it is therefore considered highly unlikely that an EC50, which would be based on measured concentrations, would be low enough to result in such a low PNEC that a risk to the aquatic compartment would be identified.

In a 72-hour algal growth inhibition test with *Selenastrum capricornutum*, the ErC50 was > 180 µg difethialone/l. The NOEC was 32 µg/l with respect to specific growth rate. The study is not considered valid as no measurement of the concentrations was conducted. As difethialone is photo-labile and adsorbs to glassware and probably also to algae, it can be assumed that exposure concentrations during the test are considerably lower than nominal concentrations. As algae are not the most sensitive species to difethialone the study is considered acceptable for the assessment.

The effect of difethialone on aerobic biological sewage treatment processes was assessed by determining inhibition of respiration of the micro-organisms present in activated sludge following three hour contact. The EC50 was greater than 100 mg/l, the highest concentration

applied, which exceeds the limit of solubility of difethialone in water considerably. Concentrations causing 20% and 80% respiration suppression also exceeded 100 mg/l.

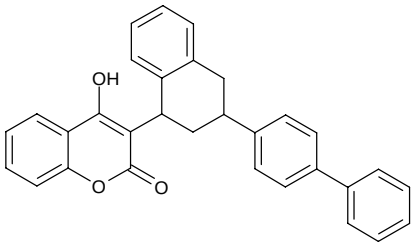
Effects on terrestrial organisms

The effect of difethialone on earthworms was assessed in an acute toxicity test in which *E. foetida* in artificial soil was exposed to concentrations of difethialone up to 1,000 mg /kg. The 14-day LC50 was greater than 1,000 mg/kg dry soil, the highest concentration applied, which is equal to 885 mg/kg wet weight. Observed mortality at this level was 23 %.

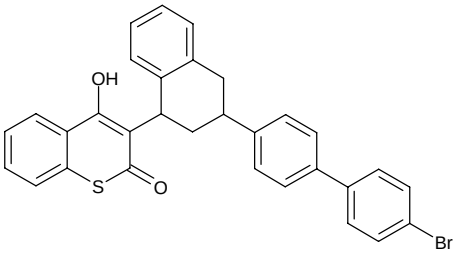
Difethialone is acutely toxic to birds with the lowest LD50 value of 0.264 mg/kg bw (Bobwhite quail, single dose). Difethialone was similarly toxic in short-term dietary tests with the lowest LC50 values of 0.56 mg/kg food (Bobwhite quail, 5 days feeding).

An avian reproduction study with difenacoum has been carried out at low exposure concentrations. Since no long-term data for difethialone is available the study with difenacoum is used as the basis for a read-across from difenacoum to difethialone. Difenacoum is structurally closely related to difethialone and is an anti-vitamin K anticoagulant rodenticide with a similar mode of action.

Difenacoum:



Difethialone



The nature of the toxic effects is expected to be similar for all rodenticides with this mode of action, although the dietary concentrations at which effects are observed may differ. The NOEC from the avian reproduction study with difenacoum is greater than the highest dietary concentration (0.1 mg/kg food). Few other avian toxicity endpoints are available for difenacoum, but the short-term dietary LC_{50} obtained with mallard ducks was 18.9 mg difenacoum/kg diet. The corresponding endpoint for difethialone, obtained with mallards under similar conditions, was 1.9 mg difethialone/kg diet. Based on this comparison, a factor of 10 has been applied to derive tentative long-term endpoints for difethialone from those obtained with difenacoum, as follows: For risk assessment purposes the NOEC for difethialone is assumed to be 0.01 mg/kg food and the NOAEL 0.001138 mg/kg bw/day.

A dietary secondary poisoning study where barn owls were fed with poisoned rats is described in a recent article. The study had some deficiencies; however, it gives valuable insight into the availability of prey ingested difethialone for predators. The study gave a low LD100 in the range of 0.27 to 0.39 mg/kg bw. This indicates that excretion/metabolism during the 56 day period is low in birds and that ingested difethialone in rats is readily available to the owls.

2.2.2.3. PBT and POP assessment

PBT assessment

As difethialone is not readily biodegradable, has a high predicted bioconcentration factor and is very toxic both to aquatic organisms and mammals a PBT assessment has been carried out.

Persistence

The persistence criteria laid down in the TGD require a half-life > 60 days in marine water (or > 40 days in fresh water) or > 180 days in marine sediment (or > 120 days in freshwater sediment). The very persistence criteria require a half-life > 60 d in marine- or freshwater or half-life > 180 d in marine or freshwater sediment.

Difethialone is not readily biodegradable (< 6 % biodegradation within 28 days). In addition, the use of the BIOWIN-model for the estimation of the aerobic biodegradability also points to the lack of biodegradation of difethialone. Difethialone is not anaerobically biodegradable (< 5 % after 63 days). The substance is predicted to adsorb strongly onto organic matter and difethialone present in sediment is therefore expected to persist in anaerobic sediments.

Aerobic biodegradation of difethialone in soil shows an average half-life in soil of 635 days. This is another indication that difethialone might also be persistent in sediment and that its half-life in sediment is more than 120/180 d. Based on the presented results difethialone is considered potentially persistent/very persistent (P/vP).

Bioaccumulation

A substance is considered to fulfil the B criterion when the bioconcentration factor (BCF) exceeds a value of 2,000 l/kg and the vB criterion (very bioaccumulative) when the BCF exceeds a value of 5,000 l/kg.

For difethialone no measured bioconcentration factors are available. According to the TGD a substance is considered to potentially fulfil the screening B criterion when logKow exceeds a value of 4.5. Difethialone has a logKow of 6.29 and the BCF for fish was calculated from the relationship between Kow and BCF according to the TGD and resulted in a BCF_{fish} of 39,974 l/kg. Calculating the BCF with the programme Episuite3.1 gave a BCFfish of about 14,000 l/kg. In order to clarify whether difethialone meets the definitive B/vB-criteria further testing might become necessary.

Based on these results, it can be concluded that difethialone meets the screening criteria for B as well as for vB.

Toxicity

The toxicity criterion used in the TGD is a chronic NOEC for aquatic organisms of less than 0.01 mg/l. For difethialone no chronic ecotoxicity data are available. However, in the context of the PBT assessment a substance is considered to be potentially toxic when the $L(E)C_{50}$ to aquatic organisms is less than 0.1 mg/l. The acute data for difethialone show clearly that difethialone

might also fulfil the T-criterion of the PBT assessment. The lowest acute test with *Daphnia magna* gave a 48-h EC_{50} of 4.4 µg/l.

According to the testing strategy of the TGD for the T criterion, substances which are toxic to mammals and classified as Very Toxic or Toxic after oral dosing are considered to fulfil the T criterion. Difethialone is acutely toxic (lowest LD50 (rat) = 0.4-0.8 mg/kg bw) and the lowest chronic LOAEL (90 d) for rat after repeated dosing is 4 µg/kg bw/day. Difethialone is proposed classified as T+; R26/27/28, T; R48/23/24/25 and Repr. Cat. 1; R61 Therefore it can be concluded that difethialone fulfils the T criterion.

Therefore difethialone is considered to be a potential PBT and a potential vPvB substance.

POP assessment

- The substance fulfils the screening criteria (Annex D of the Stockholm Convention) for persistency (evidence that the half-life of the chemical in water/sediment might be greater than two/six months or that its half-life in soil is greater than six months).

- Screening criteria for bioaccumulation are also fulfilled (evidence that the bioconcentration factor in aquatic species for the chemical is greater than 5,000 or, in the absence of such data, that the log Kow is greater than 5). No measured bioconcentration factor in fish is available, but difethialone has a log Kow>5. There is evidence that the chemical has as high bioaccumulation potential in mammals/birds.

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

The substance does not fulfil the numerical screening criteria for potential for long-range environmental transport: The expected half life in air is about 2 hours and thus does not fulfil the criterion (half-life more that 2 days). Moreover, the vapour pressure and Henry's law constant are low and the adsorption potential to organic matter is high. However, atmospheric transport e.g. in particles cannot be excluded. There is no monitoring data available or other evidence indicating potential for long range environmental transport.

In conclusion, difethialone exhibits certain POP characteristics (persistence, adverse effects) but there is no sufficient information to allow a full assessment on bioaccumulation and long-range environmental transport potential.

2.2.2.4. Exposure assessment

Aquatic compartment

Exposure of surface water to the active substance following its use in the scenario "in and around buildings" is considered negligible.

The use of products containing the active substance for application in sewers is limited to the product Difethialone Blocks. From the use of wax blocks in sewers exposure to the aquatic compartment occurs. Based on worst case assumptions the maximum predicted environmental concentration (PEC) of the active substance in sewage treatment plants is 7.2 ng/l and in surface water 0.72 ng/l.

A secondary poisoning risk assessment for the aquatic food chain is conducted according to the TGD as there is exposure of surface water due to the use of difethialone containing blocks in sewer systems. The calculated BCF for fish of 39,974 l/kg and 50 % of the $PEC_{aquatic}$ from routine baiting is used for this assessment and results in a $PEC_{oral,predator}$ of 6 µg/kg wet fish.

Atmosphere

The use pattern and means by which difethialone is deployed together with its low volatility, ensure that exposure of the atmosphere is highly unlikely.

Terrestrial compartment

Exposure of soil to the active substance occurs via residues present in sewage sludge after using wax blocks in sewers and via direct (spillages) and disperse release (deposition only by faeces as difethialone is not excreted by urine) after the use of all three products in the scenario "in and around buildings".

Based on worst case assumptions of these typical usage patterns and release mechanisms, the maximum concentration in agricultural soil after 10 years of sludge application is 6.0×10^{-4} mg/kg wwt. The highest concentration of difethialone in soil around one bait station from the use of bait blocks and/or pellets in the scenario "in and around buildings" is 0.008 mg/kg wwt.

A secondary poisoning risk assessment for the terrestrial food chain is conducted according to the TGD. The food-chain soil → earthworm → worm-eating birds or mammals is assessed, using as a worst case situation 50 % of the maximum PECsoil from the scenario "in and around buildings", for calculations. This results in a $PEC_{oral,predator} = C_{earthworm}$ of 0.4 µg/kg.

Primary and secondary poisoning

An exposure assessment for the food chain rodenticide/bait → (rodent) → bait or rodent-eating mammal or bird is presented below together with the risk assessment for this scenario.

2.2.2.5. Risk characterisation

Environmental risk in the aquatic compartment (incl. sediment)

PNEC derivation

The 48 hours EC50 (*Daphnia magna*) of 4.4 µg/l was the lowest acute value and an assessment factor of 1000 according to the TGD, has been applied.

PNECaquatic = 4.4 ng/l

No inhibitory effect on microorganisms was observed at 100 mg/l in the respiration inhibition test. As a conservative approach it has been assumed that the PNEC is at the water solubility limit for difethialone of 0.39 mg/l.

$PNEC_{microorganisms}$ = 390 µg/l

Risk characterisation for the aquatic compartment

$PEC_{aquatic}$ (worst case) = 0.72 ng/l
$PNEC_{aquatic}$ = 4.4 ng/l
PEC/PNEC (worst case) = 0.16

Due to the likely low concentrations in soil, the restricted usage patterns and the strong adsorption of the active substance to soil, it is anticipated that the active substance will not move to groundwater in significant quantities. Therefore no risk characterisation for groundwater was conducted.

Risk characterisation for sediment

The risk characterisation for the sediment has been carried out according to the Equilibrium Partitioning Method described in the TGD. The PEC/PNEC ratio for the aquatic compartment was increased by a factor of 10 to take into account uptake via ingestion as difethialone has a log Kow greater than 5. For assessing the risk to sediment dwelling organisms, the maximum PECaquatic of 7.2 ng/l, which arises from pulse-baiting, is used.

$PEC/PNEC_{aquatic}$ (worst case) = 0.16
$PEC/PNEC_{sediment}$ = 1.6

Risk characterisation for microorganisms in STPs

PEC_{STP} =7.2 ng/l
$PNEC_{microorganisms}$ = $3.9*10^{5}$ ng/l
PEC/PNEC = $2*10^{-5}$

Risk characterisation for secondary poisoning via the aquatic food chain

For $PNEC_{oral}$ derivation see section below on primary and secondary poisoning for the food chain rodenticide/bait → (rodent) → bait or rodent-eating mammal/bird

$PEC_{oral,predator}$ = 6 µg/kg wet fish
$PNEC_{oral,\ bird}$ = 0.33 µg/kg food
$PNEC_{oral,\ mammal}$ = 0.44 µg/kg food
PEC/PNEC bird = 18
PEC/PNEC mammal = 14

Summary aquatic risk assessment

No risk to the aquatic organisms and to microorganisms in STPs could be identified. For sediment and for non-target mammals and birds, a risk ratio of > 1 is calculated, respectively.

There are several uncertainties related to the calculation of surface water (and sediment) concentrations:

1. They have been calculated using a 15 % removal in a STP according to Appendix II, TGD. If using the measured Koc as input parameter for the distribution calculations in a STP, only in 8 % difethialone would be directed to surface waters. This reduces the surface water and therefore sediment concentrations and the risk ratio for sediment would become below 1. Due to the strong adsorption properties of difethialone to organic matter it seems reasonable to conclude that the amount of difethialone reaching the surface water is probably closer to 8 % than to 15 %. It is further assumed that adsorption to organic matter in surface water would further reduce surface water concentrations.
2. The PECs for surface water (and sediment) have been calculated under the assumption that no mechanical removal takes place in a STP. In reality, primary screening systems are installed in most STPs to remove particles of variable sizes down to a diameter of 2-3 mm. The calculated PECs are clearly unrealistic worst case values and it can be assumed that the real PEC surface water would be considerably lower.

Because of these uncertainties the PEC surface water (and sediment) is considered to be overestimated and the conclusion should be that sediment dwelling organisms are not likely to be at risk. Regarding the secondary poisoning assessment it is not anticipated that this exposure pathway really would lead to a risk to fish-eating birds and mammals due to the fact that concentrations in surface water are likely to decrease quickly due to adsorption to organic matter. The exposure pathway for the food chain rodenticide (bait) → rodent → rodent-eating mammal or bird is considered much more relevant (see section below).

Environmental risk in the atmosphere

The active substance has a low vapour pressure of < 1.33×10^{-5} Pa at ambient temperature. Exposure to the atmosphere is highly unlikely and no risk assessment for the atmosphere has been carried out.

Environmental risk in the terrestrial compartment

PNEC derivation

As a conservative approach it is anticipated that the highest tested concentration of 1,000 mg/kg dwt, respective 885 mg/kg wwt from the acute earthworm test, is equal to the LC50. Applying an AF of 1000 leads to the PNECsoil of 0.89 mg/kg wwt.

Risk characterisation:

PEC_{soil} (worst case) = 0.008 mg/kg wwt
$PNEC_{soil}$ = 0.89 mg/kg wwt
PEC/PNEC = 0.009

Risk characterisation for the secondary poisoning assessment via the terrestrial food chain

The food-chain soil → earthworm → worm-eating birds or mammals is assessed here. For $PNEC_{oral}$ derivation see section below on primary and secondary poisoning for the food chain rodenticide/bait → (rodent) → bait or rodent-eating mammal/bird.

PECoral,predator = Cearthworm = 0.4 µg/kg
PNECoral, bird = 0.33 µg/kg food
PNECoral, mammal = 0.44 µg/kg food
PEC/PNEC bird = 1.2
PEC/PNEC mammal = 0.9

Summary terrestrial risk assessment

The worst case PEC/PNEC ratio for the maximum soil concentration is below 1 indicating no risk to terrestrial organisms. The PEC/PNEC ratio for the secondary poisoning assessment for birds is slightly above 1. It is based on an unrealistic high PNEC and the PECsoil is the result from the use of baits during a 21 days pulse-baiting campaign in an area of 10 cm around a bait box. This is considered to be an extremely worst case situation. When using the PECsoil arising from sludge application via STPs, which represents a more widespread exposure, the risk ratio would be 0.2. Therefore it seems unlikely that worm-eating birds are at risk in this scenario.

Primary and secondary poisoning for the food chain rodenticide/bait → (rodent) → bait or rodent-eating mammal/bird

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

Primary and secondary poisoning of non target mammals and birds following the use of products containing the active substance in sewers is considered negligible.

For the scenario "in and around buildings" a primary and secondary poisoning assessment is carried out as non-target mammals and birds may be both exposed to bait and to poisoned rodents.

PNEC derivation

- For primary and secondary poisoning at Tier 1 the $PNEC_{oral}$ is related to a food concentration and values for $PNEC_{oral}$ were derived according to the TGD.

  For birds, the NOEC (reproduction) for difethialone based on a read across from the avian reproduction study with difenacoum is 0.01 mg/kg food. An assessment factor of 30 has been applied according to the TGD.

  $PNEC_{oral}$ (birds) = 0.33 µg/kg food

  As the effect mechanism of difethialone is not target specific but general for warm blood organisms, the lowest NOAEL from a 90 days repeated dose study with rats (2 µg/kg bw) is used for PNEC derivation for mammals. A conversion factor of 20 and an assessment factor 90 have been applied.

  $PNEC_{oral}$ (mammal) = 0.44 µg/kg food

- At Tier 2 of the primary and the secondary poisoning assessment, the PEC_{oral} is related to the dose and therefore the $PNEC_{oral}$ has also to be expressed on the basis of the dose.

  The NOAEL for difethialone from the read across from the avian reproduction study with difenacoum is 0.001138 mg/kg bw/day. An AF of 30 is applied according to the TGD.

  $PNEC_{oral}$ (bird) = 0.04 µg/kg bw/day

  The PNECoral (mammals) is based on a NOAEL (rat, 90 days repeated dose) of 2 µg/kg bw/day, applying an AF of 90.

  $PNEC_{oral}$ (mammals) = 0.02 µg/kg bw/day

For primary poisoning a quantitative risk assessment is carried out for Tier 1and for the long-term exposure assessment at Tier 2. For secondary poisoning a quantitative risk assessment is carried out for the long-term exposure assessment at Tier 1 and 2. This is in accordance with Addendum relevant to Biocides to the TGD on Risk Assessment on PNECoral derivation for the primary and secondary poisoning assessment of anticoagulant rodenticides (European Commission; Directorate - General Environment, 2006).

Primary poisoning

As an absolute worst case the risk at Tier 1 is quantified as the ratio between the concentration of difethialone in food and the $PNEC_{oral}$. It is assumed that non-target animals have direct access to an unlimited amount of formulated product. All three products contain 25 mg/kg difethialone and hence the PEC_{oral} is 25 mg/kg food.

Birds: PEC/PNEC ≈ 76,000
Mammals: PEC/PNEC ≈ 57,000
Dogs: PEC/PNEC ≈ 5,700

This conservative approach clearly highlights a high risk to birds and non-target mammals if difethialone containing products are freely consumed.

At Tier 2, the Emission Scenario Document for Biocides used as Rodenticides (EUBEES 2) suggests a long-term scenario for 5 days exposure, considering elimination (excretion). In a first step, the avoidance factor AV is 1 (no avoidance), the fraction of diet obtained in the treated PT is 1 and fraction of food type in the diet PD is also 1 (non-target animal feds 100% on rodenticide). In step 2 AV and PT are reduced (AV = 0.9, PT = 0.8 and PD = 1) to represent a more realistic worst case situation. For the paste in sachets formulation AV = 0.5 for both steps.

At Tier 2 the worst-case PEC/PNEC ratio for birds at step 1 is about 383,000 (sparrow) and about 126,000 for mammals (cat).

At step 2 the ratio for birds is about 275,000 (sparrow) and about 90,000 for mammals (cat).

Secondary poisoning

Rodents targeted by baiting campaigns are likely to roam outdoors and within the hunting ranges of predatory birds and mammals. A potential for secondary poisoning of birds and mammals therefore exists.

The long-term assessment at Tier 1 compares the concentration in the rodent immediately after a last meal on day 5 with the PNEC. It is assumed that non-target animals consume 50 % of their daily intake on poisoned rodents.

The worst-case PEC/PNEC ratios at Tier 1 are about 10,500 for birds and 7,900 for mammals.

At Tier 2 the PECoral is the concentration in the non-target animal after a single day of exposure to poisoned rodents. It is assumed that non-target animals consume 50 % of their daily intake on poisoned rodents.

The worst-case PEC/PNEC ratio for birds at Tier 2 is about 33,000 (kestrel) and 68,000 for mammals (weasel).

The values for secondary poisoning represent only a single day of exposure. However, poisoned rodents are likely to be available for at least several days during a rodenticide treatment and a predator could therefore be exposed over several days. Therefore these values do not necessarily represent a realistic worst case.

Summary primary and secondary poisoning

Due to the highly toxic nature of the active substance, primary and secondary poisoning poses a risk to non target mammals and birds following the use of difethialone containing products in the scenario "in and around buildings". High PEC/PNEC ratios have been estimated both for primary and for secondary poisoning.

To minimise the risk of primary and secondary poisoning to non-target mammals and birds risk reduction measures have to be in place. Careful management of anticoagulant rodenticides is essential to reduce the opportunity for exposure of non-target species to a minimum whilst maximising necessary impact on the target rodents. Risk reduction measures (see chapter 3) also reduce a possible risk of secondary poisoning for the terrestrial food chain soil → earthworm → worm-eating birds or mammals.

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

Difethialone has been evaluated as a rodenticide against rats and mice for the use pattern "in and around buildings" and "sewers".

Difethialone is a very potent rodenticide and its use poses a high risk of primary and secondary poisoning to non-target mammals and birds. Moreover, the substance can be considered as a potential PBT substance (persistent, bioaccumulative and toxic) and vPvB (very bioaccumulative, very persistent). Therefore difethialone containing products have to be handled with great caution and proper measures have to be in place (see chapter 3.3).

It is stated in the TNsG on Annex I inclusion that "Substances which fulfil the PBT or vPvB criteria shall not be included in Annex I unless releases to the environment can be effectively prevented". Emissions to the environment from the use of anticoagulant rodenticides in general can not be prevented entirely. However, it is important to have a range of active ingredients for use in rodenticides in the EU in the interest of public health and hygiene, and the hazard of e.g. primary and secondary poisoning of non-target animals or exposure to soil can be reduced by the risk reduction measures/restrictions proposed.

Difethialone is a candidate for a comparative risk assessment due to its potential PBT/vPvB properties and the risk to the environment. Such a comparative assessment can only be performed when possible alternative rodenticides have all been evaluated.

There is a risk for development of resistant strains through the use of anticoagulant substances, unless measures are taken. Therefore, there is a need for having a variety of active substances available due to the problems of resistant populations of rodents. Difethialone is a very effective

rodenticide that could become an important substance in situations when problems with resistance occur. However, difethialone should not be the first rodenticide to be chosen; on the contrary its use shall be as limited as possible.

Risk to infants accidentally ingesting bait has been identified. There are only a few reported incidents of poisonings of humans or pets due to difethialone containing products, but the use of difethialone rodenticides has been limited. However, many incidents of poisonings have been reported for anticoagulant rodenticides in general. The inclusion of a bittering agent (denatonium benzoate or similar) in all ready to use products with difethialone to prevent oral consumption is considered an adequate risk mitigation measures to reduce the risk of incidents of humans poisonings. The addition of a colouring agent to baits, that could be mistaken as being food or feedstuff, should be mandatory when the intended use of the specific product is in areas were access to the bait of the general public or animals other than the target organisms can not be totally excluded.

Formulated products containing 25 mg/kg difethialone show sufficient effectiveness, and higher concentrations in ready to use baits should not be allowed in authorised products. The applicant has not indicated any marketing of premixes or of products with higher difethialone concentrations than 25 mg/kg and therefore no such uses have been evaluated (see Appendix II).

It is recognised that anticoagulants like difethialone 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.

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 a work on possible risk mitigation measures for all anticoagulant rodenticides. A 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

The substance difethialone 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:

In view of the fact that the active substance characteristics render it potentially persistent, liable to bioaccumulate and toxic, or very persistent and very liable to bioaccumulate, the active substance is to be subject to a comparative risk assessment in accordance with the second

subparagraph of Article 10(5)(i) of Directive 98/8/EC before its inclusion in this Annex is renewed.

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

(1) The nominal concentration of the active substance in the products shall not exceed 0.0025% w/w and only ready-for-use baits shall be authorised.

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

(3) Products shall not be used as tracking powder.

(4) 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

- The applicant has not applied for a usage of difethialone in open areas, e.g. on waste dumps. As a consequence, such use has not been evaluated. If the use of difethialone in open areas is applied for at product authorisation stage at national level, a full risk evaluation of such a use of the substance has to be performed at that stage and the assessment report should be amended accordingly.
- As professionals are likely to be exposed more often, products containing difethialone may be used by professional users if data are provided to show that occupational exposure is acceptable and/or the dermal absorption of difethialone from these products is below the percentage that would give an estimated exposure equal to the threshold level (AOEL) for repeated exposure (when calculations are based on the operator exposure study). The cut off values for dermal absorption are 11.4 - 77.5 % for different products and use areas (See 2.2.1.2).
- Difethialone 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 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.
- 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 or 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 the 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 them of 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 an 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 the 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 difethialone 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 anticoagulant 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 has been provided to verify the outcome and conclusions, and permit the proposal for the inclusion of difethialone in Annex I to Directive 98/8/EC. No further information has to be submitted. However, in order to clarify whether difethialone meets the definitive B/vB- and P/vP- criteria from the PBT assessment further testing might become necessary. This would have to be decided by the PBT working group under the Existing Substances Regulation.

When submitting the dossier the applicant provided a waiving argument for the avian reproduction study. This waiving was accepted by the Rapporteur but this decision was not fully supported by all experts at Technical meeting level. However, an avian reproduction study was performed with another structurally closely related anticoagulant active substance, supported by the CEFIC rodenticide group (of which the applicant for difethialone is a member). This study has been submitted by the applicant at a late stage in the evaluation process. At the Technical Meeting III in 2006 this study was accepted for read across to difethialone and no further studies on this endpoint are deemed necessary.

A unanimous agreement to accept the waiving of the two generation reproduction study in rodents for anticoagulant rodenticides was reached at an expert meeting under the Technical Meeting in May 2006.During the completeness check process justifications to waive several studies were preliminary accepted. In the evaluation process these justifications were confirmed. However, a need to re-discuss the waiving could be necessary when all the anticoagulant rodenticides have been fully evaluated under the Biocides Directive. As a consequence additional testing could be required before the possible renewal of the Annex I inclusion.

3.5. Updating this Assessment Report

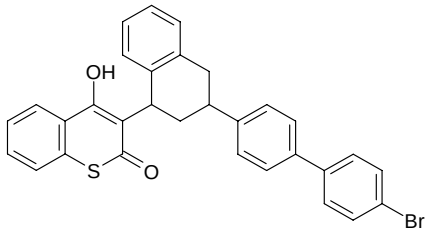
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information referred to in Articles 7, 10.4 and 14 of Directive 98/8/EC. Such adaptations will be examined and finalised in connection with any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

Appendix I: List of endpoints

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

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

Identity

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

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

Physical and chemical properties

Melting point (state purity)	233°C at the beginning of melting, 236 °C at the final stage of melting (purity 99%)
Boiling point (state purity)	No boiling point has been determined
Temperature of decomposition	No decomposition below the melting point
Appearance (state purity)	Yellow powder (purity 99%)
Relative density (state purity)	1.36 g/ml at 25 °C (purity 99%)
Surface tension	Not required, water solubility is below 1 mg/l
Vapour pressure (in Pa, state temperature)	< 1.33 x 10^{-5} Pa (22.6°C)
Henry's law constant (Pa m^3 mol^{-1})	< 1.8 x 10^{-2} Pa.m^3.mol^{-1}
Solubility in water (g/l or mg/l, state temperature)	Pure water: 0.39 mg/l at 25°C pH not stated
Solubility in organic solvents (in g/l or mg/l, state temperature)	Results at 20°C Dichloromethane: 10 to 14 g/l Hexane: 0.2 g/l
Stability in organic solvents used in biocidal products including relevant breakdown products	No studies available. However, the stability of the products, where solvent is used, is documented. Moreover, data on stability in the premix is available.
Partition coefficient (log P_{OW}) (state temperature)	6.29 at pH 7.3 (ambient temperature)
Hydrolytic stability (DT_{50}) (state pH and temperature)	Results at 25°C pH 5: > 1 year pH 7: 175 days pH 9: 155 days No specific degradation products were detected.
Dissociation constant	Due to low water solubility, difethialone is not considered ionisable
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Approximately 234nm, 260nm and 330nm (ε not stated).

Photostability (DT_{50}) (aqueous, sunlight, state pH)	Study with natural sunlight at 28-35°C: DT 50 (pH 5) = 59.7 min DT 50 (pH 7) = 61.9 min DT 50 (pH 9) = 54.5 min Study with artificial sunlight at 20°C: DT 50 (pH 7) = 23.4 min In both studies photolysis of difethialone led to the formation of multiple components but none of these were identified with respect to its chemical identity
Quantum yield of direct phototransformation in water at Σ > 290 nm	6.183×10^{-3} mol/photon from the study with artificial sunlight
Flammability	Not highly flammable
Explosive properties	Not explosive
Oxidizing properties	Not oxidizing
Reactivity towards container material	No reactivity towards container material known

Proposed classification and 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; R61	
with regard to fate and behaviour data	N; R53	
with regard to ecotoxicological data	N; R50	
Specific concentration limits for human health and environmental effects	C ≥ 0.5%	T+, N; R61 - 26/27/28 - 48/23/24/25 - 50/53
	0.25 ≤ C <0,5%	T+, N; R26/27/28 - 48/23/24/25 - 50/53
	0.025% ≤ C< 0.25%	T, N; R23/24/25 - 48/23/24/25 - 51/53
	0.0025% ≤ C <0.025%	Xn; R20/21/22 - 48/20/21/22 - 52/53

Chapter 2: Methods of Analysis

Analytical methods for the active substance

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

Analytical methods for residues

Soil (principle of method and LOQ)	Soil is extracted by shaking with acetone. Determination of the concentrated extract is by reverse-phase LC-MS (target ion 539 amu, confirmatory ions 541 and 561 amu). A Lichrospher C-18 column is used with methanol/water/phosphoric acid (92.5/7.5/0.1, v/v/v) mobile phase. The limit of determination is 0.01 mg/kg (defined as the lowest concentration at which acceptable recovery has been demonstrated).
Air (principle of method and LOQ)	Air is bubbled through a tube containing 1-methoxyethanol collecting liquid. Determination is by reverse-phase HPLC/UV at a wavelength of 254 nm. A Nucleosil C-18 column is used with acetonitrile/ 0.0425% phosphoric acid (80/20, v/v/v) mobile phase. The limit of determination is 0.2 µg/m3 (defined as the lowest concentration at which acceptable recovery has been demonstrated).
Water (principle of method and LOQ)	Acetonitrile is added to the water sample and clean up is by passage through a C-8 column solid phase extraction cartridge. Determination is by reverse-phase HPLC/MS-MS (two ion transitions monitored 536.9>79 and 538.9>81). An Inertsil ODS-EP column is used with acetonitrile/water/acetic acid (85/15/0.1, v/v/v) mobile phase. The limit of determination is 0.05 µg/l (defined as the lowest concentration at which acceptable recovery has been demonstrated).
Body fluids and tissues (principle of method and LOQ)	**Blood** Blood is diluted with methanol. Phosphate buffer, a mixture of ethanol/ethyl acetate and trichloroacetic acid solution is added. The sample is shaken and the organic phase removed. The sample is re-

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

method and LOQ for methods for monitoring purposes)	methanol. After centrifugation the samples are diluted with methanol/water. Determination with LC-MS-MS. Primary method (m/z: 81.0). Confirmation ion (m/z: 79.3). Calibration range 0.05 to 5.0 ng/ml. Limit of determination is 0.01 mg/kg Linearity R^2 = >0.9995 RSD < 20%, Recovery rates within 70-110%

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Difethialone was rapidly and extensively absorbed by rats. Radioactivity was first detected in blood 30 minutes after dosing (0.5 mg ^{14}C-difethialone/kg bw), reaching the maximum level, 0.09 µg eq. LM 2219/mL, approximately 24 hours after dosing
Rate and extent of dermal absorption:	No studies on the end use formulations of difethialone. An in vivo human dermal absorption of 4% may be calculated by combining rat *in vivo* data and rat:human *in vitro* data. This represents a reasonable worst case value to be used in the risk assessments of the products, derived from the dermal delivery (absorbed dose and amounts retained in the epidermis and dermis layers of the skin, but excluding amounts in stratum corneum) of difethialone in glycol solvent (25 g/l) 24h after application
Distribution:	Difethialone was distributed to body organs with the highest levels found in liver
Potential for accumulation:	Difethialone has the potential to bioaccumulate in the liver. The plasma half-life was 2.3 days following an exposure to 0.5mg difethialone /kg bw. The liver concentrations reached a peak within 24 hours after administration (22.8 to 42.5% of administered dose in males and females). At the end of the six month observation period approximately 10% of the administered dose was still present in the liver. The half-life in the liver was in the region of 18 weeks for both males and females
Rate and extent of excretion:	Elimination was exclusively in the faeces as unchanged parent material, with 37% excreted in the first 3 days, 57% within 14 days following an

	exposure of 0.5mg difethialone/kg bw. There was no excretion via expired air or urine
Toxicologically significant metabolite(s)	Essentially the entire radioactivity found in liver and faecal samples was from unchanged labelled difethialone. No major metabolites were identified

Acute toxicity

Rat LD_{50} oral	Combined sexes - between 0.4 and 0.8 mg/kg bw. In a second study LD_{50} for males was 0.55 mg/kg bw and for females was calculated to be 0.58 mg/kg bw.
Dog LD_{50} oral	Combined sexes - 11.81 mg/kg bw
$LOAEL_{acute}$	Dog study (oral administration): 5 mg/kg bw (50 % reduction in plasma prothrombin level)
Rat LD_{50} dermal	Combined sexes - 6.5 mg/kg bw
Rat LC_{50} inhalation	Whole body exposure: LC_{50} = <10.7 µg/l/4h Nose only exposure: LC_{50} = >5.0 µg/l/4h but <19.3 µg/l/4h
Skin irritation	Non-irritating
Eye irritation	Slightly irritating. EU criteria for classification not fulfilled.
Skin sensitization (test method used and result)	Maximisation test using Freund's Complete Adjuvant (test of low reliability) No indications of delayed contact hypersensitivity among guinea pigs subject to an induction and challenge regimen that included dose concentrations up to lethal levels.

Repeated dose toxicity

Species/ target / critical effect	Pig (30 + 14 days, oral administration) Rat (13 weeks, oral administration) Dog (13 weeks, oral administration) Critical effect observed in the studies: Haemorrhagic effects (consistent with the known mode of action, impairment of the clotting cascade, and increased prevalence of haemorrhages, eventually leading to death), No toxic endpoints except haemorrhage reported.
Lowest relevant oral NOAEL / LOAEL	Rat (90d) LOAEL = 4 µg/kg bw/day

	Dog (90d): NOAEL = 2 µg/kg bw/day LOAEL = 20 µg/kg bw/day NOAEL = 10 µg/kg bw/day
Lowest relevant dermal NOAEL / LOAEL	No data available – not required.
Lowest relevant inhalation NOAEL / LOAEL	No data available – not required

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

Carcinogenicity

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

Reproductive toxicity

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

	bw/day. Rabbit maternal LOAEL – 10 µg/kg bw/day Rabbit maternal NOAEL – 5 µg/kg bw/day Embryofoetal toxicity – LOAEL - >10 µg/kg bw/day

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Difethialone was investigated, in various screening tests for potential pharmacological activity other than its known anticoagulant properties. Difethialone showed no antianginal activity *in vivo* or *in vitro;* no antihypertensive activity; no sedative activity; no anticonvulsant activity; no antidepressant activity; no antispasmodic activity in a variety of *in vitro* tests and no analgesic, anti-inflammatory or gastric antiacid activity in various tests designed to investigate these endpoints. Difethialone, has a highly specific mode of action, blocking regeneration of vitamin K in the liver, and no other pharmacologic activity has been established for the molecule.
Lowest relevant developmental NOAEL / LOAEL.	Not established

Other toxicological studies

	Studies to investigate antidotal treatment of intoxicated rats or dogs were completed. Two studies in dogs demonstrated the effect of antidotal vitamin K1 therapy (phytomenadione) following single lethal doses of difethialone. In another study in rats (25 ppm end use product given as a diet replacement for 1, 2 or 3 days) antidotal treatment was successful following 24 hour exposure, but less successful with longer periods of exposure (the majority of rats died after 48 or 72 hours exposure to difethialone).

Medical data

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

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

Summary

	Value	Study	Safety factor
ADI (acceptable daily intake, external long-term reference dose)	Not applicable		
AOEL-S (Operator Exposure)[5]	2.8 µg/kg bw (acute)	Acute oral toxicity to dog	1800[6]
	0.007 µg/kg bw/day (repeated dose)	90 day oral toxicity to rat	300[7]
ARfD (acute reference dose)	Not applicable		

5 At the Technical Meeting on Biocides, May 2007 it has been decided to derive the acute AOEL from the maternal NOAEL established in a teratogenicity study.

6 Normal inter- and intraspecies safety factor of 100, a factor of 2 for LOAEL to NOAEL extrapolation, a factor of 3 for use of a moderate sensitive species and a factor of 3 due to the severity of the potential developmental effect

7 Interspecies and intraspecies safety factor of 100 and an additional assessment factor of 3 due to the severity of the potential developmental effect

Acceptable exposure scenarios (including method of calculation)

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

Indirect exposure as a result of use	Exposure scenario: Infants ingesting 10 mg (TNsG on Human Exposure to Biocidal products – default of bait treated with reppelent) or 5 gram bait (User Guidance to TNsG on Human Exposure – Poison Information Specialists general estimate of "one bite"). MOE= 2 x 10^5 (Infants ingesting 10 mg), 400 (Infants ingesting 5 gram) Scenario concerning handling of dead rodents is not presented as it is considered as unrealistic

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Results at 25°C pH 5: > 1 year pH 7: 175 days pH 9: 155 days No specific degradation products were detected
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Study with natural sunlight at 28-35°C: DT 50 (pH 5) = 59.7 min DT 50 (pH 7) = 61.9 min DT 50 (pH 9) = 54.5 min Study with artificial sunlight at 20°C: DT 50 (pH 7) = 23.4 min In both studies photolysis of difethialone led to the formation of multiple components but none of these were identified with respect to its chemical identity
Quantum yield of direct phototransformation in water at Σ > 290 nm	6.183 x 10^{-3} mol/photon from the study with artificial sunlight
Biodegradation in seawater	Not applicable (exposure to seawater extremely limited in space and levels
Non-extractable residues	Not applicable (exposure to aquatic systems extremely limited in space and levels).
Distribution in water / sediment systems (active substance)	Not applicable (exposure to aquatic systems extremely limited in space and levels).
Distribution in water / sediment systems (metabolites)	Not applicable (exposure to seawater extremely limited in space and levels).

Route and rate of degradation in soil

Mineralization (aerobic)	< 2% after 100 days (3 soils).
Laboratory studies (range or median, with number of measurements, with regression coefficient)	Two aerobic biodegradation studies available: 1. DT_{50lab} (20°C, aerobic): DT_{50} = 224 to 524 days DT_{90} = 746 to 1741 days 2. DT_{50lab} (25°C, aerobic): DT_{50} = 190 days DT_{90} = 631 days Normalised to 12°C the DT_{50} values range from 417 to 976 days and the DT_{90} values from 1390 to 3244 days.
Field studies (state location, range or median with number of measurements)	Not applicable.
Anaerobic degradation	Not applicable.
Soil photolysis	Not applicable.
Non-extractable residues	Under aerobic conditions the bound residues exceeding 10% were 10.9% at day 208 day (final day) in the first aerobic biodegradation study and 11-24% during the second aerobic biodegradation study. The NER results in the second aerobic biodegradation study may be due to the extraction technique used, which is not as efficient as the technique use in the first aerobic biodegradation study. As the risk associated with bound residues is assumed to be less than for the active compound and the exposure to soil is restricted to only small areas there seems to be no need for further testing in order to identify bound residues at present.
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	In the first aerobic biodegradation study degradation of difethialone led to the formation of two unidentified metabolites which were present in quantities exceeding 10% applied radioactivity. As the risk associated with bound residues is assumed to be less than for the active compound and the exposure to soil is restricted to only small areas there seems to be no need for further testing in order to identify metabolites at present.
Soil accumulation and plateau concentration	Not applicable.

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Soil distribution (partition) coefficient, KD: Not determined. Freundlich soil adsorption coefficient, KF: 2.3 x 105 to 2.4 x 107 ml/g (adsorption) 1.6 x 105 to 1.8 x 106 ml/g (desorption). Freundlich soil adsorption coefficient normalised for organic carbon content, KOC: 1.0 x 108 to 5.3 x 109 ml/g (adsorption) 5.4 x 107 to 3.9 x 108 ml/g (desorption). No pH effects observed/expected. Difethialone is considered immobile in soil.

Fate and behaviour in air

Direct photolysis in air	Concerning the overall relevance of the atmospheric fate of difethialone the very low vapour pressure of the compound has to be taken into account. Air will not be an environmental compartment of concern for difethialone used in rodenticides.
Quantum yield of direct photolysis	Not determined.
Photo-oxidative degradation in air	The estimated half-lives for the hydroxyl and ozone reactions in air are 2.2 and 2.0 hours, respectively (calculated with AOPWIN, v1.90)
Volatilization	Vapour pressure < 1.3 x 10^{-5} Pa. Henry's law constant < 1.8 x 10^{-2} $Pa.m^3.mol^{-1}$ (based on a water solubility of 0.39 mg/l) Difethialone is not expected to volatilise to air in significant quantities.

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} = 51 µg/l
Invertebrates			
Daphnia magna	48 hours	Immobilisation	EC_{50} = 4.4 µg/l
Algae			
Selenastrum capricornutum	72 hours	Growth rate	E_rC_{50} > 180 µg/l
Microorganisms			
Activated sludge	3 hours	Respiration inhibition	EC50 > 100 mg/l

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia foetida* .	14-day LC_{50} > 1000 mg/kg dry soil (synthetic OECD substrate)
Reproductive toxicity to	Not appropriate

Effects on soil micro-organisms

Nitrogen mineralization	Waived
Carbon mineralization	Waived.

Effects on terrestrial vertebrates

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

Effects on honeybees

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

Effects on other beneficial arthropods

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

Bioconcentration

Bioconcentration factor (BCF) aquatic	Waived No study available. The BCF_{fish} was calculated from the logKow of 6.29 according to the TGD and resulted in BCF_{fish} of about 40,000 l/kg.
Depration time (DT_{50}) (DT_{90})	Waived.
Level of metabolites (%) in organisms accounting for > 10 % of residues	Waived.

Bioconcentration factor (BCF) terrestrial	Waived No study available. The $BCF_{earthworm}$ was calculated from the logKow of 6.29 according to the TGD and resulted in $BCF_{earthworm}$ of 23,943 l/kg..

Chapter 6: Other End Points

Not applicable.

Appendix II: List of Intended Uses

Product type

Rodenticide (PT14)

Claim of the participant

For the control of rats and mice

Target organisms:

Brown rat *(Rattus norvegicus)*
Black rat *(Rattus rattus)*
House mouse (*Mus domesticus)*

Concentration:

The active substance is used at a nominal concentration of 25 mg/kg (range 0.001875 - 0.003125%).

Categories of users:

Professionals and non-professionals

Type of application:

Difethialone is used in products as the active substance for the urban and agricultural control of rodents indoors (i.e. in grain silos, warehouses), in and around farms, buildings and in sewer systems. In sewer systems only block bait is applied, whereas all three products are used for the other applications.

The active substance is used in three, partly cereal-based, products.

- Block bait (green blocks, ready for use), supplied loose or in protective sachets made of LDPE
- Paste bait (blue paste, ready for use), supplied in sachets made of paper
- Pellet bait (blue cereal pellets, ready for use), supplied loose and in protective sachets made of LDPE

Difethialone containing products are manually placed at secured bait points. To maximise exposure of the target rodents, the products are placed where they are most likely to be encountered by the target organisms (e.g. on habitual rat-runs).

Formulated products containing difethialone are not applied directly on food or feeding stuffs. Products are not intended to be applied directly on surfaces intended for contact with food or

feeding stuffs. However, difethialone containing products are intended to be used in premises were food or feeding stuffs are prepared or stored.

The applicant has not supported a usage of difethialone in open areas, e.g. on waste dumps. As a consequence, such an open use has not been evaluated in this CA-report. If the use of difethialone in open areas is applied for when products will be evaluated at national level, a full risk evaluation of such use of the substance should be performed at that stage.

Appendix III: List of studies

Data protection is claimed by the applicant 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 applicant. 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.

Section No / Reference No	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company** **Report No.** **GLP (where relevant)** **(Un)Published**	**Data Protection Claimed (Yes/No)**	**Owner**
III-A 6.12.2/02	Alejandro Vásquez, G. and Angeles Rodríguez, S.	2000	Title: Bleeding disorder caused by exposure to a rodenticide, report of one case. Med. Chile 2000;128:647-649.	N	Public
III-B2 6.1.1/01	.	2001a	Rodilone paste, Study for acute oral toxicity in rats. Bayer AG, Toxicology, Wuppertal, Germany. Laboratory report number PH 31396. GLP, unpublished	Y	Bayer
III-B2 6.1.2/01		2001b	Rodilone paste, Study for acute dermal toxicity in rats. Bayer AG, Toxicology, Wuppertal, Germany. Laboratory report number PH 31397. GLP, unpublished	Y	Bayer
III-A 5.7.2/01	Anon	2003a	RRAC (Rodenticide Resistance Action Committee), Checklist for rodenticide users experiencing difficulties. Not GLP, Published.	N	Public
III-A 5.7.2/02	Anon	2003b	Technical monograph 2003. Anticoagulant resistance management strategy for Pest Management professionals, Central and Local government and other competent users of rodenticides. CropLife International, Not GLP, Published.	N	Public
III-A 6.12.1/02	Anon	--	Title: Principles of medical supervision of employees exposed to Difethialone, Bromadiolone and Chlorophacinone-based rodenticides. The treatment of anticoagulant rodenticide poisoning – Advice to physicians Personal communication	N	Lipha
III-A 6.12.1/03	Anon	2005	Worker Exposure Report Rodenticide Formulation at Liphatech S.A.S., Pont du Casse, France *This report contains confidential information.*	Y	Lipha
III-A 6.13/01	Anon	--	Title: The treatment of anticoagulant rodenticide poisoning – Advice to veterinarians	N	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-B2 4.1/01	Anon	2003c	Difethialone in Rodilon paste formulation. Method validation report as of 02/01. Bayer CropScience AG, report number VALDIFPATE-01. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/09	Anon	2001a	Report on the official evaluation of plant protection products. Landwirtschaftskammer Weser-Ems, Report No. P2-73110409. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/19	Anon	2001b	Report on the official evaluation of plant protection products. Landwirtschaftskammer Weser-Ems, Report No. not stated. Not GLP, Unpublished.	Y	Bayer
(Doc II-A Section 2.4)	Bayer AG, ICI Public Health, Lipha, Rentokil Limited, Shell International Chemical, Company Limited, Sorex Limited	1992	Anticoagulant rodenticide humaneness, data overview Report Number GR-959-0075	N	-
III-A 6.10/01		1991	Compared hepatic kinetics of brodifacoum and difethialone in the rat after oral administration of 0.06 mg/kg once weekly for 4 consecutive weeks. Lipha Research Center, Lyons, France, laboratory report no. L-AV/VN GLP/Unpublished	Y	Lipha
III-A 6.2/01		1986	Toxicokinetic and metabolism. 1. Study performed with the molecule marked ^{14}C. 2. Study performed with the cold molecule. Lipha Research Center, Lacassagne, France, laboratory report no. MET-RAD/LM2219-5-85-3 GLP/Unpublished	Y	Lipha
III-A 6.2/02		1987	LM 2219 Sanguine and hepatic levels after single oral administration of 0.5 and 1 mg/kg to rats. No laboratory name or study identification number provided. Non-GLP/Unpublished	Y	Lipha
(Doc II-B1 Section 3)	Berning, C.K., Griffith, J.F. and Wild, J.E.	1982	Research on the effectiveness of denatonium benzoate as a deterrent to liquid detergent ingestion by children. Fundamental and applied toxicology 2:44-48.	N	Public
(Doc II-B2 Section 3)	Berning, C.K., Griffith, J.F. and Wild, J.E.	1982	See (Doc II-B1 Section 3)	N	Public
(Doc II-B3 Section 3)	Berning, C.K., Griffith, J.F. and Wild, J.E.	1982	See (Doc II-B1 Section 3)	N	Public
III-A 6.12.1/01	Bressot Perrin, H.	1999	Personal communication	N	Lipha
III-A 4.2(c)/01	Brice, A. and Harrand, C.	2004	Difethialone: Validation of an analytical method for the determination of residues in drinking and surface water. Covance Laboratories Limited, Report No. 2336/007-D2149. GLP, Unpublished.	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-A 6.8.1/01		1985a	Preliminary teratology in the rat - Difethialone. Hazleton Institute Francais de Toxicologie, France, laboratory report no. 504211 GLP/Unpublished	Y	Lipha
III-A 6.8.1/02		1986a	Oral teratology in the rat. Hazleton Institute Francais de Toxicologie, France, laboratory report no. 509202 GLP/Unpublished	Y	Lipha
III-A 6.8.1/03	.	1985b	Preliminary teratology in the rabbit - Difethialone. Hazleton Institute Francais de Toxicologie, France, laboratory report no. 504212 GLP/Unpublished	Y	Lipha
III-A 6.8.1/04	.	1986b	Oral teratology in the rabbit. Hazleton Institute Francais de Toxicologie, France, laboratory report no. 512229 GLP/Unpublished	Y	Lipha
(Doc II-C Section 2.4)	Brunner, H. and Coman, B.J.	1983	The ingestion of artificially coloured grain by birds, and its relevance to vertebrate pest control Australian Wildlife Research 10: 303-310	N	Public
(Doc II-C Section 2.4)	Caithness, T.A. and Williams, G.R	1971	Protecting birds from poisoned baits New Zealand Department of Internal Affairs, Wildlife Publication No. 129	N	Public
III-A 2.8.9/02	Caruel, H.	2005	Difethialone active ingredient 5 batches analysis. Centre R&D de Sangosse, Report No. DIF0510A. GLP, Unpublished. *This report contains confidential information.*	Y	Lipha
III-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
III-B2 6.6/02	Chambers, J.G., Snowdon, P.J.	2004	See III-B1 6.6/02	Y	Lipha
III-B3 6.6/02	Chambers, J.G., Snowdon, P.J.	2004	See III-B1 6.6/02	Y	Lipha
III-A 6.2/05		1995	Compared hepatic kinetics of LM 2472 and LM 2473 after single oral administration of 0.5 mg/kg in rats. Lipha Research Center, Lyons, France, laboratory report no. Translation of AV/VN of 11.09.1990 Non-GLP/Unpublished	Y	Lipha
(Doc II-A Section 3.8)	Competent Authority Report	2005	Draft competent authority (CA) report on warfarin of August 2005 prepared by the Irish Competent Authority as a part of the review programme referred to in Article 16(2) of Directive 98/8/EC.	N	-
(Doc II-C Section 2.4)		1992	Rodenticide ecology: pre-lethal effects of anticoagulants on rat behaviour. Proc. 15th Vertebrate Pest Conf. (J.E. Borrecco and R.E. Marsh: Eds.) University of California, Davis, CA., USA	N	Public
(Doc II-C Section 2.4)	Cramp, S. and Perrins, C.M.: Eds.)	n.s.	Handbook of the Birds of Europe, the Middle East and North Africa. The Birds of the	N	Public

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Western Palearctic Vols. III and VIII. Oxford University Press		
(Doc II-C Section 2)	Crop Life International, Rodenticide Resistance Action Committee	2003	Anticoagulant resistance management strategy for pest management professionals, central and local government and other competent users of rodenticides Technical Monograph	N	Public
(Doc II-B1 Section 3.3)	Crop Life International, Rodenticide Resistance Action Committee. Techn. Monograph	2003	Anticoagulant resistance management strategy for pest management professionals, central and local government and other competent users of rodenticides.	N	Public
(Doc II-B2 Section 3.3)	Crop Life International, Rodenticide Resistance Action Committee. Techn. Monograph	2003	See (Doc II-B1 Section 3.3)	N	Public
(Doc II-B3 Section 3.3)	Crop Life International, Rodenticide Resistance Action Committee. Techn. Monograph	2003	See (Doc II-B1 Section 3.3)	N	Public
III-A 7.3.1/01	Curl, M.G.	2004	The estimation of photochemical oxiditive degradation of difethialone. TSGE, laboratory report no. 12-1-10.POD Non-GLP/Unpublished	Y	Lipha
III-A 7.1.1.2.1/01	Daniel, M. and Swarbrick, R.H.	2003a	Difethialone: Determination of 28 day ready biodegradability (CO_2 headspace test). AstraZeneca UK Ltd., laboratory report no. 01-0450/C GLP/Unpublished	Y	Lipha
III-A 7.1.2.1.2/01	Daniel, M. and Swarbrick, R.H.	2003b	Difethialone: Determination of anaerobic biodegradability. AstraZeneca UK Ltd., laboratory report no. 01-0450/E GLP/Unpublished	Y	Lipha
III-A 6.9/01		1986	LM 2219 Pharmacological approach. Research Centre, Lyonnaise Industrielle Pharmaceutique, 69359 Lyon Cedex, France. Report Number: No identification stated Non GLP/Unpublished	Y	Lipha
III-B2 5.10/01		2000a	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a 1-day no-choice feeding trial with individually caged Norway rats. Hygieneinstitut Sachsen-Anhalt, Report No. ZEWR 06/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/03		2000b	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a 4-day choice feeding trial with individually caged Norway rats. Hygieneinstitut Sachsen-Anhalt, Report No. WEWR 05/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/05		2000c	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a 4-day choice trial with a group of Norway rats in pens.	Y	Bayer

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Hygieneinstitut Sachsen-Anhalt, Report No. WGWR 07/00. Not GLP, Unpublished.		
III-B2 5.10/06		2000d	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a 4-day choice trial with a group of Norway rats in pens. Hygieneinstitut Sachsen-Anhalt, Report No. WGWR 08/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/08		2001a	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a field trial with Norway rats. Hygieneinstitut Sachsen-Anhalt, Report No. BWR 12/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/10		2000e	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a 4-day choice study in a group of roof rats in pens. Hygieneinstitut Sachsen-Anhalt, Report No. WGHR 03/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/11		2000f	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a four-day choice study in a group of roof rats in pens. Hygieneinstitut Sachsen-Anhalt, Report No. WGHR 04/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/13		2000g	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a three day no-choice feeding trial in a group of house mice in an enclosure. Hygieneinstitut Sachsen-Anhalt, Report No. ZGHM 09/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/15		2000h	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a six-day choice feeding study in a group of house mice in an enclosure. Hygieneinstitut Sachsen-Anhalt, Report No. WGHM 10/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/16		2000i	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a six-day choice feeding study in a group of house mice in an enclosure. Hygieneinstitut Sachsen-Anhalt, Report No. WGHM 11/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/17		2001b	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a field trial with house mice. Hygieneinstitut Sachsen-Anhalt, Report No. BHM 13/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/18		2001c	Evaluation of the efficacy of Rodilon paste in 100 g paper sachets in a field trial with house mice. Hygieneinstitut Sachsen-Anhalt, Report No. BHM 14/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/24		2000j	Efficacy of Rodilon paste in 100 g paper sachets in a 4-day choice feeding trial with individually caged black rats.	Y	Bayer

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Hygieneinstitut Sachsen-Anhalt, Report No. WEHR 01/00. Not GLP, Unpublished.		
III-B2 5.10/25		2000k	Efficacy of Rodilon paste in 100 g paper sachets in a one-day no-choice feeding trial with individually caged black rats. Hygieneinstitut Sachsen-Anhalt, Report No. ZEHR 02/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/02		2000a	Efficacy of Rodilon paste (0.0025% difethialone) administered for one day in a no-choice trial with wild rats (Rattus norvegicus). Bayer Animal Health, Report No. END077/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/04		2000b	Palatability and efficacy of Rodilon paste (0.0025% difethialone) administered for four days in a choice trial with wild rats (Rattus norvegicus) in pens. Bayer Animal Health, Report No. END024/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/07		2001a	Efficacy of Rodilon paste (0.0025% difethialone) administered for four days in a choice trial with individually caged wild rats (Rattus norvegicus). Bayer Animal Health, Report No. END031/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/14		2001b	Palatability and efficacy of Rodilon paste (0.0025% difethialone) administered for four days in a choice trial with wild house mice (Mus musculus) in pens. Bayer Animal Health, Report No. END025/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/26		2000c	Efficacy of Rodilon paste (0.0025% difethialone) administered for one day in a no-choice trial with wild mice (Mus musculus). Bayer Animal Health, Report No END027/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/27		2000d	Field trial with a rodenticide paste bait containing 25 ppm difethialone against rats (Rattus norvegicus) at an animal home. Bayer Animal Health, Report No END052/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/28		2000e	Field trial with a rodenticide paste bait containing 25 ppm difethialone against rats (Rattus norvegicus) on a farm in Extertal, Westfalia. Bayer Animal Health, Report No END051/00. Not GLP, Unpublished.	Y	Bayer
III-B2 5.10/29		2000f	Field trial with a rodenticide paste bait containing 25 ppm difethialone against mice (Mus musculus) in a rabbit enclosure. Bayer Animal Health, Report No END053/00. Not GLP, Unpublished.	Y	Bayer
(Assessment rep. Section 3.1)	European Chemicals Bureau (ECB)	2002	TNsG on Annex I inclusion. Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market.	N	Public
(Doc II-A Section 4)	European Chemicals Bureau (ECB)	2000	Technical Guidance Document in Support of the Directive 98/8/EC Concerning the Placing of Biocidal Products on the Market	N	Public

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Guidance on Data Requirements for Active Substances and Biocidal Products		
(Doc II-B1 Section 3)	European Chemicals Bureau (ECB) a	2002	Technical Notes for Guidance on Human Exposure to Biocidal Products (June 2002)	N	Public
(Doc II-B1 Section 3)	European Chemicals Bureau (ECB) b	2004	Technical Notes for Guidance on human exposure to Biocidal products (June 2002), User Guidance version 1	N	Public
(Doc II-B2 Section 3)	European Chemicals Bureau (ECB) a	2002	See (Doc II-B1 Section 3)	N	Public
(Doc II-B2 Section 3)	European Chemicals Bureau (ECB) b	2004	See (Doc II-B1 Section 3)	N	Public
(Doc II-B3 Section 3)	European Chemicals Bureau (ECB) a	2002	See (Doc II-B1 Section 3)	N	Public
(Doc II-B3 Section 3)	European Chemicals Bureau (ECB) b	2004	(Doc II-B1 Section 3)	N	Public
(Doc II-C Section 1)	European Chemicals Bureau (ECB) a	2002	(Doc II-B1 Section 3)	N	Public
(Doc II-C Section1.4)	European Chemicals Bureau (ECB) b	2004	(Doc II-B1 Section 3)	N	Public
(Doc II-A Section 4)	European Commission, Joint Research Centre	2003	Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.	N	Public
(Doc II-B1 Section 3.3)	European Commission, Joint Research Centre	2003	See (Doc II-A Section 4) (TGD)	N	Public
(Doc II-B2 Section 3.3)	European Commission, Joint Research Centre	2003	See (Doc II-A Section 4) (TGD)	N	Public
(Doc II-B3 Section 3.3)	European Commission, Joint Research Centre	2003	See (Doc II-A Section 4) (TGD)	N	Public
(Doc II-C Section 2)	European Commission, Joint Research Centre	2003	See (Doc II-A Section 4) (TGD)	N	Public
(Assessment rep. Section 3)	European Commission; Directorate – General Environment	2007	Risk mitigation measures for anticoagulants used as rodenticides 24. CA-March07-Doc.6.3 – final	N	Public
(Doc II-C Section 2.4)	European Commission; Directorate – General Environment	2006	Addendum relevant to Biocides to the TGD on Risk Assessment – PNECoral derivation for the primary and secondary poisoning assessment of anticoagulant rodenticides Technical Guidance Document adopted by CA23rd Competent Authority Meeting (CA-Nov06-Doc.4.3)	N	Public

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
(Assessment rep. Section 2.2.1.2)	European Commission, Health & Consumer Protection Directorate General	2004	Guidance Document on Dermal Absorption, Sanco/222/2000 rev. 7	N	Public
(Doc IIA, Section 3.1)	European Commission, Health & Consumer Protection Directorate General	2004	See (Assessment rep. Section 2.2.1.2)	N	Public
III-B1 5.10/05		1994a	Difethialone miniblocks in albino rats. Standard Norway rat anticoagulant dry bait laboratory test method. LiphaTech Inc., Report No. 94040. GLP, Unpublished.	Y	Lipha
III-B1 5.10/06		1995a	Difethialone miniblocks in albino rats. Standard Norway/roof rat acute dry bait laboratory test method. LiphaTech Inc., Report No. 95022. GLP, Unpublished.	Y	Lipha
III-B1 5.10/07		1994b	Difethialone miniblocks in Swiss-Webster mice. Standard house mouse anticoagulant dry bait laboratory test method. LiphaTech Inc., Report No. 94041. GLP, Unpublished.	Y	Lipha
III-B1 5.10/08		1995b	Difethialone miniblocks in Swiss-Webster mice. Standard house mouse acute dry bait laboratory test method. LiphaTech Inc., Report No. 95024. GLP, Unpublished.	Y	Lipha
III-B3 5.10/07		2000a	Difethialone pellets in Peromyscus. Standard Peromyscus species acute dry bait laboratory test method 1.215 (6-28-91). LiphaTech Inc., Report No. 99098. GLP, Unpublished.	Y	Lipha
III-B3 5.10/08		2000b	Difethialone pellets in Peromyscus mice. Standard Peromyscus species anticoagulant dry bait laboratory test method 1.216. LiphaTech Inc., Report No. 99092. GLP, Unpublished.	Y	Lipha
(Doc II-C Section 2.4)		1987	Rat movements and control on an Oxfordshire farm J. Zoology, London. 213, 745-749	N	Public
III-B1 3.2		1987	See (Doc II-C Section 2.4)	N	Public
III-B2 3.2		1987	See (Doc II-C Section 2.4)	N	Public
III-B3 3.2		1987	See (Doc II-C Section 2.4)	N	Public
III-A 7.5.3.1.1/02		1988a	30-day acute oral toxicity study with LM-2219 technical in bobwhite quail. Bio-Life Associates Ltd., laboratory report number 87 QD 93 GLP/Unpublished	Y	Lipha
III-A 7.5.3.1.2/01		1986	30-day dietary LC_{50} study with LM-2219 technical in mallard ducklings. Bio-Life Associates Ltd., report number 85 DC 64 GLP/Unpublished	Y	Lipha
III-A 7.5.3.1.2/02		1988b	30-day dietary LC_{50} study with LM-2219 technical in bobwhite quail. Bio-Life Associates Ltd., laboratory report number 87 QC 89	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			GLP/Unpublished		
III-B1 3.7/03	Gambert, C.	2001	Stability study: difethialone green blocks at 25 mg/kg. LiphaTech Centre de recherche et developpement, laboratory report no. STADIFBLOCV/0901 Not GLP/Unpublished	Y	Lipha
III-A 6.1.2/01		1986	Acute dermal toxicity to rats of LM2219. Huntingdon Research Centre Ltd, laboratory report no. 861068D/LPA135/AC GLP/Unpublished	Y	Lipha
(Doc II-C Section 2.4)		2000	Fraßabschreckende Wirkung von gefärbtem Saatgut auf Vögel. http://www.bba.de/oekoland/oeko3/voegel.htm	N	Public
(Doc II-C Section 2.4)		1988	Versuche mit Antikoagulantien zur Abschätzung des Vergiftungsrisikos bei Beutegreifern. Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft 245, 401	N	Public
(Doc II-C Section 2.4)		1990a	Untersuchungen zur Abschätzung des Sekundärvergiftungsrisikos bei Beutegreifern durch Rodentizide Nachrichtenbl. Deut. Pflanzenschutzd. 42 (2): 22-25.	N	Public
(Doc II-C Section 2.4)		1990b	Untersuchungen zur Abschätzung des Gefährdungspotentials von Rodentiziden für Waldkäuze (Strix aluco L.). Nachrichtenbl. Deut. Pflanzenschutzd. 42 (10): 153-156.	N	Public
III-B1 6.1.1/01		1993a	Acute oral toxicity study (limit test) of Difethialone mini blocks in rats. Hazleton Wisconsin Inc, laboratory report no. HWI 30702260 GLP/Unpublished	Y	Lipha
III-B1 6.1.2/01		1993b	Acute dermal toxicity study (limit test) of Difethialone mini blocks in rabbits. Hazleton Wisconsin Inc, laboratory report no. HWI 30702261 GLP/Unpublished	Y	Lipha
III-B1 6.2/01		1993c	Primary dermal irritation study of Difethialone mini blocks in rabbits. Hazleton Wisconsin Inc, laboratory report no. HWI 30702262 GLP/Unpublished	Y	Lipha
III-B1 6.2/02		1993d	Primary eye irritation study of Difethialone mini blocks in rabbits. Hazleton Wisconsin Inc, laboratory report no. HWI 30702263 GLP/Unpublished	Y	Lipha
III-B1 6.3/01		1993e	Dermal sensitization study of Difethialone mini blocks in Guinea pigs – Closed patch technique. Hazleton Wisconsin Inc, laboratory report no. HWI 30702264 GLP/Unpublished	Y	Lipha
III-B3 6.1.2/01		1997a	Acute Dermal Toxicity Study (Limit Test) of Generation™ Pellets (Difethialone 0.0025%) in rabbits. Corning Hazleton Inc, laboratory, report no.	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			CHW60802656 GLP/Unpublished		
III-B3 6.2/01		1997b	Primary Dermal Irritation Study of Generation™ Pellets (Difethialone 0.0025%) in rabbits. Corning Hazleton Inc, laboratory report no. CHW60802655 GLP/Unpublished	Y	Lipha
III-A 6.1.4/01		1985a	Difethialone local tolerance tests in the rabbit. Primary cutanous irritation. Ocular irritation. Hazleton Institute Francais de Toxicologie. France, laboratory report no. 503340 GLP/Unpublished	Y	Lipha
III-A 6.1.4/02		1985b	Difethialone local tolerance tests in the rabbit. Primary cutanous irritation. Ocular irritation. Hazleton Institute Francais de Toxicologie. France, laboratory report no. 503340 GLP/Unpublished	Y	Lipha
III-A 6.1.4/04		1985c	LM2219: local tolerance test in the rabbit. Ocular irritation. Hazleton Institute Francais de Toxicologie. France, laboratory report no. 509380 GLP/Unpublished	Y	Lipha
(Doc II-C Section 2.4)		1982	Single-feeding anticoagulants. Pest Control 50 (2): 32.	N	Public
III-B3 3.2/01		2004a	Difethialone grain compressed pellets (RODILON): Evaluation of physico-chemical properties Covance Laboratories Limited, laboratory report no. 2336/005-D2149 GLP/Unpublished	Y	Lipha
III-B1 3.1.1/01		2004b	Difethialone extruded blocks (FRAP bloc): Evaluation of physico-chemical properties Covance Laboratories Limited, laboratory report no. 2336/006-D2149 GLP/Unpublished	Y	Lipha
III-B1 3.1.1/02		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.1.1/03		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.2/01		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.3/01		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.4/01		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.4/02		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.5/01		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B1 3.6/01		2004b	See III-B1 3.1.1/01	Y	Lipha
III-B3 3.1.1/01		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.1.1/02		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.1.1/03		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.3/01		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.4/01		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.4/02		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.5/01		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.6/01		2004a	See III-B3 3.2/01	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-B3 3.7/02		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.8/01		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.8/02		2004a	See III-B3 3.2/01	Y	Lipha
III-B3 3.8/03		2004a	See III-B3 3.2/01	Y	Lipha
III-A 5.3/04		1992a	Field efficacy trial of an anticoagulant rodenticide - LM 2219 - on the Norway rat, Rattus norvegicus B. INRA, Report No. not stated. Not GLP, Unpublished.	Y	Lipha
III-A 5.3/05		1987	Field efficacy trial of an anticoagulant rodenticide - LM 2219 - on the roof rat, Rattus rattus L. INRA, Report No. not stated. Not GLP, Unpublished.	Y	Lipha
III-A 5.3/06		1992b	Field efficacy trial of an anticoagulant rodenticide - LM 2219 - on the house mouse, Mus musculus L. INRA, Report No. not stated. Not GLP, Unpublished.	Y	Lipha
III-B2 5.10/12		2000	Palatability and efficacy of a soft paste bait containing 0.0025% of difethialone by the black rat (Rattus rattus). INRA Report No. 151.127. Not GLP, Unpublished.	Y	Lipha
(Doc II-A Section 3.8)	Guillaumont, M.J. et al.	1988	Vitamin K1 diffusion across the placental barrier in the gravid female rat. Dev. Pharmacol. Ther., 11; 57-64.	N	Public
(Doc II-C Section 2.4)	Gurney, J., Perrett, J. and Crocker D.R.	1997	Mammals and farming: information for risk assessment Central Science Laboratory, Project No. K93	N	Public
III-A 6.1.3/01		1986	LM2219 acute inhalation toxicity in rats four hour exposure. Huntingdon Research Centre Ltd, laboratory report no. LPA118/86263 GLP/Unpublished	Y	Lipha
III-A 6.4.1/02		1986	LM-2219 Oral Toxicity Study in Beagle Dogs. Huntingdon Research Centre Ltd., Huntingdon, Cambs, UK. Laboratory report no. 119G/86199 GLP/Unpublished	Y	Lipha
(Doc II-C Section 2.4)	Harrison, E.G., Porter, A.J. and Forbes, S.	1988	Development of methods to assess the hazards of a rodenticide to non-target vertebrates Proceedings of the British Crop Protection Symposium	N	Public
III-A 3.1.1/01	Hoffman, M.	1988a	Determination of melting point/melting range of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-242. GLP, Unpublished.	Y	Lipha
III-A 3.1.3/01	Hoffman, M.	1988b	Density determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-243. GLP, Unpublished.	Y	Lipha
III-A 3.2/01	Hoffman, M.	1988c	Vapor pressure determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-245. GLP, Unpublished.	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-A 3.5/02	Hoffman, M.	1988d	Water solubility determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-244. GLP, Unpublished.	Y	Lipha
(Doc II-A Section 3.10)	Horton, J. and Bushwick, B.M.,	1999	Warfarin therapy: Evolving strategies in anticoagulation. American Family Physician, February 1, 1999.	N	Public
(Doc II-A Section 3.8)	Howe, A.M. and Webster, W.S.	1990	Exposure of the pregnant rat to Warfarin and Vitamin K1: An animal model of intraventricular haemorrhage in the foetus. Teratology 42; 413-420.	N	Public
(Doc II-A Section 3.8)	Howe, A.M. and Webster, W.S.	1992	The warfarin embryopathy: A rat model showing maxillonasal hypoplasia and other skeletal disturbances. Teratology 46: 379-390.	N	Public
(Doc II-A Section 3.8)	Howe, A.M. and Webster, W.S.	1994	Vitamin K- its essential role in craniofacial development. A review of the literature regarding vitamin K and craniofacial development.	N	Public
(Doc II-A Section 3.8)	Howe, A.M. et al.	1992	Binder's syndrome due to prenatal vitamin K deficiency; a theory of pathogenesis. Australian Dental Journal 37(6):453-460.	N	Public
III-A 7.5.1.2/01	Hughes, J.M. and Paterson, K.	2003	Difethialone: Determination of acute toxicity (LC_{50}) to earthworms. Inveresk Research, laboratory report number 802620 GLP/Unpublished	Y	Lipha
(Doc II-A Section 3.8)	IPCS, Word Health Organization	1995	Environmental Health Criteria. 175. Anticoagulant rodenticides. WHO Geneva, 1995 ISBN 92 4 157175 1	N	Public
(Doc II-B1 Section 3)	IPCS, Word Health Organization	1995	See (Doc II-A Section 3.8)	N	Public
(Doc II-B2 Section 3)	IPCS, Word Health Organization	1995	See (Doc II-A Section 3.8)	N	Public
(Doc II-B3 Section 3)	IPCS, Word Health Organization	1995	See (Doc II-A Section 3.8)	N	Public
III-A 3.10/01	Jackson, W.A.	2002	Determination of physical and chemical properties: Difethialone. Syngenta, Report No. HT02/251. GLP, Unpublished.	Y	Lipha
III-A 3.11/01	Jackson, W.A.	2002	See III-A 3.10/01	Y	Lipha
III-A 3.15/01	Jackson, W.A.	2002	See III-A 3.10/01	Y	Lipha
III-A 3.16/01	Jackson, W.A.	2002	See III-A 3.10/01	Y	Lipha
III-B1 3.7/02	Joers, D.	1997	24 month storage stability determination of Difethialone mini blocks. LiphaTech Inc, laboratory report no. 95033 GLP/Unpublished	Y	Lipha
III-A 4.2(d)/02	Jones, A	2004b	Validation of analytical methodology to determine bromadiolone, chlorophacinone and difethialone in liver. Central Science Laboratory, Report No. PGD-142, GLP, Unpublished.	Y	Lipha
III-A 4.2(d)/01	Jones, A.	2004a	Validation of analytical methodology to determine bromadiolone, chlorophacinone and difethialone in blood. Central Science Laboratory, Report No. PGD-137. Not GLP, Unpublished.	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
(Doc II-C Section 2.4)	Kalmbach, E.R.	1943	Birds, rodents and colored lethal baits Transactions of the North American Wildlife Conference, 8: 408-416	N	Public
(Doc II-C Section 2.4)	Kalmbach, E.R. and Welch, J.F.	1946	Coloured rodent baits and their value in safeguarding birds J. Wildlife Management, 10: 353-360	N	Public
(Doc II-B1 Section 3)	Kaukeinen, D.E and Buckle, A.P.	1992	Evaluations of aversive agents to increase the selectivity of rodenticides with emphasis on denatonium benzoate (Bitrex) bittering agent. In: Borrecco JE & Marsh RE ed. Proceedings of the 15th Vertebrate Pest Conference. Davis, California, University of California, pp 192-198.	N	Public
(Doc II-B2 Section 3)	Kaukeinen, D.E and Buckle, A.P.	1992	See (Doc II-B1 Section 3)	N	Public
(Doc II-B3 Section 3)	Kaukeinen, D.E and Buckle, A.P.	1992	See (Doc II-B1 Section 3)	N	Public
III-A 7.4.1.1/01	Kelly, C.R. and Paterson, K.	2004	[^{14}C]-difethialone: Determination of acute toxicity (LC_{50}) to rainbow trout (96 h, semi-static) Inveresk Research laboratory report No. 23461 GLP/Unpublished	Y	Lipha
(Doc II-B1 Section 3)	Klein-Schwartz W.	1991	Denatonium benzoate: Review of efficacy and safety. Vet. Hum. Toxicol 33: 545-547.	N	Public
(Doc II-B2 Section 3)	Klein-Schwartz W.	1991	See (Doc II-B1 Section 3)	N	Public
(Doc II-B3 Section 3)	Klein-Schwartz W.	1991	See (Doc II-B1 Section 3)	N	Public
III-B3 5.10/14		2002a	Field test to determine the efficacy of blue-coloured difethialone pellets in controlling the Norway rat (Rattus norvegicus) on a livestock farm in Muensterland, Germany, using BayTool. Report No. 142349-1 Unpublished.	Y	Lipha
III-B3 5.10/15		2002b	Field test to determine the efficacy of blue-coloured difethialone pellets in controlling the house mouse (mus musculus) on a pig-fattening unit in Muensterland, Germany. Report No. 142808-1 Unpublished.	Y	Lipha
III-A 6.1.1/03		1986	Acute oral toxicity to mice of LM2219. Huntingdon Research Centre Ltd, laboratory report no. 86612D/LPA2/AC GLP/Unpublished	Y	Lipha
(Doc II-B1 Section 3.3)	Larsen, J.	2003	Emission Scenario Document for Biocides used as Rodenticides. Supplement to the methodology for risk evaluation for biocides CA-Jun03-Document.8.2-PT14. Report prepared in the context of the EU project entitled "Gathering, review and development of environmental emission scenarios for biocides" (EUBEES 2).	N	Public
(Doc II-B2 Section 3.3)	Larsen, J.	2003	See (Doc II-B1 Section 3.3) (ESD)	N	Public
(Doc II-B3 Section 3.3)	Larsen, J.	2003	See (Doc II-B1 Section 3.3) (ESD)	N	Public
(Doc II-C Section 2)	Larsen, J.	2003	See (Doc II-B1 Section 3.3) (ESD)	N	Public

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
III-B2 6.2/01		2001a	Leuschner, J. Acute skin irritation test (patch test) of Rodilone paste in rabbits Bayer AG, Toxicology, Wuppertal, Germany. Laboratory report number R 8076. GLP, unpublished	Y	Bayer
III-B2 6.2/02		2001b	Acute eye irritation study of Rodilone paste by instillation into the conjunctival sac of rabbits. Study for acute oral toxicity in rats. Bayer AG, Toxicology, Wuppertal, Germany. Laboratory report number R 8075. GLP, unpublished	Y	Bayer
III-A 3.3.1/01	Loken, R.	1988a	Physical state determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-240. GLP, Unpublished.	Y	Lipha
III-A 3.3.2/01	Loken, R.	1988b	Munsell color determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-239. GLP, Unpublished.	Y	Lipha
III-A 3.3/01	Loken, R.	1988c	Odor determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-241. GLP, Unpublished.	Y	Lipha
III-A 3.9/02	Loken, R.	1988d	Octanol/water partition coefficient determination of difethialone. Hazleton Laboratories America, Inc., Report No. HLA 6001-247. GLP, Unpublished.	Y	Lipha
III-A 5.3/01		1985a	Efficacy and palatability tests of LM 2219 rodenticide compound in wild rodents. ENVL, Report No. not stated. Not GLP, Unpublished.	Y	Lipha
III-A 5.3/02		1986a	Efficacy and palatability tests of LM 2219 liquid concentrate rodenticide carried out in Rattus norvegicus, Rattus rattus, Mus musculus (warfarin-susceptable and -resistant strains). ENVL, Report No. not stated. Not GLP, Unpublished.	Y	Lipha
III-A 5.3/03		1986b	Efficacy and palatability tests of semolina and wheat treated with LM 2219 (Lipha preparation) in Rattus norvegicus and Mus musculus. ENVL, Report No. not stated. Not GLP, Unpublished.	Y	Lipha
III-A 6.1.1/04		1986c	Oral acute toxicity study of LM 2219 in cats. Toxicology Laboratory of Ecole Nationale Veterinaire de Lyon, laboratory report no. Not stated Non GLP/Unpublished	Y	Lipha
III-A 6.1.1/05		1985b	Toxicity by single administration of the compound LM2219 orally to dogs of any breed, of any age and for both sexes. Determination of the lethal doses. Toxicology Laboratory Ecole Nationale Veterinaire de Lyon, laboratory report no. 85-3 LM2219 Non GLP/Unpublished	Y	Lipha
III-A 6.1.1/06		1984	Toxicity by single oral administration of the compound LM2219 to dogs. Toxicology Laboratory Ecole Nationale	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Veterinaire de Lyon, laboratory report no. 84-1 LM2219 Non GLP/Unpublished		
III-A 6.1.1/08		1986d	Study of the acute toxicity of LM 2219 in chickens, male and female. Determination of the LD50. Toxicology Laboratory Ecole Nationale Veterinaire de Lyon, laboratory report no. No report/ study identification Non GLP/Unpublished	Y	Lipha
III-A 6.3.1/01		1985c	Toxicity by repeated administrations –30 days - of the compound LM2219 orally to dogs. Toxicology Laboratory Ecole Nationale Veterinaire de Lyon, laboratory report no. 85/3 LM2219 Non GLP/Unpublished	Y	Lipha
III-A 7.5.3.1.1/01		1987	Determination of the LD_{50} of LM-2219 given orally to the Japanese quail (*Coturnix coturnix*). INRA-ENVL Ecotoxicology Laboratory, report number 86/3 GLP/Unpublished	Y	Lipha
III-B1 5.10/01		1998a	Study on the efficacy of difethialone green blocks in the mouse, wild strain Mus musculus. ENVL, Report No. P 98.04. Not GLP, Unpublished.	Y	Lipha
III-B1 5.10/02		1998b	Study on the efficacy of difethialone green blocks in the Norway rat, wild strain Rattus norvegicus. ENVL, Report No. P 98.03. Not GLP, Unpublished.	Y	Lipha
III-B1 5.10/03		1999a	Study on the efficacy of difethialone blue blocks in the mouse, wild strain Mus musculus. ENVL, Report No. P 99.02. Not GLP, Unpublished.	Y	Lipha
III-B1 5.10/04		1999b	Study on the efficacy of difethialone blue blocks in the rat, wild strain Rattus norvegicus. ENVL, Report No. P 99.01. Not GLP, Unpublished.	Y	Lipha
III-B1 5.10/09		1998c	Study on the efficacy of difethialone red blocks in the Norway rat, wild strain Rattus norvegicus. ENVL, Report No. P 98.05. Not GLP, Unpublished.	Y	Lipha
III-B1 5.10/10		1998d	Study on the efficacy of difethialone red blocks in the mouse, wild strain Mus musculus. ENVL, Report No. P 98.06. Not GLP, Unpublished.	Y	Lipha
III-B2 5.10/20		2002a	Study on the activity and attractivity of a blue paste based on difethialone at 25 mg/kg in the Norway rat, Rattus norvegicus, wild strain, sensitive to coumafene. Laboratoire de Toxicologie, ENVL, Report No. P 00.01/b. Not GLP, Unpublished.	Y	Lipha
III-B2 5.10/21		2002b	Study on the efficacy of an oily paste based on difethialone at 25 mg/kg in the mouse, wild	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			strain, sensitive or resistant to coumafene. Laboratoire de Toxicologie, ENVL, Report No. P 00.02/b. Not GLP, Unpublished.		
III-B2 5.10/22		2002c	Study on the efficacy and attractivity of a blue oil paste at 25 mg/kg of difethialone in the rat, Rattus norvegicus, wild strain, resistant to coumafene. Laboratoire de Toxicologie, ENVL, Report No. RE/0202/DIF/Paste/RN/R/T0. Not GLP, Unpublished.	Y	Lipha
III-B2 5.10/23		2002d	Study on the efficacy and attractivity of a blue oil paste at 25 mg/kg of difethialone in the house mouse, mus musculus, wild strain, resistant to coumafene. Laboratoire de Toxicologie, ENVL, Report No. RE/0203/DIF/Paste/Mm/R/T0. Not GLP, Unpublished.	Y	Lipha
III-A 6.10/02		1985	Toxicity of LM-2219 given orally to beagles: Establishing a therapeutic antidote for intoxicated dogs. Chempar toxicology Laboratory, Lyon, France. Laboratory report no. 83.01 LM 2219 CER. GLP/Unpublished	Y	Lipha
III-B3 5.10/11		2001	Study on the efficacy and attractivity of difethialone based pellets at 25 mg/kg in the rat, wild strain Rattus Norvegicus. Laboratoire de Toxicologie, ENVL, Report No. P 01.04. GLP, Unpublished.	Y	Lipha
III-B3 5.10/12		2002a	Study on the efficacy and attractivity of blue pellets based on difethialone at 25 mg/kg in the mouse, Mus musculus, wild strain resistant to coumafene. Laboratoire de Toxicologie, ENVL, Report No. RE/0201/DIF/Pellets/Mm/R/TO. GLP, Unpublished.	Y	Lipha
III-B3 5.10/13		2002b	Study on the efficacy and attractivity of blue pellets based on difethialone at 25 mg/kg in the mouse, Mus musculus, wild strain resistant to warfarine. Laboratoire de Toxicologie, ENVL, Report No. RE/0106/DIF/Pellets/Mm/R/TO. GLP, Unpublished.	Y	Lipha
(Doc II-C Section 2.4)	Luttik, R., Clook, M.A., Taylor, M.R. and Hart, A.D.M.	1999	Regulatory aspects of the ecotoxicological risk assessment of rodenticides. Advances in Vertebrate Pest Management' Cowan, D.P. and Feare, C.J.: Eds. Filander Verlag, Fürth	N	Public
III-A 7.1.1.1.2/02	Lynn, R., McCorquodale, G.Y. and Paterson, K.	2003	Artificial sunlight photodegradation of [^{14}C]-Difethialone in buffered aqueous solution. Inveresk Research, laboratory report no. 22883 GLP/Unpublished	Y	Lipha
III-A 6.4.1/01		1986	LM2219: thirteen-week study orally in rats. Lipha Research Center, Lyon, France, laboratory report no. 85.01.LM 2219 Rpp. GLP/Unpublished	Y	Lipha
III-A 6.1.1/01		1985a	LD50 evaluation of LM-2219 given orally to	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			rats. Lipha Research Center, laboratory report no. 85.03 LM2219 GLP/Unpublished		
III-A 6.1.1/02		1985b	LM 2219 LD50 evaluation of LM 2219 given orally to rats. Lipha Research Center, laboratory report no. 85.06 LM2219 RpL GLP/Unpublished	Y	Lipha
III-A 6.1.1/07		1985c	LD50 evaluation of LM 2219 given orally to beagles. Lipha Research Center, laboratory report no. 84.08 LM2219 Non GLP/Unpublished	Y	Lipha
(Doc II-A Section 3.8)		1988	Placental transfere of vitamin K1 and its implications in fetal hemostasis. Thromb. Haemostasis. 60; 39-43.	N	Public
III-A 6.10/03		1991a	Antidotal treatment study following oral exposure to Difethialone in rats. Hazleton Washington, USA, laboratory report no. 2624-101 GLP/Unpublished	Y	Lipha
III-A 6.10/04		1991b	Antidotal treatment study in the Beagle dog following Difethialone overexposure. Hazleton Washington, USA, laboratory report no. 2624-100 GLP/Unpublished	Y	Lipha
(Doc II-C Section 2.4)	Marsh, R.E.	1985	Techniques used in rodent control to safeguard non-target wildlife Transactions of the Wildlife Society Annual Meeting (W.F. Ladenslayer Jr.: Ed). January 25-26. Monterey, CA., USA	N	Public
III-A 4.2(a)/01	McGuire, G.M., Doran, A.M., Vance, C.J.	2003	Validation of an analytical method for the determination of difethialone in soil using LC-MS. Inveresk Research, Report No. 23244. GLP, Unpublished.	Y	Lipha
III-A 4.2(c)/02	Moede, J.	1991	Analytical method for the determination of residues of difethialone in water by HPLC. Schering AG, Report No. UPSR 8/91. Not GLP, Unpublished.	Y	Lipha
(Doc II-C Section 2.4)		1999	Rejection of dyed field rodent baits by feral pigeons and chukar partridges Phytoparasitica 27 (1): 9-17	N	Public
(Doc II-B1 Section 3.3)	Mosey, F.E.	1983	Anaerobic Processes. In: Used-Water Treatment, Vol. 2, Chapter 5. (Curds C.R. and Hawkes H.A.: Eds.) Academic Press, London.	N	Public
III-A 6.6.2/01		1992a	Mutagenicity test on difethialone technical grade in an *in vitro* cytogenetic assay measuring chromosomal aberrations in human whole blood lymphocytes: with and without exogenous metabolic activation. Hazleton Washington, USA, laboratory report no. 15136-0-449 GLP/Unpublished	Y	Lipha
III-A 6.6.4		1992b	Dose range finding acute toxicity study on difethialone technical grade. Hazleton Washington, USA, laboratory report no. 15136-1-4591P GLP/Unpublished	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
		1992c	Mutagenicity test on difethialone technical grade in an *in vivo* mammalian micronucleus assay. Hazleton Washington Inc, USA, laboratory report no. 15136-0-455 GLP/Unpublished		
III-A 6.1.4/03		1992	Difethialone technical: Primary Eye Irritancy in the Rabbit. Bushy Run Research Centre, Export, PA, USA, laboratory report no. 92N1079 GLP/Unpublished	Y	Lipha
III-B3 6.2/02		1992	Difethialone Pellets: Primary Eye Irritancy Study in the Rabbit. Bushy Run Research Centre, Export, PA, USA, laboratory report no. 92N1080 GLP/Unpublished	Y	Lipha
III-B3 5.10/01		1998a	Difethialone pellets-9802 in albino rats. Standard Norway rat anticoagulant dry bait laboratory test method. LiphaTech Inc., Report No. 98087. GLP, Unpublished.	Y	Lipha
III-B3 5.10/02		1998b	Difethialone pellets-9802 in Swiss-Webster/ND4 mice. Standard house mouse anticoagulant dry bait laboratory test method. LiphaTech Inc., Report No. 98088. GLP, Unpublished.	Y	Lipha
III-B3 5.10/03		1998c	Difethialone pellets-9802 in albino rats. Standard Norway/roof rat acute dry bait laboratory test method. LiphaTech Inc., Report No. 98101. GLP, Unpublished.	Y	Lipha
III-B3 5.10/05		1998d	Difethialone pellets-9802 in albino rats. Standard Norway rat anticoagulant wax block and wax pellet laboratory test method. LiphaTech Inc., Report No. 98085. GLP, Unpublished.	Y	Lipha
III-B3 5.10/06		1998e	Difethialone pellets-9802 in Swiss-Webster/ND4 mice. Standard house mouse anticoagulant wax block and wax pellet laboratory test method. LiphaTech Inc., Report No. 98086. GLP, Unpublished.	Y	Lipha
III-B3 5.10/09		1998f	Difethialone pellets-9802 25g placepacks in albino rats. Standard Norway/roof rat placepack penetration laboratory test method. LiphaTech Inc., Report No. 98103. GLP, Unpublished.	Y	Lipha
III-B3 5.10/10		1998g	Difethialone pellets-9802 25g placepacks in Swiss-Webster/ND4 mice. Standard house mouse anticoagulant placepack penetration laboratory test method. LiphaTech Inc., Report No. 98090. GLP, Unpublished.	Y	Lipha
(Doc II-C Section 2.4)		1976	Effects of seed and background colours on seed acceptance by birds J. Wildlife Management, 40: 769-774.	N	Public
III-A 6.1.5/01		1993	Dermal sensitization study of Difethialone technical in guinea pigs (Magnusson and Kligman procedure). TSI Redfield Laboratories, AR, USA, laboratory report no. 008-0010R	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			GLP/Unpublished		
(Doc II-A Section 2.4)	PSD (Pesticides Safety Directorate), Department for Environment, Food and Rural Affairs	1997	Assessment of humaneness of vertebrate control agents Food and environment protection act, 1985, part III, control of pesticides regulations 1986, Evaluation of fully approved or provisionally approved products, Issue 171; York YO1 7PX	N	-
III-A 3.4/01	Queuche, P.	1999	NMR, MS, IR, UV/vis spectra. Difethialone active ingredient. Lipha S.A., Report No. ASDIFR300-99. Not GLP, Unpublished.	Y	Lipha
III-A 3.2.1/01	Ramsay, N.	2003b	Product chemistry of difethialone: Selected physico-chemical studies to fulfil the requirements of EEC Council Biocides Directive 98/8/EC, Report No. 21869. GLP, Unpublished.	Y	Lipha
III-A 3.5/01	Ramsay, N.	2003b	See III-A 3.2.1/01	Y	Lipha
III-A 3.7/01	Ramsay, N.	2003b	See III-A 3.2.1/01	Y	Lipha
III-A 3.9/01	Ramsay, N.	2003b	See III-A 3.2.1/01	Y	Lipha
III-A 4.1/01	Ramsay, N.	2003a	See III-A 2.7/01	Y	Lipha
III-A 2.7/01	Ramsey, N.	2003a	5-batch analysis of difethialone to fulfil the requirements of EEC Council Biocides Directive 98/8/EC. Inveresk Research, Report No. 21789. GLP, Unpublished. *This report contains confidential information.*	Y	Lipha
III-A 2.8.9/01	Ramsey, N.	2003a	See III-A 2.7/01	Y	Lipha
III-A 7.5.3.1.3/02	Riedel, B., Grün, G. and Clausing, P.	1990	Die subakute und subchronische Toxizität von Chlorophacinon an Japanwachteln (Coturnix c. japonica). Institut für Pflanzenschutzforschung Kleinmachnow der Akademie der Landwirtschaftswissenschaften der DDR – Ornithologische Forschungsstelle Seebach. Not GLP/Published	Y	Lipha
III-A 6.2/03		2003	The *in vitro* percutaneous absorption of radiolabelled Difethialone in two test preparations through rat and human skin. Inveresk Research, Tranent, Scotland. Laboratory report no. 21795. GLP/Unpublished	Y	Lipha
III-B1 6.4/01		2003	See III-A 6.2/03	Y	Lipha
III-B2 6.4/01		2003	See III-A 6.2/03	Y	Bayer
III-B3 6.4/01		2003	See III-A 6.2/03	Y	Lipha
III-A 6.2/04		2003	The *in vivo* percutaneous absorption of [^{14}C] Difethialone in two test preparations in the rat. Inveresk Research, Tranent, Scotland. Laboratory report no. 21796. GLP/Unpublished	Y	Lipha
III-B1 6.4/02		2003	See III-A 6.2/04	Y	Lipha
III-B2 6.4/02		2003	See III-A 6.2/04	Y	Bayer
III-B3 6.4/02		2003	See III-A 6.2/04	Y	Lipha
III-B3 6.1.1/01		1987	Acute Oral Toxicity (Limit) Test and Single Dose Dermal Toxicity Test with LM-2219 Pellets. Toxikon Laboratory, laboratory report no. 87G-0020 and 87G-0019	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			GLP/Unpublished		
III-B3 6.1.2/02		1987	See III-B3 6.1.1/01	Y	Lipha
III-A 6.1.1/09		1998	Toxic effect of Difethialone on the liver of Swiss albino mice *(Mus musculus*); J. Anim. Morphol. Physiol., 45, pp137-141.	N	Public
III-A 7.5.3.1.2/03		2004	Evaluation of secondary poisoning of difethialone, a new second- generation anticoagulant rodenticide to Barn owl, *Tyto alba* under captivity. Indian Journal of Experimental Biology Vol. 42, October 2004, pp 1013-1016	N	Public
III-A 4.2(b)/01	Schultz, M., Ullrich-Mitzel, A.	1996	Analytical method for the determination of difethialone in air. RCC Umweltchemie AG, Report No. 385841. GLP, Unpublished.	Y	Lipha
III-B3 6.3/01		1987	EPA Guinea pig sensitization (Buehler). Product Safety Labs, laboratory report no. T-6562 GLP/Unpublished	Y	Lipha
(Doc II-B1 Section 3)	Sibert, J.R. and Frude, N.	1991	Bittering agents in the prevention of accidental poisoning: children's reactions to denatonium benzoate (Bitrex). Archives of emergency medicine 8: 1-7.	N	Public
(Doc II-B2 Section 3)	Sibert, J.R. and Frude, N.	1991	See (Doc II-B1 Section 3)	N	Public
(Doc II-B3 Section 3)	Sibert, J.R. and Frude, N.	1991	See (Doc II-B1 Section 3)	N	Public
III-B3 5.10/04		1998	Difethialone pellets in Swiss-Webster mice. Standard house mouse acute dry bait laboratory test method 1.210. LiphaTech Inc., Report No. 98123. GLP, Unpublished.	Y	Lipha
III-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	CEFIC Rodenticides Working Group
III-B2 6.6/01	Snowdon, P.J.	2003	See III-B1 6.6/01	Y	CEFIC Rodenticides Working Group
III-B3 6.6/01	Snowdon, P.J.	2003	See III-B1 6.6/01	Y	CEFIC Rodenticides Working Group
III-A 7.1.1.1.1/01	Spare, W.	1986	Determination of the hydrolysis rate constants of LM2219. Agrisearch Inc., laboratory report no. 1403 GLP/Unpublished	Y	Lipha
III-A 7.1.1.1.2/01	Spare, W.	1987a	Determination of the solution photolysis rate of LM2219 (Difethialone). Agrisearch Inc., laboratory report no. 1404 GLP/Unpublished	Y	Lipha
III-A 7.1.3/01	Spare, W.	1992	Adsorption/desorption of difethialone (amended final report). Agrisearch Inc., laboratory report no. 1421 GLP/Unpublished	Y	Lipha
III-A 7.2.1/01	Spare, W.	1987b	Aerobic soil metabolism of LM2219 (Difethialone).	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Agrisearch Inc., laboratory report no. 1401 GLP/Unpublished		
III-B2 3.1.1/01	Stöcker, R.	2004	Difethialone paste - Rodilon paste: Data on physical and chemical properties. Bayer AG, Laboratory report number PA00, 0025. GLP, unpublished	Y	Bayer
III-B2 3.1.1/02		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.1.1/03		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.2/01		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.3/01		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.4/01		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.4/02		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.4/03		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.5/01		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.6/01		2004	See III-B2 3.1.1/01	Y	Bayer
III-B2 3.7/01		2004	See III-B2 3.1.1/01	Y	Bayer
III-A 7.4.1.1/02	Suprenant, D.C. and Nicholson, R.	1986b	Acute toxicity of LM2219 to rainbow trout (*Salmo gairdneri*). Springborn Bionomics, Inc., laboratory report number 11219.0286.6101.103 GLP/Unpublished	Y	Lipha
III-A 7.4.1.1/03	Suprenant, D.C. and Nicholson, R.	1986c	Acute toxicity of LM2219 to bluegill sunfish (*Lepomis macrochirus*). Springborn Bionomics, Inc., laboratory report number 11219.0286.6101.100 GLP/Unpublished	Y	Lipha
III-A 7.4.1.2/01	Suprenant, D.C. and Nicholson, R.	1986a	Acute toxicity of LM-2219 to daphnids (*Daphnia magna*). Springborn Bionomics, Inc., laboratory report number 11219.0286.6101.110 GLP/Unpublished	Y	Lipha
III-A 7.4.1.3/01	Swarbrick, R.H.	2003	Difethialone: Toxicity to the green alga *Selenastrum capricornutum*. AstraZeneca UK Ltd. Brixham Environmental Laboratory, laboratory report number BL7286/B GLP/Unpublished	Y	Lipha
III-A 7.4.1.4/01	Swarbrick, R.H.	2002	Difethialone: Effect on the respiration of activated sludge. AstraZeneca UK Ltd. Brixham Environmental Laboratory, report number BL7287/B GLP/Unpublished	Y	Lipha
(Doc II-A Section 3.10)	The Medical Products Agency in Sweden	2004	Summary of Product Characteristics for Waran, The Medical Products Agency in Sweden (www.mpa.se)	N	Public
(Doc II-A Section 3.10)	The Norwegian Medicines Agency	2003	Summary of Product Characteristics for Marevan, Norwegian Medicines Agency (www.noma.no)	N	Public
(Doc II-C Section 2.4)	Tkladec, E. and Rychnovsky, B.	1990	Residues of zinc phosphide in the common vole (Microtus arvalis) and secondary poisoning hazards to predators Polia Zoologica, 39 (2), 147-156	N	Public
III-A 6.8.1/05		1994	Developmental toxicity evaluation of difethialone administered by gavage to New	Y	Lipha

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Zealand White rabbits. Reproductive and Developmental Toxicology Laboratory Center for Life Sciences and Toxicology, Research Triangle Institute, NC, USA, laboratory report no. 65C-5724-05/06 GLP/Unpublished		
(Doc II-B1 Section 3.3)	UK Health and Safety Executive	2003	Urban rodent control and the safe use of rodenticides by professional users Information Sheet MISC515:	N	Public
(Doc II-B1 Section 3.3)	UK Health and Safety Executive	1999	Safe use of rodenticides on farms and holdings. Agriculture Information Sheet No. 31	N	Public
(Doc II-B1 Section 3.3)	UK Health and Safety Executive	1999	See (Doc II-B1 Section 3.3)	N	Public
(Doc II-B2 Section 3.3)	UK Health and Safety Executive	1999	See (Doc II-B1 Section 3.3)	N	Public
(Doc II-B2 Section 3.3)	UK Health and Safety Executive	2003	See (Doc II-B1 Section 3.3)	N	Public
(Doc II-B3 Section 3.3)	UK Health and Safety Executive	1999	See (Doc II-B1 Section 3.3)	N	Public
(Doc II-B3 Section 3.3)	UK Health and Safety Executive	2003	See (Doc II-B1 Section 3.3)	N	Public
(Doc II-A Section 3.8)	Van Driel, D. et al.	2002	Teratogen Update: Fetal Effects After In Utero Exposure to Coumarins. Overview of Cases, Follow-Up Findings, and pathogenesis. Teratology, 66, 127-140.	N	Public
(Doc II-B1 Section 3.2)	Vetter, D. & Sendor,T, EBRC Consulting (under contract to the CEFIC Rodenticides Working Group)	2006	Estimation of the Frequency of Dermal Exposure During the Occupational Use of Rodenticides of 28th July 2006 (TMIIITOX-item4-Bait Handling-Report.doc)	N	CEFIC Rodenticides Working Group
(Doc II-B2 Section 3.2)	Vetter, D. & Sendor,T, EBRC Consulting (under contract to the CEFIC Rodenticides Working Group)	2006	See (Doc II-B1 Section 3.2)	N	CEFIC Rodenticides Working Group
(Doc II-B3 Section 3.2)	Vetter, D. & Sendor,T, EBRC Consulting (under contract to the CEFIC Rodenticides Working Group)	2006	See (Doc II-B1 Section 3.2)	N	CEFIC Rodenticides Working Group
(Doc II-C Section 1)	Vetter, D. & Sendor,T, EBRC Consulting (under contract to the CEFIC Rodenticides Working Group)	2006	See (Doc II-B1 Section 3.2)	N	CEFIC Rodenticides Working Group
III-B2 6.3/01		2002	Rodilone paste, (PNR 1286) Study for the skin sensitisation effect in guinea pigs (guinea pig maximisation test according to Magnusson and Kligman). Bayer AG, Toxicology, Wuppertal, Germany.	Y	Bayer

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
			Laboratory report number 31708. GLP, unpublished		
III-A 7.2.2.1/01	Völkl, S. and Galicia, H.	1993	14C-Difethialone (LM 2219): Degradation and metabolism in soils incubated under aerobic conditions. RCC Umweltchemie AG., laboratory report no. 286378 GLP/Unpublished	Y	Lipha
III-A 6.6.1/01	Weill, N.	1988a	LM2219: mammalian microsome incorporation assay *(Salmonella typhimurium*). Hazleton Institute Francais de Toxicologie, France, laboratory report no. 504241 GLP/Unpublished	Y	Lipha
III-A 6.6.3/01	Weill, N.	1988b	Test to evaluate the induction of genic mutations in CHO cells (HGPRT locus). Hazleton Institute Francais de Toxicologie, France, laboratory report no. 811471 GLP/Unpublished	Y	Lipha
(Doc II-C Section 2)	WHO	1995	Anticoagulant rodenticides Environmental Health Criteria 175. International Programme on Chemical Safety. World Health Organisation Geneva	N	Public
III-B3 3.7/01	Zobel, M	2000	24 month storage stability and corrosion characteristic determination of Difethialone pellets 9802. LiphaTech Inc. laboratory report no. 98089 GLP/Unpublished	Y	Lipha
III-B1 3.7/01	Zobel, M.	2004	Determination of accelerated storage stability of Difethialone block. LiphaTech Inc, laboratory report no. 03184 GLP/Unpublished	Y	Lipha
III-B1 4.1/01	Zobel, M.L.	2004a	Method validation: Analytical technique for the concentration of difethialone in DFN block. Liphatech Inc., report number 03182, 20 GLP, Unpublished.	Y	Lipha
III-B3 4.1/01	Zobel, M.L.	2004 b	Method validation: Analytical technique for the concentration of difethialone in DFN pellets 9802. Liphatech Inc., report number 03188, 20. GLP, Unpublished.	Y	Lipha