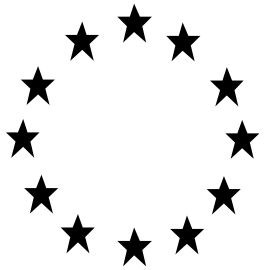
Directive 98/8/EC concerning the placing of biocidal products on the market

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

Assessment Report



Brodifacoum

Product-type 14 (Rodenticide)

17 September 2009, revised 16 December 2010

Annex I - Italy

Brodifacoum (PT 14)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on 17 September 2009 in view of its inclusion in Annex I to Directive 98/8/EC, revised 16 December 2010 to take into account data from the second notifier

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of *Brodifacoum* as product-type **14** (Rodenticide), 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.

Brodifacoum (CAS no. 56073-10-0) was notified as an existing active substance, by Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force, hereafter referred to as the applicants, in product-type **14**.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, Italy was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for *Brodifacoum* as an active substance in product-type **14** was 28 March 2004 in accordance with Article 9(2) of Regulation (EC) No 1451/2007.

On 26 March 2004, Italian competent authorities received the dossiers from all of the applicants. The Rapporteur Member State accepted the dossier of Syngenta as complete for the purpose of the evaluation on 29 September 2004.
The dossier of Activa / Pelgar Brodifacoum and Difenacoum Task Force was not considered as complete on 28 September 2004 and the Rapporteur Member State stated that relevant information was lacking and data requirements were not fulfilled. On 3 November 2005, the Rapporteur Member State accepted the dossier, including study reports and summaries, as complete for the purpose of the evaluation. On 19 July 2006 the time period was suspended, the evaluation was not taken up on 18 July 2007 but was stopped again at the same date in order to obtain from the applicant the necessary data requested. After that, the evaluation phase was taken up on 15 November 2007. During the evaluation period communication between the RMS and the applicant has resulted in revised documents at all document levels.

On 23 November 2005, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant (*i.e.*, Syngenta) a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States

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 1451/2007 of 4 December 2007 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. OJ L 325, 11.12.2007, p. 3

by electronic means on 10 December 2005. The competent authority report of the Activa / Pelgar Brodifacoum and Difenacoum Task Force was submitted on 25 September 2008. The Commission made the report available to all Member States by electronic means on 26 September 2008. The competent authority report included a recommendation for the inclusion of *Brodifacoum* in Annex I to the Directive for product-type **14**.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on 2 June 2006 and 6 October 2008. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority 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 *Brodifacoum* in Annex I to Directive 98/8/EC and consulted the Standing Committee on Biocidal Product on 17 September 2009.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 17 September 2009.

1.2. Purpose of the assessment report

This assessment report has been developed and finalised in support of the decision to include *Brodifacoum* 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 *Brodifacoum*. 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

The overall conclusion from the evaluation is that it may be expected that there are products containing *Brodifacoum* for the product-type **14**, which will fulfil the requirements laid down in Article 5 of Directive 98/8/EC. This conclusion is however subject to:

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

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

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

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

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

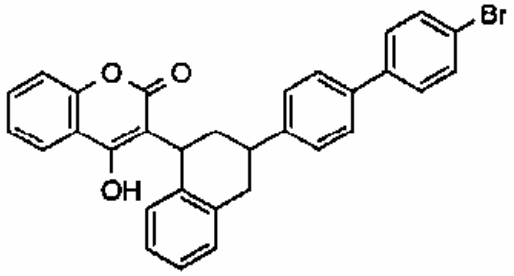
2. OVERALL SUMMARY AND CONCLUSIONS

The data from the two Applicants for the *Brodifacoum* dossier have been reported in the following chapters. In particular, the data from Syngenta Limited and Activa / Pelgar Brodifacoum and Difenacoum Task Force have been indicated as **A** and **B**, respectively.

2.1. Presentation of the Active Substance

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

Identification of the active substance (A, B)

CAS-No.	56073-10-0
EINECS-No.	259-980-5
Other No.	370 (CIPAC) 607-172-00-1 (Annex I of Dir. 67/548/EEC Index)
IUPAC Name	*3-[3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin*
CAS Name	*2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-*
Common name, synonym	*Brodifacoum*, PP581 (applicant A)
Molecular formula	$C_{31}H_{23}BrO_3$
Purity	≥ 950 g/kg (based on both *cis* and *trans* isomers; either isomer is active)
Structural formula	
Molecular weight (g/mol)	523.4 g/mol
Isomeric composition	*cis* isomer (CA Index name *2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-, cis-*, CAS-No. 72654-66-1) is a racemic mixture of (1R,3S) and (1S,3R); *trans* isomer (CA Index name *2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-, trans-*, CAS-No. 72654-67-2) is a racemic mixture of (1R,3R) and (1S,3S); full details on the isomeric composition are confidential information. Note that either applicant A or applicant B has a separate Confidential Annex.

Brodifacoum does not contain additives or impurities that would be of toxicological or environmental concern. For either applicant, the full details on the identity of the active substance are commercially sensitive and can be found in the relevant Confidential Annex. The minimum purity of 950 g/kg is supported by the analytical data (5-batch analysis) and has been used in most toxicity and ecotoxicity tests in the Dossier of applicant A. A higher minimum purity of 992 g/kg is supported by the analytical data (5-batch analysis) and has been used in most toxicity and ecotoxicity studies in the Dossier of applicant B. Both specifications have been accepted and, therefore, the minimum purity of 950 g/kg shall apply for *Brodifacoum.*

Identification of the product (A)

Trade name	Klerat Pellets
Manufacture's development code number(s)	BROD80338
Active substance	*Brodifacoum*
Content of the a.s. [g/kg]	0.05
Function of preparation	rodenticide
Physical state of preparation	solid
Nature of preparation	ready-for-use pellet bait

Identification of the product (B)

Trade name	Vertox Wax Block
Manufacture's development code number(s)	none
Active substance	*Brodifacoum*
Content of the a.s. [g/kg]	0.05
Function of preparation	rodenticide
Physical state of preparation	solid
Nature of preparation	wax bait block

Physico-Chemical Properties (A, B)

Brodifacoum does not exhibit hazardous physical-chemical properties. *Brodifacoum* is not highly flammable and it shows no self-ignition below its melting point. *Brodifacoum* does not show oxidizing or explosive properties, either. The remaining of the physical-chemical data are listed below. Values in many endpoints are highly or reasonably similar and the reasons for deviations can usually be regarded as experimental.

There is no risk to be expected due to the physical-chemical properties of the biocidal products Klerat Pellets and Vertox Wax Block, either.

Test	**A**	**B**	**Explanation of difference**

Melting point (purity) [method]	232 °C with decomposition (98.7% w/w) [capillary method]	*Brodifacoum* was observed to darken and decompose at 235.8 °C (100% w/w) [capillary method]	Experimental
Test	**A**	**B**	**Explanation of difference**
Boiling point	Not applicable	Not determinable	--
Temperature of decomposition (purity) [method]	232 °C (98.7% w/w) [capillary method]	235.8 °C (100% w/w) [capillary method]	Experimental
Relative density (purity) [method]	1.42 g/cm^3 (density) at 25 °C (92.5% w/w) [pycnometer method]	D^{20}_4 = 1.530 (>99% w/w) [pycnometer method]	Different purity degree of the test items and different temperature conditions
Vapour pressure (purity) [method]	<< 10E-6 Pa at 20 °C (98.7% w/w) [gas saturation method]	2.6E-22 Pa at 20°C 1.9E-21 Pa at 25°C (99.7% w/w) [estimated by the VP curve – experimental data by VP balance method]	Methodology
Henry's law constant (H)	<< 2.18E-3 Pa m^3 mol^{-1} (pH 7) << 5.23E-5 Pa m^3 mol^{-1} (pH 9)	2.35E-18 Pa m^3 mol^{-1} (pH 7)	Methodology (H is the result of a calculation based on the values of vapour pressure and of solubility in water)

Appearance (purity) [method]	Fine powdery solid; colour: cream (92.5% w/w) [visual inspection, standard laboratory fluorescent lighting]	White to off-white fine powder (99.7% w/w) [visual assessment under natural light]	Different purity degree of the test items

Test	A	B	Explanation of difference
UV/VIS (purity)	263 and 308 nm (methanol) ε308 (l $mol^{-1}cm^{-1}$) = 14400 (98.7% w/w)	266 nm and 308 nm (methanol; 10% 1N HCl methanolic solution); 263 nm and 312 nm (10% 1N NaOH methanolic solution) ε308 (l $mol^{-1}cm^{-1}$) = 14089 (methanol), 15629 (10% 1N HCl methanolic solution) ε312 (l $mol^{-1}cm^{-1}$) = 16677 (10% 1N NaOH methanolic solution) (>99% w/w)	Experimental
Solubility in water (purity) [method]	pH 5.2: 3.83E-3 mg/l, 20°C pH 7.4: 0.24 mg/l, 20 °C pH 9.3: 10 mg/l, 20 °C (98.7% w/w) [generator column method]	pH 5: ≤ 3.17E-6 g/l 20 °C pH 7: 5.80E-5 g/l at 20 °C pH 9: 1.86E-3 g/l at 20 °C (99.7% w/w) [column elution method with re-circulating pump]	Methodology
Dissociation constant (pKa) [method]	4.5 [PETE database calculation/estimation]	4.50 [QSAR estimation by ACD/I-Lab Web service]	--

Solubility in organic solvents (purity) [method]	Acetone: 23 g/l Toluene: 7.2 g/l Ethylacetate: 12 g/l Methanol: 2.7 g/l Dichloromethane: 50 g/l Acetonitrile: 3.2 g/l Hexane: 0.088 g/l Temperature: 20°C (92.5% w/w) [flask method]	Acetone: 21. 2 g/l Toluene: 5.89 g/l Ethyl acetate: 10.1 g/l Methanol: 1.61 g/l Dichloromethane: 29–33 g/l Temperature: 20°C (99.7% w/w) [flask method, CIPAC MT181 for dichloromethane]	Experimental/ different purity degree of the test items
Test	**A**	**B**	**Explanation of difference**
Partition coefficient (log Kow) (purity) [method]	8.5 [by clogp Algorithm of Hansch and Leo] 6.12 [estimated from measured Koc] – used for risk assessment	6.16–6.27 (at pH 5, 10°C) 5.99–6.13 (at pH 5, 20°C) 5.80–5.98 (at pH 5, 30°C) 5.09 (at pH 7, 10°C) 4.92 (at pH 7, 20°C) 4.78 (at pH 7, 30°C) 4.91 (at pH 9, 10°C) 4.78 (at pH 9, 20°C) 4.58 (at pH 9, 30°C) (99.7% w/w) [HPLC method]	Methodology
Thermal stability (purity) [method]	Stable for at least 14 days at 54 °C (92.5% w/w) [CIPAC MT 46]	Thermally stable below 150°C, with no decomposition or transformation observed (99.5% w/w) [CIPAC MT 46, combined Thermogravimetric Analysis and Differential Scanning Calorimetry]	--
Surface tension	Not applicable	Not applicable (solubility < 1 mg/l)	--

	(solubility < 1 mg/l)		
Reactivity towards container materials	On the basis of experience in use, not reactive towards container materials, including polyethylene, high density polyethylene, polypropylene, steel and stainless steel	No signs of reaction with container materials on the basis of widespread experimental and commercial use over many years Besides, pure *Brodifacoum* is immediately diluted to form a 0.25% concentrate within the manufacturing plant	--

Analytical methods

A:

Adequate methodology exists for the determination of *Brodifacoum* (either *cis* and *trans* isomer) in the technical active substance including impurity determination (five-batch analysis, see table below), as well as in the biocidal product Klerat Pellets.

	Common name	CAS number	Concentration range
Purity of the a.s.	*Brodifacoum*	56073-10-0	96.2-99.4% w/w (mean: 98.1 % w/w)
Isomeric composition	*cis* isomer *trans* isomer	72654-66-1 72654-67-2	*Confidential*
Impurity profile	*Confidential*	*Confidential*	*Confidential*

Furthermore, fully-validated analytical methods for the determination of *Brodifacoum* residue in water, food/feeding stuff, plasma and liver have been submitted, whereas a new study for the determination of *Brodifacoum* residue in soil has been required, being the submitted method obsolete and incompletely validated.

Since *Brodifacoum* is a non-volatile substance and intended to be used only in solid formulations, a method for the analysis of *Brodifacoum* residues in air has not been considered necessary.

For the determination of *Brodifacoum* residues in drinking, ground and surface water as well as in/on food or feeding stuff, analytical methods based on LC with MS/MS detection have been presented. Analysis is enabled down to a level of 0.05 µg/l and 0.01 mg/kg for water

samples and food/feed matrices (cucumber, lemon, oil-seed rape, wheat and meat), respectively.

With regard to plasma and liver tissue, the determination of *Brodifacoum* residues has been accomplished by HPLC with fluorescence detection down to 0.010 mg/l and 0.01 mg/kg, respectively. Since meat has already been taken into account, as described above, no further analytical method for *Brodifacoum* residue determination in tissues is required.

B:

A fully-validated analytical procedure by RP-HPLC/UV (five-batch analysis) for the determination of *Brodifacoum* in the active substance as manufactured (technical grade material) is described. A non-validated RP-HPLC/UV method for the determination of the relative isomeric content of *Brodifacoum* in the technical grade material is also available. Overall data from the five-batch analysis are summarized as follows:

	Common name	CAS number	Concentration range
Purity of the a.s.	*Brodifacoum*	56073-10-0	99.23-99.91% w/w (mean: 99.46% w/w)
Isomeric composition	*cis* isomer *trans* isomer	72654-66-1 72654-67-2	*Confidential*
Impurity profile	*Confidential*	*Confidential*	*Confidential*

A method for the determination of *Brodifacoum* in pellet and wax block baits has been also developed and satisfactorily validated.

Fully-validated analytical methods based on LC with MS/MS detection for the determination of *Brodifacoum* residues in drinking, ground and surface water as well as in/on food or feeding stuff have been presented. Analysis is enabled down to a level of 0.05 µg/l for drinking and ground water (0.5 µg/l for surface water) and 0.01 mg/kg for food/feed matrices (cucumber, lemon, oil-seed rape, wheat and meat).
Since *Brodifacoum* is a non-volatile substance and is intended to be used only in solid formulations, a method for the analysis of residues in air is not considered necessary.
As for the analysis of *Brodifacoum* in human and animal body fluids and tissues, a study has been re-submitted by the Applicant, where the LC-MS/MS analysis of *Brodifacoum* residues in blood serum down to a level of 0.06 mg/l is described. The method is adequately validated. Body tissues are covered under food of animal origin.
With regard to *Brodifacoum* residues in soil, neither the HPLC/UV method originally submitted in the Dossier nor the HPLC/MS method newly submitted by the Applicant were deemed acceptable, due to remarkable deficiencies affecting the validation work and major reporting deficiencies.

2.1.3 Intended Uses and Efficacy

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

A, B: *Brodifacoum* is used as a rodenticide pest control substance (Main group 03, Product type **14**). *Brodifacoum* is used to control:

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

2.1.3.2. Effects on target organisms – the active substance

A, B: *Brodifacoum* is a second-generation single-dose anticoagulant rodenticide. It disrupts the normal blood clotting mechanisms resulting in increased bleeding tendency and, eventually, haemorrhage and death. Effectiveness of the active substance depends on exposure (*i.e.* consumption of the bait by the target organism). However, for effective and comprehensive control of rats and mice, including those strains that may be resistant to other anticoagulant compounds, a bait concentration of 50 mg/kg is proposed. Documentation on effectiveness of *Brodifacoum* against target organisms is well conducted, according to the standard methods for efficacy testing of biocidal products and active substances (rodenticides) presently available in Europe. Results are satisfying and reliable. The formulated product type has no significant difference on the effects of the active substance on the target organisms. *Brodifacoum* is used in products as the active substance for domestic, industrial and commercial buildings including in and around farm buildings, and in sewers. On the basis of the existing literature efficacy tests with *Mus domesticus* and *Rattus norvegicus* were provided and they were acceptable; no tests were carried out with *Rattus rattus.* And more, the guidelines by MAFF (1990) and EPPO (1982) for field efficacy trial consider these two species only. Therefore, we think that such chose is based on a actual difference in the behaviour between the two species of *Rattus*. In urban areas *Rattus norvegicus* penetrate sewers, ditches, banks of rivers and canals and when occurring in the buildings, it uses to colonize the ground and low-levels of them (Capizzi & Santini, 2007), being more frequent in the environments attending by humans. *Rattus rattus* is a synanthropic species dwelling in urban green parks pushing on to buildings where it generally colonize the high-levels like attics, roofs and terraces It is more frequent in the countryside, nearby villages, rural buildings and animal shelters (Capizzi & Santini, 2007). On the base of these considerations the field trial on *Rattus rattus* is more difficult to realize and consequently less representative of the effectiveness of the active substance on this species, deriving from this the uselessness of the field trial.

A: *Effects on target organisms – Brodifacoum pellets*

The effectiveness of the *Brodifacoum*-based product *Brodifacoum* pellets, a ready-to-use bait containing 50 ppm of the active substance, on target organisms (synanthropic rodents *Mus musculus, Rattus norvegicus, R. rattus*) was evaluated through a number of laboratory and field bioassays. Field tests were carried out in different environmental scenarios, with different levels of rodent infestation (from low to high), using methods which are compliant with current guidelines (TNsG on Product Evaluation, Chapter 7 and its appendices – Product Type **14** – Rodenticides. EPPO, 1999, Guidelines for the efficacy evaluation of rodenticides. MAFF, 1990. Guidelines on efficacy tests for rodenticides, MAFF Working Document 10/2). On the whole the efficacy studies presented by the applicant are considered satisfactory and reliable. A laboratory test with albino Norway rats (*Rattus norvegicus*) was conducted in which a dose-mortality relationship was derived for *Brodifacoum* pellets under limited feeding test no-choice conditions. The dose required to kill 99% of the test animals was found to be 0.496 mg per kg body weight. This is the dose of *Brodifacoum* contained in 1.984 g of *Brodifacoum* pellets. A similar test was conducted using albino House mice (*Mus musculus domesticus*) and showed that the dose of *Brodifacoum* required to kill 99% of House mice is contained in 0.286 g of *Brodifacoum* pellets. These tests demonstrated a high degree of effectiveness of *Brodifacoum*, formulated as *Brodifacoum* pellets, when offered under limited feeding no-choice test conditions to albino Norway rats and House mice. Palatability tests were conducted in which individually-caged albino Norway rats and House mice were offered a choice between *Brodifacoum* pellets and EPA meal (containing a mixture of oatmeal, corn grits, sugar and corn oil). Acceptance of the test bait (*Brodifacoum* pellets) was 69.5% for House mice and 42.6% for Norway rats, indicating that the bait was highly palatable to the test animals. Although the test was not permitted to proceed to mortality due to statutory requirements relating to animal welfare, it was estimated from the quantities of the active substance consumed that 100% mortality would have been achieved had this been the case. A series of four field trials were conducted against wild Norway rats infesting farmsteads in the south of the United Kingdom. Two independent methods were used to assess treatment efficacy, census baiting and tracking patches, and these showed that efficacy of 95-100% was achieved at the four farms. A field trial was conducted against House mice at a farmstead in Wales. Once again, two independent methods of assessing treatment efficacy, census baiting and tracking patches, were used. Treatment efficacy was estimated to be at least 97.3% at the site after the application of *Brodifacoum* pellets for 16 days. A series of field trials of a pellet bait formulation containing 50 ppm *Brodifacoum* was also conducted in the USA. Although these trials were carried out using a slightly different product formulation (Talon pellets), these trials also demonstrated the capability of baits containing 50 ppm *Brodifacoum* to provide effective control of Norway rat, House mice and Roof rat (*Rattus rattus*) infestations. The laboratory and field trial data submitted by the participant, and the extensive reports in the published literature, provide categorical evidence that baits containing 50 ppm *Brodifacoum* are effective for the control of rats and mice.

Brodifacoum pellets can be used indoors, around buildings and in sewers. It should be applied by manually placing measured amounts of product into protected bait points, at discrete locations throughout a rodent infested area.

B: *Effects on target organisms – Brodifacoum wax blocks*

The active substance is used in wax block products. The effectiveness of the *Brodifacoum*-based product *Brodifacoum* wax block, on target organisms (synanthropic rodents *Mus musculus*, *Rattus norvegicus*, *R. rattus*) was evaluated through a number of laboratory and field bioassays. Field tests were carried out in different environmental scenarios, with different levels of rodent infestation (from low to high), using methods which are compliant with current guidelines (TNsG on Product Evaluation, Chapter 7 and its appendices – Product Type **14** – Rodenticides. EPPO, 1999, Guidelines for the efficacy evaluation of rodenticides. MAFF, 1990. Guidelines on efficacy tests for rodenticides, MAFF Working Document 10/2). On the whole the efficacy studies presented by the applicant are considered satisfactory and reliable.

Brodifacoum 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 *Brodifacoum* 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, *Brodifacoum* 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 *Brodifacoum* 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 *Brodifacoum* 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. Wax blocks are blocks with a matrix containing impregnated grain and wax. The Task force supplies wax blocks of 20g, being approximately 35 mm x 35 mm x 10mm. The treatment frequency is 2-4 applications per year, 3-6 month apart. The amount of used product per application is often 1-5 blocks (20-100 g) per baiting point. Bait points are placed typically every 2 to 5 m for mouse infestation and 5 to 10 m for rat infestation. Closer placement is required for heavier infestations.

2.1.3.3. Humaneness

A, B: The use of *Brodifacoum* 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.

2.1.3.4. Resistance

A, B: Actually, the phenomenon of resistance to rodenticides is almost all referred to populations of rats or mice to the anticoagulant of first generation, *i. e.* the *Warfarin*.

Out of 28 articles cited in the references, 21 are referred to *Warfarin* resistance or to older rodenticides now considered obsoletes. Most of the articles have been written from the 1970's to 1990's. Of the remaining articles, five deal on resistance, or to presumed changes in the susceptibility of rats populations to anticoagulants and only 2 are referred to single events of "suspected" resistance to *Brodifacoum* products.

In conclusion there is no reason to suspect a lack of efficacy of *Brodifacoum*-based products and it is possible to state that *Brodifacoum* is fully active against rodents populations that developed resistance to warfarin.

2.1.4 Classification and Labelling

A (data from Syngenta) and B (data from Activa/PelGar)

2.1.4.1 Proposal for the classification and labelling of the active substance

Risk phrases	R26/27/28, R43, R48/23/24/25, R61*, R50/53
Safety phrases	S20/21, S35, S36/37, S45, S60, S61 (S1/2 is not required as the substance is never available to the public.)
Proposal for labelling	as in Directive 67/548/EEC, 99/45/EC and on the basis of data and pragmatism: T+; R26/27/28, R43, R48/23/24/25, R61 N; R50/53
Existing classification and labelling	as in Directive 67/548/EEC: T+; R27/28, T; R48/24/25, N; R50/53 (S1/2), S36/37, S45, S60, S61
Specific concentration limits for human health and environmental effects	C ≥ 2.5% T+, N; R26/27/28-48/23/24/25-43-61-50/53 1% ≤ C <2.5% T+, N; R26/27/28-48/23/24/25-43-61-51/53 0.5% ≤ C< 1% T+, N; R26/27/28-48/23/24/25-61-51/53 0.25% ≤ C< 0.5% T+, N; R26/27/28-48/23/24/25-51/53 0.025% ≤ C< 0.25% T ; R23/24/25-48/20/21/22-52/53 0.0025% ≤ C <0.025% Xn; R20/21/22

*Based on the classification for developmental effect by read across to Warfarin.

2.1.4.2 Proposal for the classification of the active substance based on Regulation EC 1272/2008:

Physical/chemical properties	**None**		
Health hazards	**Acute Tox. 2** **Acute Tox. 1** **Acute Tox. 1** **STOT RE 1** **Repr. 1B**	**H300** **H310** **H330** **H372** **H360D***	

Environment	**Skin Sens 1** **Aquatic acute 1**	**H317** **H400**	
	Aquatic chronic 1	**H410**	

Proposal for the labelling of the active substance based on Regulation EC 1272/2008:

Signal Word	**Danger**		
Symbol	**GHS06** **GHS08** **GHS07** **GHS09**		
Hazard statement codes	**H300: Fatal if swallowed;** **H310: Fatal in contact with skin** **H317: May cause an allergic skin reaction** **H330: Fatal if inhaled** **H372: Causes damage to organs through prolonged or repeated exposure** **H360d: May damage the unborn child.** **H410: Very toxic to aquatic life with long lasting effects**		

Justification for the proposal

On basis of study results classification of *Brodifacoum* is 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.

Brodifacoum is a second-generation anticoagulant, with vitamin K-inhibiting properties, rather similar to Warfarin, which is recognized human teratogen. 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 *Brodifacoum* for acute and repeated dose toxicity was agreed upon. In May 2007 the provisional 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 *Brodifacoum* were agreed upon as proposed.

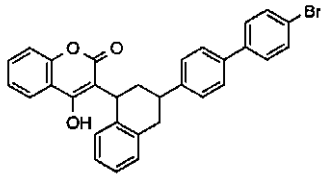
A classification of *Brodifacoum* as R61 was purely based on read-across from Warfarin, without any evidence for significant developmental effects being indicated by studies performed on Brodifacoum. For a similar second-generation anticoagulant, flocoumafen classification R63 has been recently proposed by the RMS (at TMIII2010): the classification is based on a) adequate studies indicating no developmental toxicity at doses not eliciting significant maternal toxicity, as indicated but inhibited blood coagulation and b) the due, conservative consideration to the areas of uncertainties still existing about the actual similarity with the human teratogen Warfain, in particular, the ability to cause extrahepatic vitamin K deficiency, the transplacental passage and the higher sensity of humans as compared to rodents. A classification of Brodifacoum as **R63** ("limited evidence" of developmental toxicity) appears therefore appropriate.

2.2. Summary of the Risk Assessment

2.2.1 Human Health Risk Assessment

The active substance, *Brodifacoum*, whose structure is shown in Fig. 1, is a so-called second generation anticoagulant rodenticide, which like other coumarin derivatives, is a vitamin K antagonist. They function by inhibiting the ability of the blood to clot at the site of a haemorrhage, by blocking the regeneration of vitamin K in the liver. Death of target organisms is due to massive internal haemorrhages after several days of ingestion of a lethal dose.

Figure.1. The structure of *Brodifacoum*



Briefly, blood clots form when the soluble protein fibrinogen, normally present in the blood, is converted by the enzyme thrombin to the insoluble fibrous protein fibrin, which binds platelets and blood cells to form a solid mass referred to as a blood clot, sealing the site of the haemorrhage and preventing further blood loss. Thrombin is not present in the blood, and is formed at the site of injury from prothrombin. Conversion of prothrombin to thrombin occurs via the coagulation cascade, in which the blood clotting factors are employed. Without these blood factors clotting cannot take place, and the haemorrhage will not be controlled by clot formation. The synthesis of a number of blood coagulation factors is dependent upon vitamin K hydroquinone, which acts as a co-enzyme.

The anticoagulant rodenticide active substances such as *Brodifacoum* work by blocking the regeneration of vitamin K 2,3-epoxide to vitamin K hydroquinone. Since, the amount of vitamin K in the body is finite, the progressive block of the regeneration of vitamin K will lead to an increasing probability of a fatal haemorrhage.

2.2.1.1. Toxicokinetics

A:

Brodifacoum (0.21 mg/kg bw) administered orally to rats was rapidly absorbed (T_{max} =8h; C_{max} 16.1 ng/ml whole blood). The levels declined slowly and about 10% (1.3 ng/ml) was still present at 10 days after dosing. Almost all (82.5 %) the radioactivity in whole blood was found to be associated with the plasma. Based on the radioactivity still associated to the animal tissues, 10 days after the treatment, the **oral absorption was > 75%.** After a single oral dose of 10 mg/kg of *Brodifacoum* about 64.0% was absorbed and could be accounted for in the liver, carcass and bile 48h after dosing. The rest was recovered in the faeces, as unabsorbed material.

After absorption the product was widely distributed. 10 days after dosing the proportion of the retained dose was highest in the liver (22.8 %), followed by the pancreas (2.3 %), and then the kidney (0.8 %), heart (0.1 %) and spleen (0.2 %). The remainder of the dose (≅50%) was in the carcass and skin.

Brodifacoum was only partially metabolised. 31.3% and 19.6% of the residues in the carcass and liver, respectively, was unchanged *Brodifacoum*. Two more polar metabolites were detected in the bile, the major one being identified as the glucuronide.

Brodifacoum shows a high potential for bioaccumulation: in all studies undertaken and at all dose levels tested, the liver retained the largest % of the dose, even very long time after dosing. Analyses of the rat livers from the 90 day feeding study, indicate a non-linear accumulation of *Brodifacoum vs* dose and time.

A small amount (11 – 14%) of the radioactivity was slowly eliminated in urine and faeces over 10 days following a single oral dose of 0.25 mg/kg. Biliary and renal routes are of equal significance in the elimination of *Brodifacoum*. The rate of elimination as given by the biological half-life, was calculated to be 150 – 200 days.
The elimination from the liver was biphasic at higher doses. There was a rapid phase (days 1-4) which also corresponded to a reduction in clotting factor synthesis, followed by a slower terminal phase (days 28-84) during which blood clotting function was normal. The half-life of elimination from the liver during the rapid and the slow phase was ≅4 and 128 days, respectively. At low dose levels, clotting factor synthesis was unaffected indicating that probably only the slow elimination phase was present in the liver. The half-life of *Brodifacoum* in the liver was calculated in the range of 282-350 days.

Dermal absorption was assessed by using a formulation (ready-for-use pellet bait) containing 0.0048% *Brodifacoum* w/w tested in vitro test on human skin samples. Over the entire 24 h exposure *Brodifacoum* (determined by LC-MS-MS) was found below the LOQ in the receptor fluid (<3.53% of the applied dose) and in the epidermis (<1.64%), after tape stripping. The applied dose was readily removed by mild skin washing and recovered (108 ±6.25%) in the washing fluid. **A 'surrogate value' of 5% dermal absorption was calculated** by summing up the amount in the receptor fluid and in the epidermis after tape stripping, which can be considered as systemically available material. This value has been taken forward to the risk characterization as the worst case, also taking into account that the exposure period exceeds the usual time (*i.e.* 8 hours) of professional handling.

B:

Read across to data from some related 2nd generation anticoagulants (*i.e. Difenacoum*, *Flocoumafen*) is requested for ADME data, including dermal absorption, and has been applied for other end-points by the RMS.

Beside the similar mode of action, the read across is supported by bridging studies demonstrating the similarity in physico-chemical and toxicological properties of these substances which are presented up-front to Doc. IIA- Section 3.

Anticoagulant rodenticides including *Brodifacoum* are rapidly absorbed via the gastro-intestinal tract and oral absorption is assumed to be 100%, on the basis of amount of radioactivity recovered in the excreta and retained in the tissues. The major route of elimination after oral administration is via the faeces, both as polar metabolites and parent

compound. *Brodifacoum* is widely distributed and bioaccumulates in the liver with minor concentrations in the kidney.

Elimination processes are very slow with 50-75% of the administered dose being retained in the liver ($t_{1/2}$ for hepatic residues more than 200 days).

The metabolism of *Brodifacoum* is limited, although in repeated dose studies evidence of induction of metabolism was reported, with increasing levels of radioactivity associated to polar metabolites recovered in the urine. The toxicologically relevant chemical species is the parent compound.

No study on dermal absorption of *Brodifacoum* has been presented. *Brodifacoum* is expected to be slowly absorbed through the skin, due to the lipophylicity of the molecule, allowing passive transport through the membrane. The read across principle can be applied, based on the close structural relationship, the similar physico-chemical properties and the same mode of action displayed by *Brodifacoum* towards other 2nd generation anticoagulants, such as *Difethialone* and *Difenacoum*. A dermal absorption value =4% has been adopted for *Difethialone*, whereas in the case of *Difenacoum* two different values have been used for risk characterisation depending on the type of formulation, that is 3% (pellets and grains) or 0.047% (wax block bait).

In the CAR, by applying the read across from data on a structurally related 2nd generation anticoagulant *Difenacoum*, a 3% dermal absorption value was adopted for the exposure calculation (below reported under Section 2.2.1.8). This value was calculated from a dermal absorption study testing a pellet formulation containing *Difenacoum* as active substance.

Conclusion on toxicokinetics: An almost complete oral absorption can be considered, on the basis of amount of radioactivity recovered in the excreta and retained in the tissues. *Brodifacoum* is widely distributed and bioaccumulates mainly in the liver with lower concentrations in the kidney. Hepatic bioaccumulation of *Brodifacoum* is a non-linear *vs* dose and time. The elimination kinetic from the liver was biphasic, with an half-life in the range of 282-350 days. The excretion after oral administration is very slow (11 – 14% in 10 days), occurring via the urine and the bile, both as polar metabolites (glucuronide) and parent compound. The metabolism of *Brodifacoum* is limited and the toxicologically relevant chemical species is the parent compound.

Concerning the dermal absorption value to be used in the risk characterisation for wax block bait, in the Combined Assessment Report for *Difenacoum* (September 2009) a value of 0.047% was proposed. Therefore, on the basis of the available study and reading across from data on other 2nd generation anticoagulant rodenticides, two different values should be used for risk characterisation depending on the type of formulation: 5% (pellets and grains) or 0.047% (wax block bait).

2.2.1.2. Acute effects

A:

Brodifacoum was very toxic to rats and mice with similar oral LD_{50} of about 0.4 mg/kg bw to the male rat and mouse. *Brodifacoum* is also acutely toxic by the dermal and inhalation routes. Death was the result of internal haemorrhage.

Brodifacoum does not fulfil the EU criteria for classification as a skin or eye irritant, but is able to cause skin sensitization in guinea pig and fulfils the EU criteria for classification as a skin sensitizer.

B:

Brodifacoum is very toxic if swallow (oral LD_{50} <5 mg/kg bw) or in contact with skin (dermal LD_{50}= 7.48 mg/kg bw in rat females; even lower in males).

The waiving for the inhalation toxicity study has been accepted due to low vapour pressure of *Brodifacoum* and data on dustiness and particle size, indicating that the potential for inhalation is limited in addition to ethical and animal welfare reasons. However, based on data with structurally related compounds with the same mechanism of action (*i.e.* 2nd generation anticoagulants), it is expected that the substance is also highly toxic after inhalation.

Brodifacoum is not irritant to the skin or eyes of rabbits and showed no sensitizing potential in a LLNA study in mice.

Conclusion on acute effects: *Brodifacoum* is very toxic after oral administration and also via the dermal and inhalation routes. Death was the result of internal haemorrhage. Classification with T+; R26/27/28; 'Very toxic by inhalation, in contact with skin and if swallowed' is warranted.
Brodifacoum does not fulfil the EU criteria for classification as a skin or eye irritant. Although showed no sensitizing potential in a LLNA study in mice, it was able to cause skin sensitization in guinea pig and fulfils the EU criteria for classification as a skin sensitizer.

2.2.1.3 Repeated Dose Effects

A:

Repeated dose oral studies show that in the rat and in the dog, the clinical signs, haematological and post mortem data were consistent with the known pharmacological action of *Brodifacoum*: impairment of the clotting cascade and increased prevalence of haemorrhage leading to death. There were no indications of other secondary toxicities: any of the other parameters including histopathological analysis revealed no treatment related alterations.
The subchronic 90-day oral toxicity allowed the derivation of the lowest repeated toxicity NOEL= 0.001 mg/kg bw/day. In this study, no treatment related effects on haematological parameters were evidenced at any dose, after 45 days, but statistically significant increases in both the kaolin-cephalin time (KCT) and the prothrombin time (PT) were measured at the highest dose level, 0.004 mg/kg bw/day after 90 days. Based upon this effect on prothrombin times and based on haemorrhagic changes seen at necropsy, the NOEL was set at the next lowest dose, 0.001 mg/kg bw/day.
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 these data plus extrapolation from the acute data for the dermal and inhalation route of exposure.

B:

Repeated oral exposure to *Brodifacoum* resulted in clinical signs and toxicity consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent (lethal haemorrhages). The overall NOAEL for subchronic oral toxicity is 0.04 mg/kg/day.

No data have been submitted on dermal repeated toxicity On the basis of both physico-chemical properties and *Brodifacoum* mode of action it can be anticipated that subchronic effect due to prolonged skin contact should not be disregarded.
No data on repeated inhalation toxicity have been submitted. As indicated by the low vapour pressure, dustiness and particle size, the potential for inhalation is low and the request for a repeated dose inhalation toxicity study is not considered justified also based on ethical and animal welfare reasons.
However, based on the results of the acute dermal and inhalation toxicity studies, route-to-route extrapolation, consistently with the decision adopted for *Difenacoum* (being the read across accepted for other end-points), it is justified to assume a similar concern for serious damage to health by prolonged exposure through dermal and inhalation routes also.

Genotoxicity

A:

Brodifacoum was tested in *Salmonella typhimurium* strains TA 1535, TA 1537,TA 98, TA 100, TA 1538. with and without S9-mix, up to 5000 mg/plate, with negative results. No clastogenic activity was observed in the *in-vitro* cytogenetic assay in human lymphocytes, performed with and without metabolic activation, up to cytotoxic doses. The *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y cells also resulted negative, with and without S9-mix, while cytotoxic effects was observed at the highest doses. The applicants submitted also an *in vitro* UDS test and in an *in vitro* cell transformation assay, but because of several methodological and reporting shortcomings, they were considered of limited scientific significance. An *in vivo* mouse micronucleus test gave negative results. The studies submitted were rather dated, therefore they were not always compliant with the current guidelines. However a genotoxic potential of the active substance can be reliably ruled out.

B:

Brodifacoum was tested for genotoxic activity in the bacterial reverse mutation test in *Salmonella thyphimurium* in strains TA 98, TA 100, TA 102, TA 1535 and TA 1537, up to 5000 μg/plate, with and without metabolic activation (S9-mix). No genotoxic activity was observed in any bacterial strain. The substance resulted negative up to cytotoxic concentration also in the gene mutations assay in L5178Y mouse lymphoma cells, with and without S9-mix, and in the *in vitro* mammalian chromosome aberration test in human lymphocytes (50% mitotic inhibition at the maximum dosage tested).

Carcinogenicity/chronic toxicity

A, B:

Carcinogenicity and long-term toxicity studies were waived as infeasible and unnecessary.

Reproductive and developmental toxicity

A:

Brodifacoum did not induce developmental effects in two adequate prenatal toxicity studies in the rat and rabbit, respectively.

In particular, in the rat studies maternal hemorrhages were observed at dose levels > 0.01 mg/kg bw (NOEL 0.001 mg/kg bw) whereas no effects on conceptuses were detected up to the top dose level of 0.02 mg/kg bw. In the rabbit study, the top dose of 0.005 mg/kg b.w caused a high proportion of maternal deaths, whereas no significant effects on litters were observed. In spite of these findings, a provisional decision has been made at the Technical Meeting of Classification and Labelling that [R61] should be applied to all anticoagulant active substances on the basis of analogy to *Warfarin*.

B:

There was no evidence of developmental toxicity effects up to the dose levels of 0.04 and 0.004 mg/kg bw in rats and rabbits, respectively. In rabbit dams an increase in kaolin-cephalin and prothrombin time was present at 0.004 mg/kg bw (NOAEL 0.002 mg/kg).

Whereas it is suggested that two-generation studies may not be need for anticoagulant rodenticides, a two-generation study on rat was submitted: findings confirmed those of developmental toxicity, both qualitatively (parental toxicity with haemorrhages, no reproductive or developmental effects in the absence of general toxicity) and quantitatively (NOAEL: 0.001 mg/kg bw).

Since the conventional OECD Guideline 414 may have limitations in the detection of possible developmental effects of coumarin related compounds, and in spite of these findings, a provisional decision has been made at the Technical Meeting of Classification and Labelling that [R61] should be applied to all anticoagulant active substances on the basis of analogy to *Warfarin.*

Neurotoxicity

A:

None of the acute or subchronic performed tests gave any indication for a potential neurotoxic effect of *Brodifacoum*

B:

The toxicological studies do not indicate any neurotoxic effects.

Conclusion on repeated dose effects: Repeated oral exposure to *Brodifacoum* resulted in clinical signs and toxicity consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent (lethal haemorrhages). The NOEL for subchronic oral toxicity is in the range 0.001 – 0.04 mg/kg/day (the lowest values identified with sensitive end-points, such as increases in both the kaolin-cephalin time and the prothrombin time). Based on

results from the acute dermal and inhalation toxicity studies, route-to-route extrapolation, consistently with the decision adopted for *Difenacoum*, it is justified to assume serious damages associated to prolonged exposure through dermal and inhalation routes also. Therefore, 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.

Conclusion on Genotoxicity and Carcinogenicity: *Brodifacoum* displayed no mutagenic activity in a standard range of genotoxicity tests. No long-term carcinogenicity study was submitted by the two applicants. In fact, chronic toxicity studies were not considered to be technically feasible due to the specific action of the active substance on the test/target species. However, the anticoagulant action is apparently the only pharmacological action of *Brodifacoum*. The active substance has no structural alerts for carcinogenicity and no concern about possible non-genotoxic carcinogenic potential can be derived from the toxicological studies. Therefore the justifications of both the applicants for not-submission of carcinogenicity data was considered acceptable.

Conclusion on Reproductive toxicity: Reproductive and developmental toxicity studies on *Brodifacoum* did not reveal any specific effects. General toxicity effects were consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent. The lowest NOAELs for rabbits and rats were 0.002 and 0.001 mg/kg bw.
In spite of these findings, a provisional decision has been made at the Technical Meeting of Classification and Labelling that [R61] should be applied to all anticoagulant active substances on the basis of analogy to *Warfarin*.

None of the acute or subchronic performed tests gave any indication for a potential neurotoxic effect of *Brodifacoum*.

2.2.1.4 Medical data

A:

Routine monitoring of workers (industrial users) producing *Brodifacoum* and formulating products has been carried out for the last forty years. Between June 1981 and September 1982, three poisoning incidents occurred with successful recovery. With the exception of these incidents, routine monitoring has shown no clinical effects in any workers. During this time there has been no evidence of allergenicity, sensitisation or any other abnormal effects induced by repeated and continual exposure to these anticoagulant rodenticides.

B:

No significant effects caused by *Brodifacoum* in personnel with occupational exposure have been observed.

2.2.1.5 ADI

A:

Derivation of ADI is based on the value of 0.001 mg/kg bw/day (that is the NOAEL derived from the 90-day toxicity study in rat) and an AF of 1000 (accounting for inter – and intra-species differences, the lack of chronic toxicity study and the severity of toxic effects). Therefore an ADI value of 1x 10^{-6} mg/kg/day is proposed.

B:

The ADI is set using the most sensitive NOAEL value (Two generation study-NOEL for female 0.001 mg/kg/day) with an Assessment factor of 300 (accounting for inter – and intra-species differences, and the type of toxic effects). Therefore an ADI value of 3x 10^{-6} mg/kg/day is proposed.

Conclusion on ADI derivation: An Acceptable Daily Intake (ADI) value is applicable for *Brodifacoum* used as a biocide, since potential exposure via food and feedstuffs can occur, although exposure is unintentional as the product is not applied to food crops. Baits containing it are kept secure from foodstuffs, usually in bait boxes, and frequently in locations where foods are not present. Dead rats and mice are collected for disposal along with unused bait remains. Therefore the possibilities of the material entering the food chain are limited. For ADI derivation the use of the most appropriate NOEL value due to the better quality of the study and the lower level of uncertainty is selected. Therefore the NOEL value from the two generation study (0.001 mg/kg bw/day) and an AF of 300 (accounting for inter– and intra-species differences and the severity of toxic effects) were used to obtain ADI value= 3x 10^{-6} mg/kg/day.

2.2.1.6 Acceptable Exposure Level (AEL)

A: The Acceptable Exposure Level for acute exposure (AEL_{acute}) was based on the maternal NOEL from developmental study of 0.001 mg/kg bw/day (rat, maternal effect). A safety factor of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{acute} results to be of 3.3 x 10^{-6}mg/kg/day.

The Acceptable Exposure Level for repeated exposure (AEL_{chr}) was based on a subchronic NOEL from a 90-day oral rat study of 0.001 mg/kg bw/day. A safety factor of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{chr} results to be of 3.3 x 10^{-6} mg/kg/day.

B: The Acceptable Exposure Level for acute exposure (AEL_{acute}) was based on NOAEL from a developmental study (female rabbit) of 0.002 mg/kg bw/day. A safety factor of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{acute} results to be of 6.67 x 10^{-6} mg/kg bw/d.

The Acceptable Exposure Level for repeated exposure (AEL_{chr}) was based on NOAEL for females from the reproductive 2-generation study in rat of 0.001 mg/kg bw/day. A safety factor

of 300 (10 for intra-species variability x 10 for inter-species variability x 3 additional factor for severity of effects). The AEL_{chr} results to be of 3.3×10^{-6} mg/kg bw/day.

TMIII09 agreed to derive $AEL_{medium\ term}$ consistently with what decided for the other AVK rodenticides. Therefore, $AEL_{medium\ term}$ was calculated from the NOAEL of 0.002 mg/kg bw/day (developmental oral toxicity study in rabbit) divided by an Assessment Factor of 300 (10 for interspecies x 10 for intraspecies x 3 additional factor for severity of effects). The $AEL_{medium\ term}$ results to be of 6.67×10^{-6} mg/kg bw/day.

Conclusions:
The following AELs should be considered in the risk characterization for *Brodifacoum*:

- AEL_{acute} of 3.3×10^{-6} mg/kg/day based on the maternal NOEL from a teratogenicity study of 0.001 mg/kg bw/day (rat, maternal effect)
- $AEL_{medium\ term}$ of 6.67×10^{-6} mg/kg bw/day based on the NOAEL from a developmental study (female rabbit) of 0.002 mg/kg bw/day
- AEL_{chr} of 3.3×10^{-6} mg/kg bw/day based on the NOAEL for females from the reproductive 2-generation study in rat of 0.001 mg/kg bw/day

2.2.1.7. Health hazard of the representative products

A:

The product *Klerat Pellets* (cereal based pellets) is a ready-to-use formulation containing 50 mg/kg of *Brodifacoum* as active substance. The *Klerat Pellets* bait products contain a human taste deterrent and a warning colour to help in preventing accidental consumption,.

In the acute oral toxicity test, the LD_{50} value is above 5000 mg/kg bw. The LD_{50} is higher than 500 mg/kg bw: this could not exclude it is lower than 2000 mg/kg bw. An acute inhalation study has not been submitted.

The representative rodenticide is not irritating to the skin or to the eye. Furthermore, there is no evidence for any skin-sensitising potential.

Dermal absorption was assessed in vitro on human skin samples with a ready-for-use pellet bait formulation containing 0.0048% *Brodifacoum* w/w. Taking the LOQ of the analytical method as the detected levels of residues in the receptor fluid and in the epidermis after tape stripping, (considered as systemically available material), a 'surrogate value' of 5% dermal absorption was calculated. This value has been taken forward to the risk characterization as the worst case, also taking into account that the exposure period exceeds the usual time (*i.e.* 8 hours) of professional handling.

B:

No study on the acute toxicity of Vertox Wax Blocks have been submitted. However, on the basis of its composition, in accordance with the Dangerous Preparation Directive 1999/45/EC, Vertox Wax Blocks have been estimated not to be classified by either oral, dermal or inhalation exposure.

Although no study has been presented, on the basis of data on *Brodifacoum* and the other coformulants, it can be concluded that Vertox Wax Blocks are not skin or eye irritants neither skin sensitizers.

In the biocidal product *Brodifacoum* is absorbed to the food ingredients, which are then contained within a matrix formed by the wax. The low water solubility (< 0.1 mg/l) and the high absorption characteristics of *Brodifacoum* (log P_{ow} > 4.0, Log K_{oc} = 8.50) combined with the potential for the active substance to ionise, indicate that the active substance has a negligible potential for leaching out of the wax block. It is therefore considered that the potential for percutaneous absorption from the finished biocidal product is minimal. By applying the read across from data on a structurally related 2nd generation anticoagulant *Difenacoum*, a 3% dermal absorption value is adopted. This value was calculated for a pellet formulation containing *Difenacoum* as active substance.

2.2.1.8 Exposure assessment and risk characterisation

Human health risk for professional users

A: The exposure assessment was carried out for ready-for-use formulation containing *Brodifacoum* pellets in bait box. Potential exposure for professional applicators has been calculated based on data of frequency of handling determined in a survey in Europe (CEFIC Study). Assessment from the use of the products included the following tasks: decanting, loading/placement and clean/up. The exposure from use of *Brodifacoum* Pellets bait products considered 80 manipulation per day as worst case assumption (90%ile from the CEFIC Study).

According to the current guidance on dermal absorption (Sanco/222/2000 rev 6, 2002), the *in vitro* dermal absorption of 5% of the applied dose is used in the assessment and considered a worst case. Howeverfor professional users, reduction of dermal exposure from use of protective gloves is assumed. Therefore, workers are assumed to wear protective gloves when handling the products. Wearing gloves is assumed to reduce the exposure of hands by 90%. A body weight of 60 kg for an adult was used for the calculations.

The exposure to *Brodifacoum* resulting from the routine preparation, placement and clean up of bait points is very low. Inhalation exposure is negligible, so dermal exposure accounts for the majority of the total exposure. Therefore, the relevant exposure paths for professional users showed that, using the product in a rodent control campaign, there is potential for dermal and inhalation exposure. The use of gloves or any other Personal Protective Equipment are required when using the product in a rodent control campaign. Furthermore, gloves are recommended to help prevent exposure to rodent-borne diseases. The outcome of the exposure assessment are listed as follows:

Total Exposure	
8.87×10^{-8}	**Total Inhalation Exposure (mg/kg bw/day)**
5.26×10^{-7}	**Total Dermal Exposure (mg/kg bw/day)**
6.16×10^{-7}	**Total Exposure (mg/kg bw/day)**

The results of the risk assessment for the use of *Brodifacoum* Pellets indicates a negligible risk from the production of the active substance or the formulation of the product. The professional user of the product is estimated to have potential exposures below the AEL when PPE are worn. The estimated exposure to *Brodifacoum* resulting from the routine preparation, placement and clean up of bait points is below the AEL.

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

Risk characterisation for professional use of product type 14: AEL and MOE values for the critical effects concerning the workplace exposure towards active substance

Workplace operation	PPE	Exposure path	Systemic dose (mg/kg bw/d)	Acute toxicity (NOEL =0.001 mg/kg bw/d)				Repeated dose toxicity (NOEL = 0.001 mg/kg bw/d)			
				AEL_{acute}[a] (mg/kg bw/d)	AEL/body dose	AEL% = (Systemic dose/AEL) x 100	MOE	AEL_{chr}[b] (mg/kg bw/d)	AEL/body dose	AEL% = (Systemic dose/AEL) x 100	MOE
Exposure Study (Mean) – decant, load, place baits and clean up	YES	Dermal and inhalation	6.16×10^{-7}	3.33×10^{-6}	5.41	18.5	1623	3.33×10^{-6}	5.41	18.5	1623

[a] Based on the maternal NOEL from a teratogenicity study of 0.001 mg/kg bw/d and a total safety factor of 300 (a factor of 10 was used to account for intra-species variability, 10 to account for inter-species variability and an additional factor of 3 for the severity of effects).

[b] Based on the NOEL of 0.001 mg/kg bw/d and safety factor of 300 (a factor of 10 was used to account for intra-species variability, 10 to account for inter-species variability; 3 for the severity of the effects).

B: The exposure assessment was carried out for ready-for-use formulation containing *Brodifacoum* wax block in bait box.

The exposure assessments are based on the following assumptions:

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. According to the CEFIC Study (90%ile for the wax block application), the daily manipulations considered turn out to be 75, where 20% refers to handling baits during the clean-up phase. Therefore, the manipulations considered were 60 and 15 for the application and clean-up stage, respectively. A body weight of 60 kg for an adult was used for the calculations.

On the basis of results on a structurally related compound, the active substance is expected to be slowly but substantially absorbed through the skin, due to the lipophilicity of the molecule, allowing passive transport through the membrane. No study on dermal absorption of *Brodifacoum* has been presented. The active substance is expected to be slowly but substantially absorbed through the skin, due to the lipophylicity of the molecule, allowing passive transport through the membrane. Based on the close structural relationship, the similar physico-chemical properties and the same mode of action displayed by *Brodifacoum* towards other 2nd generation anticoagulants, the read across principle from data on Difenacoum and Difethialone is applied and therefore a values of 3% for dermal absorption is adopted.

The skin is the main exposure route. As or inhalation exposure, the only potential inhalation exposure to professionals will be from dusts containing the active substance, formed during the final mixing of the dry mix and the wax in the formulation process. LEV is not available at the formulation site.

The estimated systemic dermal exposure for professional on a single occasion is 0.94% of AEL_{acute} (for all the intended uses of Vertox Wax Block) based on TNsG default values and assuming the use of protective gloves. According to more realistic measured values taken from the operator exposure study, the exposure for the *Brodifacoum*-based product the systemic dermal exposure is estimated to be from 0.14% (for the disposal of bait boxes) to 2.33% (for the application of blocks in sewers) of the AEL_{acute} assuming the use of protective gloves.

The estimated systemic dermal exposure for professional on a single occasion is 41.7% of AEL_{chr} (for all the intended uses of Vertox Wax Block) based on TNsG default values and assuming the use of protective gloves. According to more realistic measured values taken from the operator exposure study, the exposure for the *Brodifacoum*-based product the systemic

dermal exposure is estimated to be from 6.4% (for the disposal of bait boxes) to 103% (for the application of blocks in sewers) of the AEL_{chr} assuming the use of protective gloves.

However, the dermal exposure values derived by using a dermal absorption of 3% could overestimate the exposure. In fact, in the *Difenacoum* Combined Assessment Report has been agreed that for wax block formulation containing 50mg/kg *Difenacoum* the dermal absorption value to be used is 0.047%. Being the read across with *Difenacoum* accepted, for wax block *Brodifacoum*-based products a value of 0.047% can be apply. Therefore, using a more appropriate dermal absorption value it can be expected an acceptable risks.

The inhalation dose estimated by use of the default models in the TNsG for human exposure estimation and the general exposure calculator is 3.2×10^{-4} mg active ingredient per task. This gives a systemic dose of 5.3×10^{-6} mg/kg bw/day. As for the inhalation route are derived from comparison of AEL_{chr} of 3.3×10^{-6} mg/kg bw/day against the estimated exposure for each task: Therefore, it is estimated an inhalation exposure of 176% of AEL_{chr}.

Workers and pest control operatives are not expected to be exposed by the oral route to the active substance or product. Although the active substance is very toxic by acute oral exposure (LD_{50} rat, oral = <5 mg/kg) good industrial hygiene, such as washing before eating or smoking will reduce the risk of accidental oral exposure. Vertox Wax Blocks are not classified as harmful by oral exposure. Therefore, there is no concern from oral exposure.

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

Risk assessment for professional due to dermal exposure derived according to the CEFIC exposure study and TNsG defaults

Task	PPE Gloves	Systemic dose (mg/kg bw/day)	Acute toxicity (NOAEL = 0.002 mg/kg)		Repeat dose toxicity (NOAEL = 0.001mg/kg bw/day)	
			% of AEL (AEL = 6.7×10^{-6} mg/kg bw/d)	MOE (overall assessment factor = 300)	% of AEL (AEL = 3.3×10^{-6} mg/kg bw/day)	MOE (overall assessment factor = 300)
Professional user: assessment based on CEFIC Exposure Study						
Application: loading of bait boxes	YES	2.7×10^{-6}	40.5	740.74	81.8	370
Application of blocks in sewer	YES	3.1×10^{-6}	46.5	645.16	93.9	323
Disposal of bait boxes professional	YES	1.92×10^{-7}	2.88	10416.67	5.8	5208
Professional user: assessment based on TNsG default values						
Application: loading into bait box	YES	1.251×10^{-6}	18.765	1598	37.9	799
Application of blocks in sewer	YES	1.251×10^{-6}	18.765	1598	37.9	799
Disposal of bait boxes	YES	1.251×10^{-6}	18.765	1598	37.9	799

Human health risk for non-professional users

A: The exposure assessment was carried out for ready-for-use formulation containing *Brodifacoum* pellets in bait box. Potential exposure of non-professional applicators has been calculated based on data of frequency of handling determined in a survey in (CEFIC Study). For amateur use, 2 exposure events per day are assumed for loading/placing of baits. Two manipulations per day were used to include the clean-up phase (*i.e.*, 2 stations).

Total Exposure	
8.87×10^{-8}	**Total Inhalation Exposure (mg/kg bw/day)**
8.80×10^{-8}	**Total Dermal Exposure (mg/kg bw/day)**
1.77×10^{-7}	**Total Exposure (mg/kg bw/day)**

The non-professional users may purchase *Brodifacoum* Pellets and use them in and around the home, etc. It is assumed that non-professional users are to wear no Personal Protective Equipment when using the product. Two exposure assessment calculations were performed for non-professional users: one assuming the default values and the other one resulting from an exposure study. A body weight of 60 kg for an adult was used for the calculations.

Anyhow, the risk characterization is calculated for the more relevant exposure scenarios and is based on the exposure study conducted by CEFIC which is considered to represent a reasonable worst case.

As the calculations below indicate, estimated exposures are therefore expected to be considerably below levels associated with potential health effects.

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

Risk characterisation for non-professional use of product type 14: MOE values for the critical effects concerning the non professional exposure towards active substance

Workplace operation	PPE	Exposure path	Systemic dose dose (mg/kg bw/d)	Acute toxicity (NOEL =0.001 mg/kg bw/d)	Repeated dose toxicity (NOEL = 0.001 mg/kg bw/d)
				MOE[a]	**MOE**
Exposure Study (Mean) – load, place baits and clean up	NO	Dermal and inhalation	1.77×10^{-7}	5625	5625

[a] MOE =NOEL / body dose
A minimal accepted MOE of 300 is determined for acute toxicity (a factor of 10 was used to account for intra-species variability, 10 to account for inter-species variability and an additional factor of 3 due to the suspected effect on the development).

A minimal accepted MOE of 300 is determined for repeated toxicity (a factor of 10 was used to account for intra-species variability, 10 to account for inter-species variability and an additional factor of 3 due to the severity of the effects).

B: The exposure assessment was carried out for ready-for-use formulation containing *Brodifacoum* wax block in bait box.

The exposure assessments are based on the following assumptions:

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

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

The Vertox Wax Block is assumed not to be used on a daily basis by non-professionals. The skin is the main exposure route. Non-professional users are assumed not to wear protective gloves. A body weight of 60 kg for an adult was used for the calculations.

The Margins of Exposure for the dermal route was high (*i.e.*, 634) based on default value and on more realistic measure value taken from the operator exposure study. Therefore, according to the calculated MOE, it is possible to conclude that there is no concern for human exposure from amateur use of the biocidal product.

The dermal exposure values derived by using a dermal absorption of 3% could overestimate the exposure. In fact, in the *Difenacoum* Combined Assessment Report has been agreed that for wax block formulation containing 50mg/kg *Difenacoum* the dermal absorption value to be used is 0.047%. Being the read across with *Difenacoum* accepted, for wax block *Brodifacoum*-based products a value of 0.047% can be apply. Therefore, using a more appropriate dermal absorption value it can be expected an acceptable risks.

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

Table 1. Risk assessment for non-professional operators due to dermal exposure according to the CEFIC exposure study and TNsG defaults

Task	PPE Gloves	Systemic dose (mg/kg bw/day)	Acute toxicity (NOAEL = 0.002 mg/kg)	Repeat dose toxicity (NOAEL = 0.001mg/kg)
			MOE (overall assessment factor = 300)	MOE (overall assessment factor = 300)
Professional user: assessment based on CEFIC Exposure Study				
Disposal of bait boxes	NO	$3.15x10^{-6}$	634	Not applicable
Professional user: assessment based on TNsG default values				
Disposal of bait boxes	NO	$3.15x10^{-6}$	634	Not applicable

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

A: When used in rodent control programs, this product may result in potential secondary exposures. Two scenarios are considered: dermal contact with dead rodents and ingestion of pellets by an infant. These scenarios are listed in TNsG (Part 3, Appendix 7.2.1) as recommended for evaluation of wax baits, and they have been adapted to grain baits in this assessment. None of these scenarios is likely to lead to long-term exposures, whereas acute exposures may be expected to give rise to an unacceptable risk..

Dermal Contact with Dead Rodents

In this scenario, adults are assumed to come into contact with 1g of the pellets on the exterior of dead rodents. Acute exposures are estimated below.

	Dermal contact (g)	**%** *Brodifacoum*	**dermal penetration**	**Dermal Exposure (mg/g)**	**Body weight (kg)**	**Dermal Exposure (mg/kg bw/d)**
Adult	1	0.005%	5%	9.35×10^{-4}	60	4.17×10^{-5}

Ingestion of Pellets

In this scenario, an infant is assumed to ingest 0.01 g and 5 g of pellets on a single occasion. This is a considerably conservative assumption because the taste deterrent (bittering agent: denatonium benzoate) will cause the child to spit out the pellets, thus resulting in no net ingestion. Acute exposure is estimated below.

	Quantity ingested (g)	**%** *Brodifacoum*	**Oral Exposure (mg/g)**	**Body weight (kg)**	**Systemic Exposure (mg/kg bw/d)**
INFANT	0.01	0.005%	5.0×10^{-6}	10	5.0×10^{-5}
	5.0	0.005%	5.0×10^{-6}	10	2.5×10^{-2}

Potential secondary exposure routes associated with the use of *Brodifacoum* in rodenticide products such as *Brodifacoum* Pellets include contact with dead rodents and ingestion of pellets. The exposures for these scenarios are estimated. These secondary exposures are anticipated to be acute in nature, rather than occurring over extended periods. This is particularly the case for the ingestion scenario, in which case the taste deterrent present in the product will most likely result in a child spitting out any pellets rather than ingesting them. The estimated exposures for these scenarios are: 1.70×10^{-4} mg/kg bw/day and 4.17×10^{-5} mg/kg bw/day for adults in contact with dead rodents, respectively. Furthermore, the estimated exposures is 5×10^{-5} mg/kg bw/day and 2.5×10^{-2} mg/kg bw/day for infants ingesting 0.01 g pellets and for infants ingesting 5 g, respectively.

In the risk characterisation for children and adults in contact with dead rodents an assessment factor of 300 is applied to the maternal NOEL from a teratogenicity study (0.001 mg/kg bw/day), resulting in MOE values of 6 and 24 for children and adults, respectively. These results indicate that a risk is foreseeable for children and adults in contact with dead rodents.
In the risk characterisation for infant ingesting pellets an assessment factor of 300 is applied to the maternal NOEL from a teratogenicity study (0.001 mg/kg bw/day). The resulting MOE values are of 20 and 0.04 for the 0.01 g ingestion scenario and the 5g ingestion scenario, respectively. These results indicate that a risk is foreseeable for infant ingesting 0.01 and 5 g of pellets.

NOTE*: According to the decision taken at the TMIII2010, after the finalization of the Final Competent Authority Report for Brodifacoum Notified by Syngenta, the scenario for children handling dead rodents was decided to be taken out from the risk assessment because* the risk is considered an over-estimate.

B: Adults may be present following application and may be incidentally exposed by touching unprotected Vertox Wax Block 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. Infants could be exposed orally by chewing bait or touching their mouths with contaminated fingers. However, Vertox Wax Block contains 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 (NOAELacute/Exposure) was 5000 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 ($NOAEL_{acute}$/Exposure) would be 10. In the latter case, the MOE would be below the minimal acceptable MOE of 100 (inter and intraspecies safety factor of 100). Accidental intake of 5 gram poses a risk to infants.

The dermal exposure values derived by using a dermal absorption of 3% could overestimate the exposure. In fact, in the *Difenacoum* Combined Assessment Report has been agreed that for wax block formulation containing 50mg/kg *Difenacoum* the dermal absorption value to be used is 0.047%. Being the read across with *Difenacoum* accepted, for wax block *Brodifacoum*-based products a value of 0.047% can be apply. Therefore, using a more appropriate dermal absorption value it can be expected an acceptable risks.

A summary of the risk assessment for indirect exposure is presented in the table below.

Risk assessment indirect exposure due to dermal exposure according to the TNsG default values

Task	PPE Gloves	Systemic dose (mg/kg bw/day)	Acute toxicity (NOAEL = 0.002mg/kg)
			MOE
Adult handling dead rodents	NO	2.5×10^{-5}	80
Infant transient mouthing (ingesting 10mg of wax block)	NO	5×10^{-5}	40

The MOE for adults handling dead rodents = 80; the MOE for infant transient mouthing = 40

The assessment factors of 10 for interspecies variability and 10 for intraspecies variability are used to derive a ref MOE of 100. In conclusion, there is concern from indirect exposure.

2.2.2 Environmental Risk Assessment

2.2.2.3 Fate and distribution in the environment

Biodegradation

A:

Brodifacoum is not readily biodegradable. The Closed Bottle test was selected as an appropriate method as the test item has limited solubility. *Brodifacoum* was prepared in a volatile organic solvent (acetone) and an appropriate volume added to pieces of filter paper (as an inert carrier). The solvent was allowed to evaporate before addition of filter paper to each bottle. A parallel series of filter paper discs were prepared with acetone only and added to the solvent control bottles after complete evaporation, in the same way.

No study on the inherent biodegradability has been submitted by the applicant based on the fact that the substance is poorly soluble and therefore, the test is technically very difficult to perform.

B:

Brodifacoum is not readily or inherently biodegradable.

Conclusion on biodegradation: *Brodifacoum* is not readily or inherently biodegradable.

Abiotic degradation

A:

Brodifacoum is hydrolytically stable in aqueous solution at environmentally relevant pH 5-9. *Brodifacoum* photolytically degrades in aqueous solution with a half-life < 1 day (rate constant, Kcp = 10.30 day^{-1}).

B:

Brodifacoum is stable to hydrolysis (t½ > 1 year). It is however predicted to undergo rapid indirect photolysis with OH radicals and ozone (t½ = approximately 2 hours) and undergoes rapid direct photodegradation (t½ = 0.217 days). There are no predicted effects on the atmosphere.

Conclusion on abiotic degradation: *Brodifacoum* is hydrolytically stable to hydrolysis (t½ > 1 year). *Brodifacoum* degrades rapidly by photolysis.

Distribution

A:

Under basic conditions (high pH), *Brodifacoum* is not likely to be adsorbed onto soils or sewage sludge due to the ionisation of the molecule; whereas under acidic conditions (low pH), *Brodifacoum* is likely to be adsorbed onto soils or sewage sludge as the molecule is in its neutral or non-ionised form. *Brodifacoum* degrades slowly under aerobic conditions in soil, with a measured DT50 of 157 days.

B:

Brodifacoum is a large aromatic organic compound of low volatility with two polar groups, which can potentially ionise at environmental pH. The active substance has a Log Pow (4.92), and is of low solubility in water (5.8×10^{-5} g/l at pH 7 and 20°C).

The DT_{50} value of 157 days (The Pesticide Manual 13th ed) and the Koc of 50000 (The Pesticide Manual 13th ed) indicate that *Brodifacoum* would be persistent and immobile in soil. The exposure to the groundwater is unlikely.

On the basis of its low volatility (vapour pressure of $2.6\ 10^{-22}$ Pa at 20°C) the exposure to the atmosphere is highly unlikely.

Conclusion on distribution: *Brodifacoum* is persistent (DT_{50} 157 days) and immobile in soil (Koc > 9155 l/kg). Under basic conditions (high pH), *Brodifacoum* is not likely to be adsorbed onto soils or sewage sludge due to the ionisation of the molecule; whereas under acidic conditions (low pH), *Brodifacoum* is likely to be adsorbed onto soils or sewage sludge as the molecule is in its neutral or non-ionised form.

Mobility in soil

A:

The estimated Koc varies with pH from 17.8 (pH 8.46) to 426 579 (pH 3.29). Koc value at pH 7.1-7.6 was 9155 l/kg.

As experimental evidence shows that the compound is not mobile in soil, as concentrations in leachate from column leaching studies conducted with both the active substance (soil pH 5.2-6.7) and the product (soil pH 6.2 – 7.6) were non determinable. *Brodifacoum* is therefore not expected to contaminate groundwater.

B:

The Koc value (50000 The Pesticide Manual 13th Edition) indicates that the active substance would not be mobile in soil and is not expected to contaminate groundwater (PEC < 0.1 µg/l).

Conclusion on mobility in soil: *Brodifacoum* is immobile in soil (Koc > 9155 l/kg). *Brodifacoum* is not expected to contaminate groundwater.

Accumulation

A:

Experimental data on aquatic and terrestrial bioconcentration are not available. The justification provided for non-submission of a fish bioaccumulation study is that the steady-state may not be reached within the maximum duration of a study conducted according to the guidelines of OECD 305 (179 days and 336 days for 80% and 95% of the steady state, respectively), based on a calculated log Kow of 8.5, estimated from the structural formula) This justification is not acceptable because if the log Kow value of 6.12 (calculated using measured log K_{oc}) is used instead, the predicted time to reach the steady-state would be much shorter (18 and 34 days for 80% and 95% of the steady state, respectively) and therefore the study would result feasible. Anyhow, the fish bioaccumulation study for *Brodifacoum* can be waived based on the expected limited exposure to pelagic organisms, the possibility to calculate informative BCF and related data from Kow, the difficult in successfully performing such a test, ethical grounds, and the fact that likely that it would not change the conclusions of the evaluation to be made. The waiving was agreed at the TM II07.

In the section "Physical and chemical properties", two log K_{ow} values are provided: log K_{ow} value of 6.12 (calculated using measured log K_{oc}) and log K_{ow} of 8.5, estimated from the structural formula (calculated using the CLOGP program).
The RMS judges that the log K_{ow} value of 6.12 is the most appropriate for the BCF calculation for the following reasons:

- The large difference between the two log Kow estimated values provides evidence of the inaccuracy of the estimates.
- The log Kow of 6.12 is based on measured Koc values which gives more confidence than the estimates based on structural formula.
- TGD advises to apply Eq 82d for the BCF earthworm calculation when log Kow in the range1-8. A further uncertainty in the terrestrial BCF estimates will therefore be added if the log Kow of 8.5 is used.
- the log Kow = 6.12 provides worst case BCF estimate only for the aquatic organism. For terrestrial organisms, although worst case BCF would be provided by log Kow = 8.5, the conclusion on the bioaccumulative properties of the substance does not change if the log Kow = 6.12 is used.

Therefore the RMS proposes to use the log K_{ow} of 6.12 as the key value to be used throughout the risk assessment.

The bioconcentration factors (BCF) in fish was calculated according to TGD eq 75 for substances with a $K_{ow} > 6$:

$\log BCF = -0.20 \cdot \log K_{ow}^2 + 2.74 \cdot \log K_{ow} - 4.72$

BCF_{fish} resulted equal to 35645

The BCF in terrestrial organisms has been calculated according to TGD eq 82d:

$BCF_{earthworm} = (0.84 + 0.012\ K_{ow})/RHO_{earthworm}$

$BCF_{earthworm}$ resulted equal to 15820.

B:

Based on a measured Log Kow = 4.92 it is considered that *Brodifacoum* has a potential for bioaccumulation.

At the TMIII10 it was agreed that the use of the experimentally derived log K_{ow} is not appropriate, as at environmentally relevant pH *Brodifacoum* would be under ionized form. In any case the conclusion of potentially bioaccumulative drawn in the CAR would not change.

Conclusion on bioaccumulation potential

No reliable bioaccumulation study is available.

As the experimental log K_{ow} is not considered reliable, the BCF values retained for the risk assessment are those obtained using the calculated log K_{ow} = 6.12:

BCF_{fish} = 35645

$BCF_{earthworm}$ =15820.

Atmospheric Compartment

Brodifacoum has a low vapour pressure (1 x 10^{-6} Pa) and a Henry's Law constant of 2.18 x 10^{-3} $Pa.m^3mol^{-1}$ (pH 7). Release to air via water is expected to be negligible. This is also supported by calculations using the TGD on risk assessment for percent release to air from a sewage treatment plant where a default of 0 is given (*i.e.*, no release to air). The manufacture of the active substance is in a closed system. There are no releases to air of *Brodifacoum* from manufacturing, formulating, use or disposal phases.

Biocidal Product

Leaching column studies demonstrate that concentration of difenacoum (*Brodifacoum* is a brominated form of difenacoum) in the leachates were below the detection limit of analytical method. The test substance was a wheat-based pellet product nominally containing 0.005% of difenacoum which is substantially similar to the biocidal product Syngenta's *Brodifacoum* Pellets (also a cereal-based pellet product containing 0.005% of *Brodifacoum*).

2.2.2.4 Effects assessment

2.2.2.4.1 Aquatic compartment including sediments

A:

Acute toxicity studies only are available. Based on these studies, *Brodifacoum* is very toxic to fish (LC_{50} = 0.04 mg/l), invertebrates (EC_{50} = 0.25mg/l) and algae (72h ErC_{50} = 0.04 mg/l), with fish and algae resulting the most sensitive groups. Out of the two fish studies for which summaries and study reports were submitted, only the one with *O. mykiss* provides a relevant endpoint (LC_{50}) for risk assessment purposes. This study, run in 1976, predates internationally accepted guidelines and a number of deficiencies and deviations from present standard guidelines have been noted, e.g., no mention to control performance, no solvent control included in the test design, no analytical measurement of the substance concentrations. Despite a poor reliability indicator, the study is considered acceptable for the purpose of the present risk assessment as the above deficiencies are not considered to have significantly affected the results. In fact, no death occurred at the lowest five concentrations, the use of solvent assured that the substance was dissolved and the flow through system assured a continuous exposure, the low concentration of solvent is not likely to have any effect on fish survival. Therefore, also for animal welfare considerations, the test is judged acceptable for the present risk assessment. The PNEC for aquatic organisms was derived according the TGD, applying an assessment factor of 1000 to the lowest endpoint of the aquatic acute toxicity data set: PNEC = 0.00004 mg/l.
No study has been submitted to assess the toxicity to sediment-dwelling organisms. Due to the lack of experimental exposure and toxicity data, no quantitative risk assessment can be carried out. Therefore the risk characterization for the sediment compartment is covered by the PEC/PNEC ratio for aquatic organisms increased by a factor of 10 to take into account the fact that the log Kow value is higher than 5..

The evaluation of the effects of *Brodifacoum* to aquatic microorganisms has been based on a 6h growth inhibition test with *Pseudomonas putida*. The nominal EC_{10} value obtained from this study was not judged reliable, hence a conservative EC_{10} > 0.0038 mg/l, corresponding to the worst case reported water solubility (0.0038 mg/l at pH 5.2 and T = 20 C) was retrieved. It can be concluded that *Brodifacoum* is not toxic to microorganisms at concentrations equal to solubility limits.

The PNEC for STP microorganisms was calculated from this conservative estimate of the EC_{10} and the application of an assessment factor of 1: PNEC > 0.0038 mg/l.

Due to the strong and rapid adsorption of *Brodifacoum* to sediments and its slow transformation in water, the potential for metabolites formation is negligible. Toxicity studies on metabolites are not required.

PNEC for aquatic organism = 0.00004 mg/l
PNEC for sediment organisms = a factor of 10 is applied to the PEC/PNEC ratio for aquatic organisms

PNEC for STP microorganisms = > 0.0038 mg/l

B:

Toxicity data are available for aquatic organisms exposed in acute test. In a test performed under semi-static conditions, the 96-hour LC_{50} was 42 µg/L for *Oncorhynchus mykiss*, based on measured concentrations. *Daphnia magna* was less sensitive than fish, with a 48-hour EC_{50} of 250 µg/L recorded under semi-static conditions. The endpoint was based on immobilisation and on measured concentrations of *Brodifacoum* in the test media. In a 72-hour algal growth inhibition test with *Selenastrum capricornutum* (*Pseudokirkneriella subcapitata*), the $E_rC_{50}$was 40 µg/l. The NOEC was 10 µg/l with respect to specific growth rate. Results are based on measured concentrations. *Brodifacoum* is very toxic to aquatic organisms.

PNEC is derived from the algae 72h E_rC_{50} = 0.04 mg/l (or fish 72h LC_{50} = 0.042 mg/l), and the application of an assessment factor of 1000.

No experimental data are available for sediment dwelling organisms. A $PNEC_{sediment}$ (0.043 mg/kg_{wwt}) was derived through the Equilibrium Partitioning Method described in the TGD. However, due to the absence of measured data for the determination of a $PEC_{sed,}$ according to TGD a quantitative risk characterization cannot be carried out. Therefore the risk for the sediment compartment will be covered by the risk for the aquatic compartment.

Based on the result of 3h respiration inhibition test with activated sludge from a sewage treatment plant treating predominantly domestic sewage, no effects of *Brodifacoum* on aerobic biological sewage treatment processes are expected. As the test was carried out at nominal concentration much higher than the water solubility of *Brodifacoum,* the EC_{10} was set as greater than the water solubility limit of 0.058 mg/l measured at pH=7 and T=20°C. According to TGD, PNEC is derived applying an AF=10 to the NOEC from the respiration inhibition test, hence:

$PNEC_{micro\text{-}organisms}$ > 0.0058 mg/l
(This appears to be a very conservative estimate, considering that from the "ready biodegradability study", the NOEC would result equal to 10.13 mg/l and after application of an AF=10, the PNEC would be 1.0 mg/l).

No degradation or transformation products of *Brodifacoum* in water were detected. Toxicity of **metabolites is not of concern.**

$PNEC_{aquatic\ organisms}$ = 0.00004 mg/l
$PNEC_{\ sediment\ organisms}$ = covered by the risk to the aquatic organisms*
$PNEC_{micro\text{-}organisms}$ > 0.0058 mg/l

* At TMIII10 it was agreed that the use of experimental logKow was not appropriate. Therefore for the risk characterization of the sediment compartment, a factor of 10 should be applied to the aquatic PEC/PNEC ratio.

Conclusion on hazard to the aquatic organisms: *Brodifacoum* from both sources resulted very toxic to aquatic organisms. From the two dossiers, practically identical acute toxicity

endpoints have been retrieved. For invertebrates and algae, this is explained by the fact that the same studies with *Daphnia mana* (48h EC50= 0.25 mg/l) and *Pseudokirkneriella subcapitata* (72h ErC50 = 0.04 mg/l) were submitted by the two Applicants and have been selected as key studies. Applicant A submitted the studies with Daphnia and algae owned by Applicant B. For fish, both studies with *O. mykiss* provided almost identical 96h LC50 (0.04 and 0.042 mg/l for A and B, respectively), but the quality and reliability of the more recent study (dated 2003, dossier B) is much higher than that of the older one (dated 1976, dossier A). This confirms the acceptability of the test in dossier A. The tested species of algae and fish possess the same sensitivity towards Brodifacoum, and both are more sensitive than Daphnia magna..

The PNEC $_{\text{aquatic organism}}$ is derived from the algae endpoint (72h E_rC_{50} = 0.04 mg/l, dossier A and B) and the application of a AF=1000, therefore **$PNEC_{\text{aquatic organisms}}$ = 0.00004 mg/l. (**A very similar PNEC would be calculated using the fish LC50 from dossier B).

As no specific data are available, the risk posed by *Brodifacoum* to sediment-dwelling organisms is covered by the risk to the aquatic organisms. Since the log K_{ow} is 6.12 (higher than 5), a factor of 10 is applied to the PEC/PNEC ratio calculated for the aquatic organisms, to take into account the possible higher hazard to the ingestion of contaminated sediments.Both the test with *Pseudomonas putida* (CAR A) and the respiration inhibition test with activated sludge (CAR B) indicate that *Brodifacoum* is not expected to affect microorganisms in STP at nominal concentration much higher than its water solubility. Due to the lack of measured values of test substance concentration, the EC_{10} was conservatively set greater than *Brodifacoum*' water solubility. The difference in the absolute EC_{10} figure retrieved from the two CARs is explained by the fact that different WS values were used and not by differences in toxicity. In CAR A, the lowest water solubility value was used (0.0038 mg/l at pH 5.2 and T = 20 °C) as worst case, while in the CAR B the WS = 0.058 at pH7 and 20°C was used because the solubility value at pH 5 was unbounded (≤ 0.00317 mg/l, 20°C) and it would had been extremely conservative. The application of different assessment factors (1 in A and 10 in B) resulted in very similar PNECs. The RMS proposes to carry on for the risk assessement the most conservative EC10 > 0.0038 mg/l (A). The resulting **PNEC is > 0.0038 mg/l.**

The use of this worst case value would not alter the conclusion of lack of risk in CAR for *Brodifacoum* notified by Applicant B.

Effects on terrestrial organisms

A:

A 14 day test is available, where earthworms were exposed to *Brodifacoum* technical in artificial soil up to 994 mg/kg dw, without showing any effect. Therefore *Brodifacoum* is not toxic to earthworms and the estimated 14-d LC_{50} is greater than 994 mg/kg dw.
The $PNEC_{soil}$ was calculated applying an assessment factor 1000 to this endpoint, after it was converted to 14-d LC_{50}> 879.6 mg/kg wwt, giving: PNEC > 0.88 mg/kg wwt .

B:

The effect of *Brodifacoum* on earthworms was assessed in an acute toxicity test in which *E. fetida* in artificial soil was exposed to concentrations of *Brodifacoum* up to 994 mg/kg dw. The 14-day LC_{50} was greater than 994 mg/kg dry soil (the highest concentration applied) corresponding to a 14-d LC_{50} > 879.6 mg/kg wwt.

PNEC for terrestrial organisms is derived from the LC_{50} with an AF od 1000:

$PNEC_{soil}$ = > 0.88 mg/kg wwt soil

Conclusion on hazard to terrestrial organisms: The same study on earthworms was submitted in the two dossiers A and B. Earthworms were not affected after acute exposure to *Brodifacoum* at concentration closed to 1 g/kg dw. It is concluded that *Brodifacoum* is of low toxicity to earthworms. A **$PNEC_{soil}$ = > 0.88 mg/kg** wwt soil has to be used in risk assessment.

Metabolites

A:

The results of a degradation study in soil indicate that only minor metabolites are formed (less than ~3.5% of parent compound). In rats, no toxicologically relevant metabolites have been identified (IIA sec. 3.1) which could be introduced in soil via urine or foeces.

B:

No significant amounts of metabolites are expected to be formed in soil. In rats, no toxicologically relevant metabolites have been identified which could be introduced in soil via urine or foeces.

Birds

A:

Brodifacoum is acutely toxic to birds with a LD_{50} value of 0.31 mg/kg bw in the mallard duck. Acceptable 5d dietary toxicity studies with Laughing Gulls are available, which indicated that *Brodifacoum* is (very) toxic to birds upon short term exposure. The lowest endpoint (LC_{50} < 0.72 mg/kg food) was derived from one study with Laughing Gulls fed masticated *Brodifacoum* contaminated rodent tissue, where 60% mortality occurred at the lowest dose level of 0.72 mg/kg food by day 18 of the post exposure observation period. In a second analogous study with the same species, the LC_{50} was 1.6 mg/kg food. Therefore the RMS proposes to considers the LC_{50} = 0.72 mg/kg food.

The avian reproduction toxicity of *Brodifacoum* was derived by read across from *Difenacoum* data, according to the decision taken at the TMII04 to test a single compound chosen among five second-generation anticoagulant rodenticides as representative of the group for testing effects o n birds reproduction. The read across between *Difenacoum* and *Brodifacoum* is justified by the same mode of action (anti vitamin K), similar chemical structure and similar physical-chemical properties.
The *Difenacoum* reproduction endpoint on Japanese Quail was not used as such, but a toxicity factor of 26 was applied. This because the key study for short-term toxicity of *Difenacoum* (with Mallard Duck) resulted in a 5-day LC_{50} of 18.9 mg/kg diet whilst the equivalent study with *Brodifacoum* resulted in an LC_{50} = 0.72 mg/kg diet (Laughing Gull), i.e. *Brodifacoum* resulted 26 time more toxic than *Difenacoum*.. The ratio between the toxicities of *Difenacoum* and *Brodifacoum gives a* a factor of 26. Therefore, from a NOEC > 0.1 mg *Difenacoum* /kg diet, it was estimated a NOEC = 0.0038 mg Brodifacoum/kg/diet and from a NOEL > 0.01 mg Difenacoum /kg bw/d it was estimated a NOEL = 3.85E-04 mg Brodifacoum/kg bw/d.
It is concluded that Brodifacoum is very toxic to birds upon acute, short term and long term exposure with regard to lethal and sub-lethal effects.The $PNEC_{oral\ bird}$ is calculated using an AF= 30 which provides:

$PNEC_{oral\ bird}$ = 1.3 E-05 mg/kg diet, and

$PNEC_{oral\ bird}$ = 1.28E-05 mg/kg bw/d

The RMS adds that similar PNEC values would be obtained if calculations were based on dietary toxicity data applying a factor of 3000 ($PNEC_{oral}$ = 0.00024 mg/kg food and $PNEC_{oral\ daily\ dose}$ = 1.66E-05 mg/kg bw).

B:

Brodifacoum is moderately toxic to birds upon acute oral exposure with a LD_{50} value of 19 mg/kg bw in the Japanese quail. No studies are available on the avian short term dietary toxicity. A 6 weeks reproduction test on the Japanese quail exposure to *Brodifacoum* in drinking water was submitted but it was judged not adequate for risk assessment purposes. Therefore, acknowledging the decision taken at the Biocides TMIII09, the NOEC for *Brodifacoum* is based on the results of the chronic toxicity study with *Difenacoum (*with Japanese Quail), chosen as reference chemical for second generation anticoagulants (NOEC > 0.1 mg *Difenacoum* /kg diet). An extrapolation factor of 8.05 was applied to correct for differences in toxicity based on the acute test results for *Difenacoum* (LD_{50} = 66 mg/kg, male and females) and *Brodifacoum (*LD_{50} = 19 mg/kg bw), both related to Japanese quail. *Brodifacoum* results very toxic to birds, with NOEC = 0.012 mg *Brodifacoum*/kg diet (obtained as NOEC > 0.1 mg *Difenacoum* /kg diet / 8.05) and NOEL = 0.0012 mg *Brodifacoum*/kg bw/d.

According to TGD, an assessment factor of 30 is applied to derive the PNEC:

$PNEC_{oral\text{-}birds}$ = 0.012 mg *Brodifacoum* /kg diet / 30 = 43 E-04 mg *Brodifacoum* /kg diet
Related to dose: $PNEC_{oral\text{-}birds}$ = 0.0012 mg *Brodifacoum* /kg bw/d / 30 = 4 *E-05* mg *Brodifacoum* /kg bw/d

Conclusion on hazard to birds: The avian acute toxicity of *Brodifacoum* varies markedly between the two dossiers, likely depending on the tested species. The lowest LD_{50} value of 0.31 mg/kg bw is retrieved from the study with mallard duck (A), which results to be 61 times more sensitive than Japanese quail (LD_{50} = 19 mg/kg bw, B).
Studies on dietary toxicity were submitted only in dossier A and provided a LC_{50} = 0.72 mg/kg food, referred to Laughing gull.
For both dossier A and B, the long-term toxicity was extrapolated by read across to reproduction toxicity of *Difenacoum* to Japanese Quail (NOEC > 0.1 mg *Difenacoum* /kg diet), selected as representative compound of the second generation anticoagulants. For the read across, a factor was applied to take into account differences in toxicity between the two compounds. *Brodifacoum* consistently results more toxic than *Difenacoum*. In CAR for *Brodifacoum* notified by A, an extrapolation factor of 26 was derived from comparison of dietary toxicity, while in CAR for *Brodifacoum* notified by B a factor of 8.05 was calculated based on acute toxicity (no dietary toxicity data were submitted). It is proposed that the lowest NOECs (NOEC = 0.0038 mg *Brodifacoum*/kg/diet, NOEL = 3.85E-04 mg *Brodifacoum*/kg bw/d), and consequently the lowest PNEC, as calculated in CAR for *Brodifacoum* notified by applicant A are used in risk assessment. The choice of the most conservative NOEC is justified by the following considerations: - uncertainty exists in extrapolating differences in sensitivity between Brodifacoum and Difenacoum observed in acute/short-term tests to differences in toxicity expected upon long-term exposure,

- *the sensitivity of bird species to Brodifacoum* differs significantly. In acute tests, Japanese quail appears sensibly less toxic than mallard duck (note that Japanese quail was used in the reproduction test with *Difenacoum)*
- the comparison of the toxicity of *Brodifacoum* and *Difenacoum* based on the dietary toxicity is more relevant than the comparison based on the acute toxicity.

Therefore the values to be used in risk assessment are:

$PNEC_{oral\ bird}$ = 1.3 E-05 **mg/kg diet,** and
$PNEC_{oral\ bird}$ = 1.28E-05 mg/kg bw/d

Mammals

A:

From the available studies with mammals, the lowest endpoint is derived from a rat teratogenicity study with a NOEL = 0.001 mg/kg bw/d. Using an assessment factor 300, a $PNEC_{oral,\ mammals}$ = 3.33E-06 mg/kg bw is derived. For use in secondary poisoning risk assessment, the NOELs available have been converted into NOECs, using the conversion recommended by TGD, and then in $PNEC_{oral}$ through the application of the appropriate assessment factors. The lowest PNEC was calculated from the rat teratogenicity study: $PNEC_{oral,\ mammals}$ = 6.7 E-05 mg/kg food, applying a conversion factor of 20 and an AF of 300.

B:

The lowest mammalian NOAEL (0.001mg/kg bw/day) comes from a two-generation fertility study with rats and refers to parent females. This endpoint was converted, according to TGD, to $NOEC_{mammal,food}$ =0.02 mg/kg food. As the exposure lasted 90 days as a minimum, for PNEC derivation an AF_{oral} of 90 is applied (table 23 of TGD):

$PNEC_{oral\text{-}mammals}$ = 0.02/90 = 2.22E-04 mg/kg food, corresponding to

$PNEC_{oral\text{-}mammals}$ = 0.001 mg/kg bw day/90 = 1.1 E-05 mg/kg bw.

Conclusion on hazard to mammals: *Brodifacoum* is very toxic to mammals. PNECoral mammals have been derived to be used in the risk characterisation of primary and secondary poisoning. Difference in PNEC values derived in CAR A and B are explained by the different toxicity endpoint selected as the most sensitive and, consequently, the different assessment factors applied. For the reference source (A) the lowest most conservative endpoint was used (NOEL = 0.001 mg/kg bw/d) retrieved from a teratogenesis study where exposed for a few days, hence an AF of 300 was applied, while for the new source the NOEL=0.001 mg/kg/d from a two generation study was selected and an AF of 90 was used. For the risk characterization, it is proposed to use the PNEC derived from the latter study:

$PNEC_{oral\text{-}mammals}$ = 0.02/90 = 2.22E-04 mg/kg food, corresponding to

$PNEC_{oral\text{-}mammals}$ = 0.001 mg/kg bw day/90 = 1.1 E-05 mg/kg bw.

This is justified by the following:

- According to the *ad hoc* document on rodenticides, data from repeated dose or chronic studies should be used. Therefore the use of the teratogenicity study in CAR A was probably not the most appropriate and providing overconservative PNEC.

- If the rat subchronic toxicity data (90d NOEL = 0.001 mg/kg/d) were used for reference Brodifacoum (CAR A), after application of the appropriate AF (90), the same PNEC as for the new source (CAR B) would have been calculated.

- the two generation study NOEL (0.001 mg/kg/day) with the new source *Brodifacoum* (CAR B) was used to set also the ADI and the AEC chronic because of the better quality of the study (see 2.2.1.5 and 2.2.1.6 of the present document).

2.2.2.5 PBT assessment

PBT assessment has to be done according to the TGD to substances which can be shown both to persist for long periods and bioaccumulate in biota, and can give rise to toxic effects after a greater time and greater distances than chemicals without these properties. As *Brodifacoum* is not readily biodegradable and have high potential for bioaccumulation, possibility of being PBT substance is assessed as follows.

Persistence

A, B:

According to the PTB assessment in the TGD, criteria for substance to be persistent is fulfilled when halflife is >60 days in marine water of >40 days in freshwater or halflife is >180 days in marine sediment or > 120 days in freshwater sediment. For being very persistent (vP) a halflife >60 days in marine or freshwater or >180 days in marine or freshwater sediment is required.

Experimental data available indicate that *Brodifacoum* is not readily, inherently or anaerobically biodegradable. In addition, *Brodifacoum* resulted hydrolytically stable, but undergoes rapid photolysis in water.

The DT_{50} in soil is 157 days at 20 °C, the DT_{50} considering the temperature correction to 12°C is 298 days.

As no data on degradation in marine water, freshwater or sediment are available, ***Brodifacoum*** **is considered to be potentially persistent.**

Bioaccumulation

According to the TGD a substance is considered to fulfil the B criterion when measured BCF exceeds the value of 2000 and if BCF exceeds 5000 a substance is considered very bioaccumulative (vB). If measured BCF values are not available, a substance is considered to potentially fulfil the B criterion if log Kow exceeds a value of 4.5.

There is not enough information available to finally be able to clarify the B-criterion. However, for the substance *Brodifacoum* the screening B-criterion is fulfilled as the log Kow is above 4.5. Formally BCF testing with fish would be required in order to be able to clarify if *Brodifacoum* meets the B-criterion. However, in the case of second generation anticoagulant substances, BCF testing with fish might not provide meaningful results. A BCF test with fish might be technically difficult to conduct as *Brodifacoum* is highly toxic to fish. Furthermore, second generation anticoagulant substances, which are predominantly released to the terrestrial environment, are designed to accumulate in the liver of target rodents and it can be assumed that they also accumulate in the livers of non-target mammals and birds. This is confirmed by the fact that the second generation anticoagulant substances are found in livers of wildlife. However, as no criteria exist for bioaccumulation via the terrestrial food chain and standardised test methods for bioaccumulation in other non-target animals than earthworms are not available these findings are merely an indication that *Brodifacoum* may have B-properties.

A:

The estimated BCF for *Brodifacoum*, using an estimated log Kow value of 6.12, is 35645 using the TGD equation 75, and 568.9 using the US EPA EPIWIN program. Thus based on the calculated log Kow of 6.12, ***Brodifacoum*** **potentially fulfils the criteria for B.**

B:

The experimental determination of BCF_{fish} failed due to high mortality in the fish stock at 4.0E-05 mg/l of *Brodifacoum*. As agreed at TMIII10, the estimated BCF_{fish} based on the experimental log K_{ow} is not considered appropriate as likely underestimating the bioaccumulation potential.

In conclusion, based on log Kow = 6.12 and BCF_{fish} =35645, ***Brodifacoum*** **potentially fulfils the criteria for B.**Toxicity

A:

A substance is considered to fulfil the T criterion if long-term NOEC for marine or freshwater organisms is less than 0.01 mg/l or long-term avian NOEC less than 30 mg/kg food (TGD). If no long-term data is available a substance is considered potentially toxic when the L(E)C50 to aquatic organisms is less than 0.1 mg/l. *Brodifacoum* is acutely very toxic to fish, for the rainbow trout the LC50 was 0.04 mg/l. Regarding mammalian toxicity a substance fulfils T criterion when it is classified as Carcinogenic, Mutagenic or Toxic for reproduction or when there is evidence of chronic toxicity (Classification T, R45, R46; R48, R60 and R61, or Xn, R48, R62, R63 and R64) and also when substance is classified as Very Toxic or Toxic after oral dosing (LD50<200 mg/kg bw/day). Three acute oral LD50 values have been determined for *Brodifacoum*: 0.418 mg/kg (for the male rat), 0.561 mg/kg (for the female rat) and 0.4 mg/kg (for the male mouse). On the basis of the acute oral data *Brodifacoum* should be classified as very toxic and it should be assigned the risk phrase R28 "Very toxic if swallowed". *Brodifacoum* is proposed to be classified as toxic to reproduction because it contains the same chemical moiety responsible for teratogenicity of warfarin and it has the same mode of action that is a known mechanism of teratogenicity in humans. It is obvious that possible teratogenic effects of coumarin related compounds can not be detected using conventional OECD 414 study design.

In conclusion, *Brodifacoum* is proposed to be classified as T+;R26/27/28, R43, R48/23/24/25.

In conclusion, based on information on analogical compounds, *Brodifacoum* should be provisionally classified with R61 as 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).

A classification of *Brodifacoum* as R61 was purely based on read-across from Warfarin, without any evidence for significant developmental effects being indicated by studies performed on Brodifacoum. For a similar second-generation anticoagulant, flocoumafen classification R63 has been recently proposed by the RMS (at TMIII2010): the classification is based on a) adequate studies indicating no developmental toxicity at doses not eliciting significant maternal toxicity, as indicated but inhibited blood coagulation and b) the due, conservative consideration to the areas of uncertainties still existing about the actual similarity with the human teratogen Warfain, in particular, the ability to cause extrahepatic vitamin K deficiency, the transplacental passage and the higher sensity of humans as compared to rodents. A classification of Brodifacoum as **R63** ("limited evidence" of developmental toxicity) appears therefore appropriate.

B:

Brodifacoum is acutely very toxic to aquatic organisms with a worst case 96h LC_{50fis} < 0.1 mg/l (*i.e.*: 0.040 mg/l, for algae and 0.042 mg/l, for the rainbow trout). No long-term data for aquatic organisms are available.

Due to the lack of reliable long-term study with birds, a NOEC= 0.012 mg *Brodifacoum* /kg diet was estimated by extrapolation from the reference anticoagulant *Difenacoum*.

Regarding mammalian toxicity a substance fulfils T criterion when it is classified as Carcinogenic, Mutagenic or Toxic for reproduction or when there is evidence of chronic toxicity (Classification T, R45, R46; R48, R60 and R61, or Xn, R48, R62, R63 and R64) and also when substance is classified as Very Toxic or Toxic after oral dosing (LD50<200 mg/kg bw/day).

In this respect, *Brodifacoum* is proposed to be classified as Repr. Cat 1 or 2, R61. *Brodifacoum* is also proposed to be classified as T+;R26/27/28, R43, R48/23/24/25, R61, N;R50/53.

The available data does not warrant classification of *Brodifacoum* as carcinogenic or mutagenic. **Overall conclusion is that *Brodifacoum* fulfils the T criterion.**

Conclusion: Therefore, *Brodifacoum* is considered a potential PBT.

2.2.2.6 Exposure assessment

Exposure to the aquatic environment is via sewage water through the sewage treatment plant (STP) effluent and exposure to soil is via sludge application and wet and dry aerial deposition. Exposure to the terrestrial environment is direct via release during application and indirect via ingestion of bait and return as urine, faeces and dead animals.

During the assessment process, the applicant chose not to support use in "waste dumps" and "open areas".

Aquatic compartment

A:

Using the scenarios outlined in the ESD for rodenticides and the TGD on risk assessment, for aquatic compartments have been derived the following local PECs:

Compartment/Scenario	**Realistic worst case scenario using default values**	**Realistic worst case scenario + refined metabolism + normal use**
SEWER		
– during emission from STP	1.4 x 10^{-6} mg/l	7.1 10^{-7} mg/l
Sediment		
- during emission from STP	2.8 x 10^{-4} mg/kg	1.4 x 10^{-4} mg/kg
Sewage treatment plant		
PECstp (Clocal influent)	1.4 x 10^{-5} mg/l	7.1 10^{-6} mg/l
Groundwater/soil porewater		
Through application of sewage sludge & aerial deposition	2.4 x 10^{-9} mg/l	1.2 x 10^{-9} mg/l
IN AND AROUND BUILDINGS		
Groundwater/porewater	2.9 10^{-5} mg/l	5.2 10^{-6} mg/l

B:

Using the scenarios outlined in the ESD for rodenticides and the TGD on risk assessment, for aquatic compartments have been derived the following local PECs:

Compartment/Scenario	Realistic worst case scenario using default values	Realistic worst case scenario + refined metabolism + normal use
SEWER		
– during emission from STP	3.4×10^{-6} mg/l	$1.4\ 10^{-6}$ mg/l
Sediment		
- during emission from STP	3.7×10^{-3} mg/kg	1.5×10^{-3} mg/kg
Sewage treatment plant		
PECstp (Clocal influent)	9.6×10^{-5} mg/l	$6.4\ 10^{-5}$ mg/l
Groundwater/soil porewater		
Through application of sewage sludge & aerial deposition	1.4×10^{-6} mg/l	8.7×10^{-7} mg/l

Atmosphere

Brodifacoum has a vapour pressure $<10^{-6}$ Pa at 20°C and Henry's Law constant $<2.18 \times 10^{-3}$ Pa m^3 mol^{-1} at pH 7. Release to air via water is expected to be negligible. This is also supported by calculations using the TGD on risk assessment for percent release to air from a sewage treatment plant where no release to air is predicted. The manufacture of the active substance is in a closed system. There are no releases to air of *Brodifacoum* from manufacturing, formulating, use or disposal phases.

Terrestrial compartment

According to ESD for rodenticides, the consumption is estimated to be so low that the regional contribution is negligible and thus the estimated local concentrations (Clocalsoil) are equals to the PEClocal (Clocalsoil = PEClocalsoil). The following PEClocalsoil have been derived:

A.

Compartment/Scenario		**Realistic worst case scenario using default values**	**Realistic worst case scenario + refined metabolism + normal use**
SEWER application of sewage sludge		$3.8\ 10^{-6}$ mg/kg	$1.9\ 10^{-6}$ mg/kg
IN AND AROUND BUILDINGS	direct / 0.09 m^2	0.041 mg/kg	0.0082 mg/kg
	indirect / 550 m^2	0.006 mg/kg	0.0002 mg/kg
	total / 0.09 m^2	0.047 mg/kg	0.0084 mg/kg

B.

Compartment/Scenario	Worst-case scenario using default values	Realistic worst-case scenario + refined metabolism + normal use
SEWER		
$PEClocal_{soil}$ agricultural	2.9 10^{-3} mg/kg	1.9 10^{-3} mg/kg
$PEClocal_{soil}$ grassland	1.2 10^{-3} mg/kg	7.7 10^{-4} mg/kg
PEClocalsoil, porew agricultural	3.3 10^{-6} mg/l	2.1 10^{-6} mg/l
PEClocalsoil, porew grassland	1.4 10^{-6} mg/l	8.7 10^{-7} mg/l
Use in bait boxes		
PEClocalsoil	0.047 mg/kg	0.0103 mg/kg
PECgw	2.9 10^{-5} mg/l	1.20 0^{-5} mg/l

2.2.2.7 Risk characterisation

Aquatic compartment

The PEC/PNEC ratios for the aquatic compartment from the use of *Brodifacoum* in sewers are summarised below. Due to the lack of measured data for both PEC and $PNEC_{sediment}$, the risk characterization for sediments is performed on the basis of the PEC/PNEC ratio derived for the aquatic compartment. According to the TGD, the ratio is increased by a factor of 10, so as to take into account any possible exposure via contaminants ingestion with a log Kow > 5, expected to be strongly adsorbed to sediments.
All the PEC/PNEC ratios are below of 1 showing not cause unacceptable risk to organisms in the water column, sediment or involved in the biological processes of the sewage treatment works from the proposed sewer use of *Brodifacoum* Pellets. As the worst case PEC values not cause unacceptable risk to the aquatic environment, it is clear that use of the refined normal use PECs would indicate even lower risk.

Aquatic PEC/PNEC ratios assuming worst case PECs

Exposure scenario	**PEC**	**PNEC**	**PEC/PNEC**	**PEC/PNEC >1 (*i.e.* risk indicated?)**
Surface water				
Sewer – during emission from STP	1.4×10^{-6} mg/l A 3.4×10^{-6} mg/l B (worst case)	4×10^{-5}	0.035 A. 0.085 B	No
Sediment				
Sediment - during emission from STP	-		0.035*10 = 0.35 A* 0.085*10 = 0.85 B* (worst case)	No
Sewage treatment plant				
PEC_{stp} (C local influent)	1.4×10^{-5} mg/l A 9.6×10^{-5} mg/l B (worst case)	> 0.038	<0.0024 A <0.016 B (worst case)	No

Since the potential for metabolites formation is negligible, risk characterisation is not required.
The PEC/PNEC ratio increased by a factor of 10 to take into account the log K_{ow} >5.

Atmosphere

There are no releases of *Brodifacoum* to air from manufacturing, formulating, use or disposal phases. Based on this and the physical and chemical properties of *Brodifacoum*, the compound is not expected to contribute to global warming, ozone depletions in the stratosphere, or acidification.

Terrestrial Compartment

The calculated PEC/PNEC ratios are summarised in the table below.

PEC/PNEC ratios for soil organisms

Exposure scenario	**PEC (mg/kg)**	**PNEC (mg/kg wwt soil)**	**PEC/PNEC**	**PEC/PNEC >1 (*i.e.* risk indicated?)**
Soil				
Sewer - application of sewage sludge & aerial deposition	3.8×10^{-6} mg/kg **A** 2.9×10^{-3} mg/kg **B** (Worst case)	**> 0.88**	4.32×10^{-6} **A** 0.003 **B** (Worst case)	No
In and around buildings – soil	0.047 mg/kg **A/B** (Worst case)		0.053 **A/B**	No

Estimated PEC/PNEC ratios are less than one for all uses, indicating that should not pose unacceptable risk to soil organisms from the proposed use scenarios. The lack of risk is further confirmed on account that $PNEC_{soil}$ ($\geq$ 0.88 mg/kg wwt, unbounded) is originated from a limit test with the application of an AF 1000, and worst case PECs only are considered in the risk ratios.

Summary of the risk characterisation for the environment

Aquatic compartment

The comparison of the lowest PNEC aquatic with worst case PEC $_{surface\ water}$ indicates not unacceptable risk to aquatic organisms (including sediment dwellers) from direct exposure to the estimated low levels of *Brodifacoum* in water resulting from the proposed use in sewers. No risk is also indicated for microorganisms responsible of biological processes in sewage treatment plant.

Atmosphere

There are no releases of *Brodifacoum* to air from manufacturing, formulating, use or disposal phases. Based on this and the physical and chemical properties of *Brodifacoum*, the compound is not expected to contribute to global warming, ozone depletions in the stratosphere, or acidification.

Terrestrial compartment

PEC/PNEC ratios are less than 1 for all the scenarios, indicating that not unacceptable risk to soil organisms from the proposed uses is expected. Additional elements of conservatives in the risk characterisation are represented by the unbounded $PNEC_{soi}$ and the use of worst case PEC values.

Non compartment specific effects relevant to the food chain

Non-target vertebrates may be exposed to the active substance either directly by ingestion of exposed bait (primary poisoning) or indirectly by consumption of poisoned rodents and other aquatic and terrestrial prey that contain residues of the active substance (secondary poisoning).

Based on the calculated log K_{ow} = 6.12 and the estimated BCF_{fish} and $BCF_{earthworm}$, there is concern for the bioaccumulative nature of *Brodifacoum*. Furthermore, the active substance has also a low solubility in water, is hydrolytically stable, and it is not readily or inherently biodegradable (CAR A and B).
PEC/PNEC ratios have been derived for both primary and secondary poisoning, based on the calculations described in the ESD and "Addendum relevant to Biocides to the TGD on Risk Assessment (Endorsed at the 23rd CA meeting Nov. 2006), *PNECoral derivation for the primary and secondary poisoning assessment of anti-coagulant rodenticides*". Secondary poisoning through food chains, according to TGD, has also been assessed.

Primary poisoning

The ranges of risk ratios (PEC/PNEC) for primary poisoning (considering values at step 1 and step 2 after refinement) were as follows:

A [1)]

Birds: 384615 to 1582031
Mammals: 606060 to 1269696

[1)] In Doc I the reported ranges are different because they do not include , by mistake, the risk ratio values calculated at step 2 for dog and tree sparrow.

B

Birds: 125000 to 703000
Mammals: 181818 to 529090

Conclusion for primary poisoning: Predictably there is a potential very high risk of primary poisoning to exposed non-target vertebrates, birds and mammals. Difference in actual risk ratios are explained by the use of different PNEC values derived in the CAR A and B as discussed in the "Birds" chapter. According to the "Conclusion on hazard to birds", the PNEC values from CAR A are those that should be used for risk assessment (Although the risk of primary poisoning of non-target mammals and birds is likely to be overestimated where the direct exposure to *Brodifacoum* is mitigated by the use of bait boxes, it cannot be excluded. As for the use in sewers, mammals and birds are not expected to enter sewers and feed on bait blocks, therefore the actual exposure for this scenario is considered not significant. It is also unlikely that rats living in sewer transport significant quantities of bait blocks above ground, hence it is not expected that baits are made available to non-target animals living above sewers.

Residues were measured in rabbit and non-target birds and mammals after a open-field eradication campaign against rabbits (CAR B). Levels found in dead animals were >0.05 mg Brodifacoum/Kg.

Secondary poisoning

Second-generation anticoagulants, as *Brodifacoum*, tend to be more acutely toxic than are the first-generation anticoagulants, and they are retained much longer in body tissues of primary consumers. They generally provide a lethal dose after a single feeding, although death is usually delayed 5 to 10 days and animals continue feeding. Since severe symptoms or death occur only after many days from *Brodifacoum* consumption, rats and mice will behave normally (feeding and behaviour) during this time, allowing toxicant to build-up in the organism. As a consequence highly contaminated rodents will still represent a food item for predators; more, they might represent an even easy prey due to predictable slower reactions towards predators. In a situation of repeated exposure for several days or more, anticoagulant may circulate in the blood at higher levels and for a longer time than suggested by studies in which only a single, sublethal dose was administered (Belleville 1981, cited in EPA December 19, 2002 - Potential Risks of Nine Rodenticides to Birds and Non target Mammals: a Comparative Approach).

At tier 1 the PEC oral for birds and mammals is 7.35 mg/Kg. At tier 2 the $PEC_{oral,predator}$ calculated for mammal is 2.85 mg/kg (weasel) and 2.78 mg/kg for birds (kestrel). Upon the assumptions and scenarios laid down in the above mentioned guidance documents (ESD and Addendum) following risk ratios were calculated at tier 1and tier 2 (at tier 2 also other species are considered):

A

Birds: 56538 to 217188

Mammals: 109781 to 855855

B

Birds: 18375 to 69500

Mammals: 15000 to 259090

Assessment of secondary poisoning via the aquatic food chain

For both the A and B dossiers, one of the proposed use scenarios is use in sewers, which will lead to exposure of surface water. The ranges of the PEC/PNEC ratios (before and after refinement) resulting from the application of TGD procedure are as follows:

A

Birds (fish eating): 569 to 3785

Mammals (fish eating): 1104 to 7343

B

Fish-eating birds: 21.25 to 50

Fish-eating mammals: 38.29 to 90

Assessment of secondary poisoning via the terrestrial food chain

A

The theoretical PEC/PNEC ratio calculated for the proposed use of *Brodifacoum* pellets in sewers, according to TGD, indicate that there is no secondary risk to predators eating earthworms, while a for the proposed uses in waste dumps, in and around buildings and open areas, the following risk ratios (before and after refinement) have been obtained:

Birds (earthworm-eating): 677 to 12154

Mammals (earthworm-eating): 1313 to 23582

B

The risk to earthworm-eating vertebrates was assessed for the proposed scenario "in and around building". Following the TGD approach, the following ranges of PEC/PNEC ratios (before and after exposure refinement) have been calculated:

Earthworm-eating mammals: 9.36-21486.

Earthworm-eating birds: 5.19-11925

Studies and monitoring of secondary poisoning

A

A study aimed at estimating the LC50 in captive kestrel upon ingestion of *Brodifacoum*-contaminated vole did not meet the goal. The conclusion was that, under field conditions, the degree of exposure to non-target animals would depend on dose and treatment levels, methods of use, local ecological situations and the behaviour of the target and non-target species. Other studies on crows and barn owls did not provide exhaustive conclusions.

In the laboratory, dogs and foxes mostly survived periods of 1,3,5 days feeding on Brod contaminated rats only. At worst case, one fox died after eating 5 rats wich provided a dose of 4.83 mg a.s./Kg and one dog died upon reaching a dose of 1.85 mg a.s./Kg. Survived dogs showed severe injuries.

B

The potential for secondary poisoning of *Brodifacoum* was assessed in two laboratory trials where owls were fed contaminated mice. The product used in these trials was not Vertox Wax Blocks but other formulations. In one study, the 1 day consumption of three *Brodifacoum*-

killed mice (possibly fewer) caused the death of 4 out of 6 birds. Their livers contained 0.63-1.25 mg/kg fresh weight of *Brodifacoum*. In the second study, owls were fed for 15 days poisoned mice containing different concentrations of rodenticide. Liver retained the highest concentration of rodenticide residues. The concentration appears largely independent of dose, providing supporting evidence that the owl liver contains saturable binding sites. All owls that died contained liver residues in excess of *Brodifacoum* 1.7mg/kg.

One monitoring study was conducted in Britain to investigate the contamination of barn owls with rodenticides. *Brodifacoum* was found in 4% of dead birds and its concentration in liver was 0.002-0.515µg/g. No evidence of contribution to the overall mortality of owls was concluded. Anyhow it can be argued that the mode of action of anticoagulants (death is slow and preceded by lethargy) makes the carcasses of poisoned owls difficult to find.*Conclusion for the secondary poisoning:* Following the proposed uses in dossiers A and B for products containing the active substance *Brodifacoum*, risk of secondary poisoning of non target birds and mammals via the consumption of contaminated rodents is calculated (both at tier 1 and 2 for all the species considered). As well, risk is calculated for non-target vertebrates via the aquatic and terrestrial food chains, whether fish or earthworm are caught in the proximity of STP outlet or bait boxes, respectively (with the only exception of the use "in sewer" in dossier A, for which an acceptable risk to earthworm-eating predators was predicted).

However, risk to fish-eating birds and mammals is likely to be overestimated as the PEC surface water might have been overestimated in turn. In fact, due to the low water solubility and high adsorption tendency of brodifacoum to organic matter, it is expected that the substance would preferably partition into sediments. Furthermore, the PEC calculation does not account for the mechanical removal in STPs (screens and grids) which would retain rodent carcasses, uneaten baits and some bait fragments. So, it can be assumed that the real PEC surface water would be lower than the PEC surface water considered in the risk characterisation. As this cannot be quantified it is concluded that risk to fish-eating birds and mammals in a real situation cannot be excluded although it is likely to have been overestimated.

Differences in actual values of PEC/PNEC ratios as calculated in CAR A and B are to be attributed to the different data used as inputs for PEC calculation (soil and water), PNEC derivation, and BCF estimation. The most reliable reliable risk ratios are those retrieved from CAR A, because based on the lowest $PNEC_{oral\ bird}$ = 1.28E-05 mg/kg bw/d (see chapter *"Conclusion on hazard to birds") and the log* K_{ow} = 6.12 *(see chapter „Accumulation").* These are the values to be used in the risk assessment. It is noted that the use of the above $PNEC_{oral\ bird}$ and *log* $K_{ow,}$ *as agreed at TMIII10, would not change the conclusion of unacceptable risk of secondary poisoning drawn in CAR B.*

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

Brodifacoum has been supported and evaluated as a rodenticide in the following use situations: in and around building and, in sewers. The target species are brown rat, black rat and house mouse.

Brodifacoum is a second-generation single-dose anticoagulant rodenticide, disrupting the normal blood clotting mechanisms, it results in increased bleeding tendency and, eventually, haemorrhage and death. Effectiveness of the active substance depends on exposure but, for an effective and comprehensive control of rats and mice, including those strains that may be resistant to other anticoagulant compounds, a bait concentration of 50 mg/kg is proposed. Actually, the resistance to rodenticides is almost all referred to populations of rats or mice to the anticoagulant of first generation, *i. e. Warfarin*. The resistance to *Brodifacoum* is not regarded as unacceptable and only few events are referred as "suspected" resistant to brodifacum products. In conclusion there is no reason to suspect a lack of efficacy of brodifacum-based products and it is possible to state that brodifacum is fully active against rodents populations that developed resistance to warfarin.

It is recognised that anticoagulants like *Brodifacoum* do cause pain in rodents but it is considered that this is not in conflict with the requirements of Art. 5.1 of the BPD 'to avoid unnecessary pain and suffering of vertebrates', as long as effective, but comparable less painful alternative biocidal substances or non-biocidal alternatives are not available.

Based on the assessment of data on the active substance and the representative products, health risks for the users of the biocidal products are at an acceptable level if principles of good working practice are applied and use instructions and recommendations on the label of the product are respected. The accidental ingestion of baits poses a risk to infants. Adequate measures for protection and risk mitigation have to be applied during use to control especially the risk from secondary exposure.

The environmental risk assessment shows that *Brodifacoum* does not cause unacceptable risk in the aquatic environment, terrestrial environment or in the atmosphere. *Brodifacoum* is neither expected to accumulate in sediment nor contaminate groundwater. *Brodifacoum* is persistent and exceeds the Annex I inclusion criteria for soil. On the other hand, proposed use of *Brodifacoum* may not result in unacceptable accumulation in soil because the baits should be deployed in the tamper resistant bait boxes and uneaten baits should be collected after the control campaign.

Brodifacoum poses an unacceptable risk for primary and secondary poisoning of birds and other non-target mammals. The risk for primary poisoning is likely to be overestimated and can be reduced by using bait boxes so that they cannot be reached by the non-target animals. The risk for secondary poisoning of non target mammals and birds, following the proposed

uses of product containing the active substance, cannot be excluded due to the combined effect of high toxicity, persistence and bioaccumulation potential of the active substance. Beside to the consumption of contaminated rodents, risk is calculated also for non target mammals and birds feeding on earthworms whether these are caught in the proximity of bait boxes or inside the treated area and for non target mammals and birds feeding on contaminated fish. As discussed previously, risk via the aquatic food chain is likely to be overestimated as consequence of the overestimation of $PEC_{surface\ water}$ in turn, due to the tendency of *Brodifacoum* to partition into sediments, and the mechanical removal in STPs (screens and grids) of rodent carcasses, uneaten baits and some bait fragments. As this cannot be quantified it is concluded that risk to fish-eating birds and mammals in a real situation cannot be excluded. Accordingly, label instructions should be adequate to reduce the high potential risk.
Brodifacoum is considered as a potential PBT substance and such substances should not be included in Annex I unless releases to the environment can be effectively prevented. The direct releases of *Brodifacoum* to the environment can be reduced by using the ready-for-use baits and following the measures described in connection to the secondary poisoning.

The representative products in the risk assessment were ready-for-use products and risks associated with other type of formulations have not been evaluated. The risk assessment has been done for products containing 50 mg/kg *Brodifacoum*, and higher concentrations should not be allowed in authorized products.

According to the Annex I inclusion criteria referred to in Article 10 of the Directive and TNsG on Annex I inclusion, *Brodifacoum* should not be included in Annex I. However, in the decision making also benefits of using the active substance in the biocidal products have to be considered (Paragraph 96 in Annex VI of the Directive). Rodent control is needed to prevent disease transmission, contamination of food and feedingstuffs, structural damage and social abhorrence. Currently anticoagulants are the dominating substances in rodent control. Fourteen rodenticides are included in the review programme of the existing biocidal substances, and nine of these substances are anticoagulants, two are gases and three are non-anticoagulants. It is concluded that *Brodifacoum* is needed as a rodenticide for human hygiene and public health reasons. It enables effective control of the target rodents and it can be used against rats and mice which are resistant to the first generation anticoagulants such as warfarin and coumatetralyl. In this exceptional case the benefit should take precedence over the risks and *Brodifacoum* should be included in Annex I.

Brodifacoum is suggested as a candidate for the comparative assessment due to the potential PBT properties, unacceptable risk for secondary poisoning of the non-target vertebrates and risk for secondary exposure of humans. A more detailed risk benefit analysis should be made as a part of the comparative assessment when more information is available on alternative substances.

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 *Brodifacoum* shall be included in Annex I to Directive 98/8/EC as an active substance for use in product-type **14** (Rodenticide), subject to the following specific provisions. The active substance *Brodifacoum*, as manufactured, shall have a minimum purity of 950 g/kg.

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 50 mg/kg 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 minimized, 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 package size and laying down obligations to use tamper resistant and secured bait boxes.

Member States shall in the light of new knowledge and information review and, where necessary, amend or withdraw existing authorisations for biocidal products in accordance with Articles 6 and 7 of Directive 98/8/EC. If such amendments or withdrawals are considered necessary, the Member State shall immediately notify other Member States and the Commission of such information and the actions taken.

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

- As professional users are likely to be exposed more often, products containing *Brodifacoum* may be used by professional users if data are provided to show that occupational exposure, calculated based on the operator exposure study, is acceptable.

- 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.

- Member States should only authorise products with *Brodifacoum* for use in and around buildings and in sewers. The applicants did not support the usage of *Brodifacoum* in open areas and waste dumps. If the use of *Brodifacoum* in open areas and on waste dumps is applied for at product authorisation phase, a full new risk evaluation of this type of use has to be performed at that stage and the assessment report for the active substance should be amended accordingly.

- 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.

- *Brodifacoum* baits should not be placed where food, feedingstuffs or drinking water could be contaminated.

- In case no standard safety phrases are required on the product label, adequate safety instructions should be provided in the use instructions.

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 minimize the risk of consumption by other 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 person, do not use anticoagulant rodenticides as permanent baits.

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

- Keep out of the reach of children (to be carried on the label).

This last safety precaution should always be carried on the label of the products, if not already legally required by Directive 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.

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 *Brodifacoum* 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.

- Efficacy has been shown for Mus musculus and Rattus norvegicus but not for Rattus rattus, as on the base of the existing no tests were carried out with Rattus rattus.

3.4 Requirement for further information

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

Nevertheless, additional studies are required for either Applicant for the product authorization phase as follows:

- fully-validated analytical method for the analysis of *Brodifacoum* residues in soil.

Furthermore, as regards Applicant B: details regarding the reactivity towards container materials for the technical concentrate should be given. Additional studies are also required for the unambiguous identification of impurity 1 (including the conversion of the LOQ value into % w/w) and for the assessment of technical equivalence between the two Task Force manufacturers. RMS believes that the nature of these requests for additional data is such not to affect the inclusion of *Brodifacoum* in Annex I.

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 *Brodifacoum* in Annex I to the Directive.

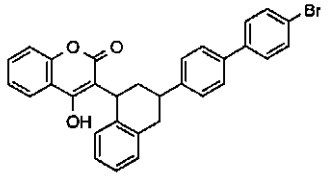
Appendix I: List of endpoints

Note: the Rappourteur Member State has indicated in **BOLD** the most reliable endpoint to be used in the Risk Assessment.

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

Active substance (ISO Common Name)	*Brodifacoum*
Product-type	Rodenticide

Identity

Chemical name (IUPAC)	*3-[3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin*
Chemical name (CA)	*2H-1-Benzopyran-2-one, 3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-*
CAS No	56073-10-0
EC No	259-980-5
Other substance No.	370 (CIPAC No), 607-172-001 (Annex I of Directive 67/548/EEC)
Minimum purity of the active substance as manufactured (g/kg or g/l)	950 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None
Molecular formula	$C_{31}H_{23}BrO_3$
Molecular mass	523.4 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	**A.** 232°C with decomposition (98.7 %w/w) **B.** *Brodifacoum* was observed to darken and decompose (100% w/w)
Boiling point (state purity)	Not applicable
Temperature of decomposition	**A.** 232 °C (98.7 %w/w) **B.** 235.8 °C (100% w/w)
Appearance (state purity)	**A.** fine powdery cream solid (92.5 %w/w) **B.** white to off-white solid, fine powder (pure) Odour: not tested due to the toxicity of *Brodifacoum*
Relative density (state purity)	**A.** 1.42 g/cm^3 at 25°C (92.5 %w/w) **B.** 1.530 at 20°C (purity: >99% w/w)
Surface tension	Not applicable (as solubility is < 1mg/L)
Vapour pressure (in Pa, state temperature)	**A.** <<10^{-6} Pa at 20°C **B.** 2.6E-22 Pa at 20°C; 1.9E-21 Pa at 25°C (estimated by the vapour pressure curve)
Henry's law constant (Pa m^3 mol $^{-1}$)	**A.** <<2.18 x 10^{-3} Pa m^3 mol^{-1} at pH 7, and <<5.23 x 10^{-5} Pa m^3 mol^{-1} at pH 9 **B.** 2.35E-18 Pa m^3 mol^{-1} (calculation based on vapour pressure at 20°C estimated by the vapour pressure curve and water solubility at pH 7 and 20°C)
Solubility in water (g/l or mg/l, state temperature)	**A.** pH 5.2: 3.8 E-06 g/l mg/l (at 20 °C) **B.** pH 5: 5.65E-07 g/l (10°C); ≤3.17E-06 g/l (20°C); 6.57E-07 g/l (30°C)
	A. pH 7.4: 2.4E-04 g/l (at 20 °C) **B.** pH 7: 8.16E-06 g/l (10°C); 5.80E-05 g/l (20°C); 1.60E-05 g/l (30°C)
	A. pH 9.3: 1.0E-02 g/l (at 20 °C) **B.** pH 9: 6.27E-04 g/l (10°C); 1.86E-03 g/l (20°C); 7.96E-04 g/l (30°C)
Solubility in organic solvents (in g/l or mg/l, state temperature)	**A.** Hexane 0.088 g/l (20 °C) Toluene: 7.2 g/l (20 °C) Dichloromethane: 50 g/l (20 °C) Ethyl acetate: 12 g/l (20 °C) Methanol: 2.7 g/l (20 °C) Acetone: 23 g/l (20 °C) Acetonitrile: 3.2 g/l (20 °C)
	B. Toluene: 5.81 g/l (10°C); 5.89 g/l (20°C); 5.85 g/l (30°C) Dichloromethane: 29-33 g/l (10°C); 29-33 g/l (20°C); 40-50 g/l (30°C) Ethyl acetate: 10.2 g/l (10°C); 10.1 g/l (20°C); 10.8 g/l (30°C) Methanol: 1.67 g/l (10°C); 1.61 g/l (20°C); 1.64 g/l (30°C) Acetone:

	20.7 g/l (10°C); 21.2 g/l (20°C); 21.8 g/l (30°C)
Stability in organic solvents used in biocidal products including relevant breakdown products	Not required since the active substance does not include any organic solvent
Partition coefficient (log P_{OW}) (state temperature)	**A.** 8.5 (calculated by CLOGP algorithm of Hansch and Leo) 6.12 (estimated from measured Koc)
	B. pH 5: 6.16-6.27 (10°C); 5.99-6.13 (20°C); 5.80-5.98 (30°C) pH 7: 5.09 (10°C); 4.92 (20°C); 4.78 (30°C) pH 9: 4.91 (10°C); 4.78 (20°C); 4.58 (30°C)
Dissociation constant	Not applicable
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	**A.** 263 nm and 308 nm **B.** 266 nm and 308 nm (methanol; 10% 1N HCl methanolic solution); 263 nm and 312 nm (10% 1N NaOH methanolic solution) ε_{308} (l $mol^{-1}cm^{-1}$) = 14089 (methanol), 15629 (10% 1N HCl methanolic solution) ε_{312} (l $mol^{-1}cm^{-1}$) = 16677 (10% 1N NaOH methanolic solution)
Quantum yield of direct phototransformation in water at Σ > 290 nm	**A.** -- **B.** 1.28 x 10^{-3} (first 60 minutes); 3.29 x 10-3 minutes (60 to 180 minutes)
Flammability	Not highly flammable
Explosive properties	Not explosive

Classification and proposed labelling based on Directive 67/548/EEC

with regard to physical/chemical data	None
with regard to toxicological data	T+; R26/27/28; R43; R48/23/24/25, Repr.Cat. 1 or 2; R61
with regard to fate and behaviour data	None
with regard to ecotoxicological data	N; R50/53
Specific concentration limits for human health and environmental effects	C ≥ 2.5% T+, N; R26/27/28-48/23/24/25-43-61-50/53 1% ≤ C <2.5% T+, N; R26/27/28-48/23/24/25-43-61-51/53 0.5% ≤ C< 1% T+, N; R26/27/28-48/23/24/25-61-51/53 0.25% ≤ C< 0.5% T+, N; R26/27/28-48/23/24/25-51/53 0.025% ≤ C< 0.25% T ; R23/24/25-48/20/21/22-52/53 0.0025% ≤ C <0.025% Xn; R20/21/22

Classification and proposed labelling based on Regulation EC 1272/2008

with regard to physical/chemical data	None
with regard to Health Hazard	Acute Tox 2 H300 Acute Tox 1 H310 Acute Tox 1 H330 STOT RE 1 H372 Repr. 1B H360D* Skin Sens 1 H317
with regard to Environment	Aquatic acute 1 H400 Aquatic chronic 1 H410
Signal Word	Danger
Symbol	GHS06, GHS08, GHS07,GHS09
Hazard statement codes	H300: Fatal if swallowed H310: Fatal in contact with skin H317: May cause an allergic skin reaction H330: Fatal if inhaled H372: Causes damage to organs through prolonged or repeated exposure H360d: May damage the unborn child. H410: Very toxic to aquatic life with long lasting effects

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	**A.** HPLC with UV detection at 254 nm using an internal standard **B.** Dissolution in methanol/dichloromethane (3:2,v/v). Determination by RP-HPLC/UV. LOQ = 0.79 μg/ml RP-HPLC/UV method for the isomeric content determination also available
Impurities in technical active substance (principle of method)	**A** HPLC with UV detection using either an internal or an external standard, or with fluorescence detection using an external standard **B.** RP-HPLC/UV

Analytical methods for residues

Soil (principle of method and LOQ)	Not available
Air (principle of method and LOQ)	Not relevant, since *Brodifacoum* is a non-volatile substance intended to be used only in solid formulations
Water (principle of method and LOQ)	Extraction from spiked samples (drinking, ground, and surface water) with dichloromethane. Extract evaporation by rotary evaporator. Residue re-dissolution in 0.5 ml of methanol for RP-HPLC/MS/MS analysis (scan in SIM and SRM mode). LOQ = 0.05 μg/l for drinking and ground water, 0.5 μg/l for surface water
Body fluids and tissues (principle of method and LOQ)	**A.** Extraction from spiked samples of plasma and liver with acetonitrile:ether (9:1) and acetonitrile, respectively. Evaporation to dryness by nitrogen. Residue redissolution in 2 ml of acetonitrile. Determination by RP-HPLC with fluorescence detection, using *Difenacoum* as internal standard. LOQ in plasma = 0.010 mg/l, LOQ in liver tissue = 0.01 mg/kg **B.** Blood serum: extraction from spiked samples (blood aqueous solution) with dichloromethane after centrifugation. RP-HPLC/MS/MS analysis. LOQ = 0.06 mg/l Body tissues covered under food of animal origin
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Extraction from spiked samples with ethyl acetate for cucumber, wheat, and lemon, with acetone in case of oilseed-rape. Clean-up procedure (if necessary) suited to the sample properties, *i.e.* water/fat/acid content. Determination by LC-MS/MS. LOQ = 0.01 mg/kg in all 4 matrices
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Extraction from spiked samples with dichloromethane : acetone (7:3, v/v). Purified extracts analysed by LC-MS/MS. LOQ = 0.01 mg/kg

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	**A.** *Brodifacoum* (0.21 mg/kg) was rapidly absorbed in rat (T_{max} in blood= 8 h after dosing; C_{max} 16.1 ng/ml). The oral absorption was>75%, based on the radioactivity associated to the tissues After a single higher oral radiolabelled dose of *Brodifacoum* (10 mg/kg) about 64.0% was absorbed (residues in the liver, carcass and bile 48h after dosing). The rest was recovered in the faeces, as unabsorbed material.
	B. **Oral absorption is assumed to be 100%**, on the basis of amount of radioactivity recovered in the excreta and retained in the tissues
Rate and extent of dermal absorption:	**A.** Absorption through human skin assessed on **pellet baits** (*Brodifacoum* 0.0048%w/w). Over 24 h, *Brodifacoum* was below the limit of quantification (<3.53% of the applied dose) in the receptor fluid and in the epidermis (<1.64%), after tape stripping. Total recovery (108 ±6.25%) in the washing fluid. A calculated 'surrogate value' of **5% dermal absorption** has been considered as the worst case.
	B. The read across from *Difethialone* and *Difenacoum* data is applied, based on the close structural relationship, the similar physico-chemical properties and the same mode of action. A dermal absorption value for *Difethialone* =4%; for *Difenacoum* two different values depending on the type of formulation: 3% (pellets and grains) or **0.047% (wax block bait)**.
Distribution:	**A.** **Widely distributed**. 10 days following a single oral dose (0.25 mg/kg bw), the retained dose was highest in the rat liver (22.8 %), followed by the pancreas (2.3 %), kidney (0.8%), heart (0.1%) and spleen (0.2%). Approximately 50% of the dose was in the carcass and skin.
	B. Widely distributed, although the liver is by far the major site of distribution and retention
Potential for accumulation:	**A.** High potential for accumulation: the liver retained the largest % of the dose, very long time after dosing. Data from feeding studies indicate a non-linear accumulation in rat livers.
	B. **High potential for bioaccumulation in the liver** ($t_{½}$ for hepatic residues unchanged a.s.>200 days).

Rate and extent of excretion:	**A.** A small amount (**11–14%**) was slowly eliminated in **urine and faeces** over 10 days following a single oral dose (0.25 mg/kg bw). Biliary and renal routes are of equal significance in the elimination The elimination from the liver was biphasic at high doses. the rapid phase (days 1-4) corresponded to a reduction in clotting factor synthesis and a slower terminal phase (days 28-84), during which blood clotting function was normal **The half-life in the liver was calculated in the range of 282-350 days**.
	B. Faecal excretion (mainly by mechanism other than biliary excretion) is the major route of elimination, independently of gender, dose, single or repeated treatment. Parent compound accounted for the vast majority (50-80%) of radioactivity found in the feaces.
Toxicologically significant metabolite(s)	**A.** **Parent compound**
	B. Parent compound

Acute toxicity

Rat LD_{50} oral	**A**. **0.4 mg/kg bw** (M rat and mouse).
	B. <5 mg/kg
Rat LD_{50} dermal	**A**. **3.16 mg/kg** bw
	B. 7.48 mg/kg bw (F)
Rat LC_{50} inhalation (4 h)	**A.** **3.05 mg/m^3** (F)
	B. No study provided
Skin irritation (rabbit)	**A.** Not irritant according to the score .
	B. **Not irritant**
Eye irritation (rabbit)	**A.** Not irritant according to the score .
	B. **Not irritant**
Skin sensitization (test method used and result)	**A.** **Skin sensitiser** (Maximisation test of Ritz and Buehler).
	B. No sensitizing reaction (LLNA test on mice)

Subchronic toxicity (Annex IIA, point 6.4)

Species/ target / critical effect	**A. /B.** Rat/Coagulation system/ Increase in blood coagulation time

Lowest relevant oral NOAEL / LOAEL	**A.** **0.001 mg/kg bw /day**
	B. 0.04 mg/kg/day
Lowest relevant dermal NOAEL / LOAEL	**A.** No study available
	B. No study available
Lowest relevant inhalation NOAEL / LOAEL	**A.** No study available
	B. No study available

Genotoxicity	**A.** Negative in Ames test, *in vitro* cytogenetic assay in human lymphocytes and mouse lymphoma L5178Y cells. Negative in *in vivo* mouse micronucleus test. **B.** Negative in Ames test, *in vitro* cytogenetic assay in human lymphocytes and mouse lymphoma L5178Y cells.

Carcinogenicity

Species/type of tumour	**A./B.** Chronic study waived as infeasible and unnecessary
lowest dose with tumours	-

Reproductive toxicity

Species/ Reproduction target / critical effect	**A.** Not performed **B.** Rat (2 generation) / adult toxicity/ haemorrhages
Lowest relevant reproductive NOAEL / LOAEL	**A.** Not performed **B. 0.001 mg kg bw/day** / 0.003mg kg bw/day
Species/Developmental target / critical effect	**A.** Rabbit (maternal toxicity): deaths with internal haemorrhages. No developmental effects Rat (maternal toxicity): internal haemorrhages. No developmental effects **B.** Rabbit (maternal toxicity): increased prothrombin time. No developmental effects Rat no significant maternal toxicity or developmental

	effects
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	**A.** LOAEL (maternal toxicity, rabbit): 0.005 mg/kg/day **NOAEL (maternal toxicity, rat): 0.001 mg/kg/day** **B.** LOAEL (maternal toxicity, rabbit): 0.004 mg/kg/day NOAEL (maternal toxicity, rabbit): 0.002 mg/kg/day

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	**A./B.** No potential for neurotoxicity
Lowest relevant developmental NOAEL / LOAEL.	**A./B.** Not applicable.

Other toxicological studies

.....	-

Medical data

.....	**A.** Routine monitoring of workers (industrial users) producing the active substance and formulating products has been carried out for the last forty years. Between June 1981 and September 1982, three poisoning incidents occurred with successful recovery. With the exception of these incidents, routine monitoring has shown no clinical effects in any workers. During this time there has been no evidence of allergenicity, sensitisation or any other abnormal effects induced by repeated and continual exposure to these anticoagulant rodenticides.
	B. No significant effects caused in personnel with occupational exposure have been observed.

Summary	Value	Study	Safety factor
Non-professional user			
ADI (acceptable daily intake, external long-term reference dose)	**A.** 1x 10^{-6} mg kg/day	90-day oral rat toxicity study	1000
	B. **3.3 x 10^{-6} mg kg/day**	**Two generation study**	**300**
AEL acute	**A.** **3.3 x 10^{-6} mg kg/day**	**Rat: developmental toxicity study (maternal toxicity; NOAEL=0.001 mg/kg bw/d)**	**300**
	B.	Rabbit: Maternal	300

	6.67 **x 10^{-6}** mg/kg/day	toxicity from a Developmental study (NOAEL = 0.002 mg/kg bw/d)	
AEL medium term	**A.** Not derived		
	B. **6.67 x 10^{-6} mg/kg/day**	**Rabbit: Maternal toxicity from a Developmental study (NOAEL = 0.002 mg/kg bw/d)**	**300**
AEL (long term	**A.** 3.3 x 10^{-6} mg kg/day	90-day oral rat toxicity study (NOAEL = 0.001 mg/kg bw /d)	300
	B. **3.3 x 10^{-6} mg kg/day**	**Reproductive 2-generation study rat (NOAEL = 0.001 mg/kg bw /d)**	**300**
ARfD (acute reference dose)	Not applicable		
Professional user			
Reference value for inhalation (proposed OEL)	-		
Reference value for dermal absorption	**A.** **5%**	***In-vitro* dermal penetration on pellet baits**	
	B. 3% (pellets and grain) **0.047% (wax block bait)**	Read across from data on *Difenacoum*	

Acceptable exposure scenarios (including method of calculation)	
Professional users	A: Exposure scenario: Application + post application •Decanting, loading of bait station with ready to use baits and emptying and disposing of bait stations Frequency of daily use: • Decanting: 80 manipulations per 50g (4kg bait handled per day) • Loading and placement: 80 manipulations per day • Clean-up: 16 manipulations per day 50g bait per bait point Concentration of active substance: 0.005 % w/w Level of protection: Yes Gloves For products used on a single occasion, the ratio AEL/Body dose is 1.41 for total exposure (dermal + inhalation exposure) derived from exposure study for decanting, loading, placing and cleaning up scenarios assuming no use of gloves. For the products used on a repetitive or daily basis, the ratio AEL/Body dose is 5.41 for total exposure (dermal + inhalation exposure) derived from exposure study for decanting, loading, placing and cleaning up scenarios. B: Exposure scenario: Application + post application Concentration of active substance: 0.005 % w/w Level of protection: Gloves worn For products used on a single occasion, the exposure accounted for 2.88-46.5% of AEL_{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 (5.8-93.9 % of AEL_{chr}) and calculations are based on an Operator Exposure study
Production of active substance:	-
Formulation of biocidal product	-
Intended uses	
Secondary exposure	-
Non-professional users	A: Exposure scenario: Application + post application • Decanting (considered only for the inhalation exposure), loading of bait station with ready to use baits and emptying and disposing of bait stations Frequency of daily use: • Decanting: 80 manipulations per 50g (4 kg bait handled per day) • Loading and placement: 2 manipulations

	per day • Clean-up: 2 manipulations per day 50g bait per bait point Concentration of active substance: 0.005 % w/w Level of protection: No Gloves MOE: 5625 when calculations are based on an Operator Exposure study. B: Exposure scenario: Disposal of bait boxes •Concentration of active substance: 0.005 % w/w Level of protection: No gloves worn MOE: 634 when calculations are based on an Operator Exposure study and TNsG
Indirect exposure as a result of use	A: Exposure scenario: Children and adults in contact with dead rodents. Infants ingesting 10 mg (TNsG on Human Exposure to Biocidal products – default of bait treated with repellent) or 5 g bait (User Guidance to TNsG on Human Exposure – Poison Information Specialists general estimate of "one bite"). Systemic Exposure = 4.17×10^{-5} mg/kg/d for adults handling of dead rodents. Systemic Exposure = 5×10^{-5} mg/kg/d (Infants ingesting 10 mg), 2.5×10^{-2} mg/kg/d (Infants ingesting 5g). B: Exposure scenario: Infants ingesting 10 mg (TNsG on Human Exposure to Biocidal products – default of bait treated with repellent) or 5 g bait (User Guidance to TNsG on Human Exposure – Poison Information Specialists general estimate of "one bite"). MOE = 80 (adults handling dead rodents) MOE = 40 (Infants ingesting 10 mg)

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)	DT_{50} values (at 25 °C): **A.** At pH5 estimated by extrapolation to be approximately 173 days; At pH7 estimated by extrapolation to be approximately 300 days; At pH9 stable to hydrolysis. **B.**

	pH 4: stable to hydrolysis pH 7: stable to hydrolysis pH 9: stable to hydrolysis
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	**A.** Study available. Half life < 1 day. **B.** $t_{1/2}$ = 0.083days
Readily biodegradable (yes/no)	No.
Biodegradation in seawater	Not applicable.
Non-extractable residues	Not applicable.
Distribution in water / sediment systems (active substance)	*Brodifacoum* is expected to rapidly partition into sewage sludge/sediment due to its high log Pow and poor water solubility.
Distribution in water / sediment systems (metabolites)	Not relevant as *Brodifacoum* is hydrolysed relatively slowly under environmentally relevant conditions, degrades slowly in soil with a half-life of 157 d. The parent will adsorb to the sediment and there will be a slow transformation with low levels of degradation products (< 10% of the applied a.s.).

Route and rate of degradation in soil

Mineralization (aerobic)	**A.** Mineralisation occurs, with a mean total of 35.80% of applied radioactivity (as radiolabelled *Brodifacoum*) being recovered as $^{14}CO_2$ at 52 weeks. The levels of radioactivity accounted for by volatiles other than $^{14}CO_2$ were less than 2% over the study period of 52 weeks.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (19.0 – 22.5°C, aerobic): 157 days DT_{50lab} (12°C, aerobic): 298 days
	DT_{90lab} (20°C, aerobic): not determined.
	DT_{50lab} (10°C, aerobic): not determined.
	DT_{50lab} (20°C, anaerobic): not determined.
	degradation in the saturated zone: not determined.
Field studies (state location, range or median with number of measurements)	DT_{50f}: not determined.
	DT_{90f}: not determined.
Anaerobic degradation	**B.** *Brodifacoum* was not degraded in anaerobic condition.
Soil photolysis	Not determined.
Non-extractable residues	**A.** Max. 23.6 % after 365 d

Relevant metabolites - name and/or code, % of applied active ingredient (range and maximum)	**A.** Up to 5 minor radiolabelled components, none exceeding 10% of the applied radioactivity at any time point, were present in the soil extracts of the aerobic soil metabolism study.
Soil accumulation and plateau concentration	**A.** Manner of use of products containing brodifacoum precludes soil accumulation with concentrations of *Brodifacoum* in soil predicted to be negligible/low, and occurring only sporadically according to bait treatment timings.

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	K_a values determined: **A.** - 635, 337, 263, 252, 301 for coarse sand soil (pH 7.6). - 1495, 811, 1280, 1379, 1358 for sandy clay loam soil (pH 7.1). - 1280, 1194, 1119, 1194, 842 for calcareous sandy loam soil (pH 7.6). K_d values could not be determined due to very slow desorption and therefore much less than required for a reversible reaction. Ka_{oc}, Kd_{oc} not determined but the adsorption of *Brodifacoum* was the lowest to the soil having the lowest organic carbon content (the coarse sand). The average value for Koc of 9155 l/kg was determined from the three Kocs. Dependence upon pH not determined. **B.** Koc = 50000 (The Pesticide Manual 13th edition)

Fate and behaviour in air

Direct photolysis in air	**B.** According to TGD the $t_{1/2}$ has been recalculated considering COH 0.5 x 106 molec/cm^3 and the time 24 h; the new value is $t_{1/2}$ = 6.61 h.
Quantum yield of direct photolysis	**B.** 1.28 x 10-3 (first 60 minutes) 3.29 x 10-3 minutes (60 to 180 minutes)
Photo-oxidative degradation in air	Latitude: ..... Season: ..... DT_{50} ..... Not applicable.
Volatilization	Not applicable.

Monitoring data, if available

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	Not available.
Ground water (indicate location and type of study)	Not available.
Air (indicate location and type of study)	Not available.

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity [1]
Fish			
Rainbow trout (*Oncorhynchus mykiss*)	96 hours	Lethality	**A.** LC_{50} = 0.04 mg/l B. **LC_{50} = 0.042 mg/l**
Invertebrates			
Daphnia magna	48 hours	Immobilisation	**A. /B.** EC_{50} = 0.25 mg/l (same study)
Algae			
Selenastrum capricornutum	72 hours	Growth rate	**A. /B.** **E_rC_{50} = 0.04 mg/l** (same study)
Microorganisms			
Pseudomonas putida	6 hours	EC_{10}	**A.** **>0.0038 mg/l (based on water solubility at pH 5.2 and T = 20°C)**
Activated sludge	3 hours	EC_{10}	B. >0.058 mg/l (based on water solubility at pH 7 and T = 20°C)

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia foetida* ……..	**A. /B.** **14-d LC_{50} >994 mg/kg dwt (> 879.6 mg/kg wwt)** (same study)
Reproductive toxicity to ……	Not available. Waived.

Effects on soil micro-organisms

Nitrogen mineralization	Not available. Waived.
Carbon mineralization	Not available. Waived.

Effects on terrestrial vertebrates

Acute toxicity to mammals	**A**. **LD50 = 0.4 mg/kg bw (rat)** **B.** LD50 = <5 mg/kg bw (rat)
Lowest endpoint from Chapter 3 Teratogenicity study	**A**. NOEL = 0.001 mg/kg bw/d (rat).
Two-generation reproduction toxicity study in rat	**B.** **NOAEL 0.001mg/kg bw/d** (rat, parent females), corresponding to **NOEC 0.02 mg/kg food.**
Acute toxicity to birds	**A**. **LD_{50}: 0.31 mg/kg bw** (Mallard Duck) **B.** LD_{50}: 19 mg/kg bw (Japanese quail)
Dietary toxicity to birds	**A**. **LC_{50} = 0.72 mg/kg food** (Laughing Gull) **B.** Not submitted
Reproductive toxicity to birds	**A**. **NOEC = 0.0038 mg/kg food** **NOEL = 0.000385 mg/kg bw/d** (read across to avian reproduction NOEC > 0.01 mg/Kg diet with *Difenacoum* applying an extrapolation factor of 26) **B.** NOEC = 0.012 mg/kg food NOEL = 0.0012 mg/kg bw/d (read across to avian reproduction NOEC > 0.01 mg/Kg dietwith *Difenacoum* applying an extrapolation factor of 8.05)

Effects on honeybees

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

Effects on other beneficial arthropods

Acute oral toxicity	Not applicable.
Acute contact toxicity	Not applicable.
Acute toxicity to ……..	-

Bioconcentration

Bioconcentration factor (BCF) aquatic	**A**. **BCF_{fish} = 35134** - Calculated according to TGD eq. 75, using log K_{ow} = 6.12 (estimated from measured K_{oc}). **B** No reliable estimate
Depuration time (DT_{50}) (DT_{90})	**A** Waiving for a bioaccumulation study acceptable. Using the estimated log K_{ow}=6.12 and the equation for the depuration phase indicated in OECD 305 (Annex 4), the following values have been obtained: (DT_{50}) = 7.96 d, (DT_{95}) = 34.4 d **B** No data available. Waiving for a bioaccumulation study acceptable.
Level of metabolites (%) in organisms accounting for > 10 % of residues	**A** No data. Waived. **B** No data. Waived.

Bioconcentration factor (BCF), terrestrial	**A** **$BCF_{earthworm}$ = 15 820** **B** No reliable estimate	**A** calculated according to TGD eq. 82d, using log K_{ow} = 6.12 (estimated from measured K_{oc}) **B**

[1] Values in bold are to be used in the risk assessment.

Chapter 6: Other End Points

Measures necessary to protect man, animals and the environment

Recommended methods and precautions concerning handling, use, storage, transport or fire (Annex IIA, point 8.1)	Handling and Use Avoid contact with skin and eyes. Do not breathe dust. Storage Keep container tightly closed, in a cool, well-ventilated place. Keep away from moisture. Stable as a solid at 50 Deg C. Transport UN No 3027, UN Proper Shipping Name COUMARIN DERIVATIVE PESTICIDE, SOLID, TOXIC. Fire Keep fire exposed containers cool by spraying with water. For small fires, use foam, carbon dioxide or dry powder extinguish ant. For large fires, use foam or water-fog; avoid use of water jet. Contain run-off water with, for example, temporary earth barriers. A self-contained breathing apparatus and suitable protective clothing should be worn in fire conditions.
In case of fire, nature of reaction products, combustion gases, etc. (Annex IIA, point 8.2)	Combustion or thermal decomposition will evolve toxic and irritant vapours.
Emergency measures in case of an accident (Annex IIA, point 8.3)	First Aid Eyes: Immediately irrigate with eyewash solution or clean water holding the eyelids apart, for at least 15 minutes. Obtain immediate medical attention. Skin: Take off immediately all contaminated clothing. Wash skin immediately with water, followed by soap and water. Such action is essential to minimise contact with skin. Contaminated clothing should be laundered before re-issue. Ingestion: TRANSFER TO HOSPITAL IMMEDIATELY. Refer to the leaflet 'The treatment of Anticoagulant Rodenticide Poisoning', 1988. Induce vomiting, if this has not already occurred by tickling the back of the throat with a clean, blunt instrument (e.g. spoon handle). Inhalation: Unlikely to be hazardous by inhalation unless present as a dust. Remove patient from exposure, keep warm and at rest. Obtain medical attention as a precaution. Remove

	from exposure. Obtain medical advice immediately. Advice to physicians: Gastric lavage may be effective when performed within 4 hours of ingestion. Doctors should refer to the leaflet 'The treatment of Anticoagulant Rodenticide Poisoning', 1988. <u>Environmental</u> Spillages or uncontrolled discharges into water courses must be alerted to the appropriate regulatory body. Cover spillage with moist sand, soil or sawdust. Transfer to a container for disposal. Wash the spillage area with water. Washings must be prevented from entering surface water drains.
Possibility of destruction or decontamination following release in or on the following: (a) air (b) water, including drinking water (c) soil (Annex IIA, point 8.4)	Any contaminated materials must be disposed of as controlled waste. Disposal should be in accordance with local, state or national legislation.
Procedures for waste management of the active substance for industry or professional users	
Possibility of re-use or recycling (Annex IIA, point 8.5.1)	Re-use and recycling are not recommended. The product should only be used for the intended purpose: A coumarin- type anticoagulant rodenticide. FOR USE AS A RODENTICIDE FOR MANUFACTURING OR EXPERIMENTAL USE ONLY
Possibility of neutralisation of effects (Annex IIA, point 8.5.2)	There is no known possibility of neutralization. Incineration is the recommended method of disposal.
Conditions for controlled discharge including leachate qualities on disposal (Annex IIA, point 8.5.3)	Not applicable. Discharge is not permitted.
Conditions for controlled incineration (Annex IIA, point 8.5.4)	Any disposal must comply with Local and National Requirements which are derived from the EU Directives 94/67/EC of 16 December 1994 on the incineration of hazardous waste and 2000/76/EC of 4 December 2000 on the incineration of hazardous waste. These Directives establish operating conditions under which hazardous/controlled waste must be incinerated and include details such as a minimum temperature of 850°C, as measured near the inner wall or at another representative point of the combustion chamber as authorised by the competent authority, for two seconds; prescribe limits for air emissions; control discharges of waste water; control the disposal of incineration residues; and provide prescriptive methods and calculations for the determination of air emissions etc.
Observations on undesirable or unintended side-effects, e.g. on beneficial and other non-target organisms (Annex IIA, point 8.6)	Refer to Chapter 5 above

Appendix II: List of Intended Uses

Object and/or situation	Member State or Country	Product Name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks:
				Type	Conc. of as	method	number	interval between applications (min)	g as/L	water L/m^2	g as/m^2	
(a)			(c)	(d-f)	(i)	kind (f-h)	min max (k)		min max	min max	min max	(m)
For the purpose of the protection of public health, including: • Prevention of transmission of disease; • Prevention of the contamination of food and feedingstuffs and other materials, at all stages of their production, storage and use; • Protection of buildings and structures including pipes, cables and overall integrity; • Protection of livestock, wild and domestic; • Social abhorrence and stigma; • Legal requirement ***The products are used indoors, in and around buildings and in sewers***	All EU Member States	Various	Rodents, for example, rats and mice	RB, BB, AB (GCPF codes)	0.05 g/kg	bait	The product is used in the same manner in all of these situations; the bait is placed in discrete locations within the infested area, it is not dispersed or broadcast within the environment. The number of bait points employed and the amount of product used is dependant on: the treatment site; the size and severity of the infestation; the user; and the users requirements and needs. For rat control, protected bait points containing up to 50g of product are used, at intervals of up to 10 metres apart. For mouse control, protected bait points containing up to 15g of product are used, at intervals of 2-5 metres apart. An adequate number of baits points are placed in dry locations, protected from the weather and in appropriate positions to help prevent access by non-target animals.					

(a) *e.g.* biting and suckling insects, fungi, molds;

(b) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(c) GCPF Codes - GIFAP Technical Monograph No 2, 1989 ISBN 3-8263-3152-4); (d) All abbreviations used must be explained

(e) g/kg or g/l;

(f) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench;

(g) Kind, *e.g.* overall, broadcast, aerial spraying, row, bait, crack and crevice equipment used must be indicated;

(h) Indicate the minimum and maximum number of application possible under practical conditions of use;(i) Remarks may include: Extent of use/economic importance/restrictions

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.

A.

Doc. IIIA

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Anon	**2.7**	2002	Brodifacoum Technical Specification	Y	Syngenta
Anon	**6.12/02**	2004	The treatment of anticoagulant poisoning: Advice to physicians. Issued jointly by Zeneca Public Health, Sorex Limited, Lipha SA, BASF and Bayer. Not GLP, unpublished.[Advice to physicians1]	Y	Syngenta
Anon	**8/01**	1999	Brodifacoum Technical, EC Safety Data Sheet, Version 7.	Y	Syngenta
Confidential Data	**6.4.1/02**	1984	Brodifacoum: 90-Day Feeding Study In Rats. ICI Central Toxicology Laboratory, Report No: CTL/P/862. GLP, unpublished. [C2.3/03].	Y	Syngenta
Confidential Data	**6.2/04**	1987	Brodifacoum: Elimination from the tissues of rats following administration of single oral doses. ICI Central Toxicology Laboratory, Report No: CTL/P/1559. GLP, unpublished. [C2.7/05].	Y	Syngenta
Beavers JB and Fink R	**7.5.3.1.2/03**	1978	Forty-Day Dietary LC50 - Mallard Ducks, Technical Brodifacoum, Final Report. Wildlife International Ltd Report No: 123-128. Not GLP, unpublished. [G2.1/03].	Y	Syngenta
Berry D	**6.18/01**	2003	Brodifacoum: Global Evaluation of Toxicological and Metabolism Studies. Central Toxicology Laboratory Report No: CTL/03A274/OVERVIEW/REPORT. No GLP, unpublished.	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company** **Report No.** **GLP or not** **(Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Bratt H	**6.2/07**	1979	Brodifacoum: Absorption, excretion and tissue retention in the rat. ICI Central Toxicology Laboratory, Report No: CTL/P/462. No GLP, unpublished. [C2.7/01].	y	Syngenta
Bratt H, Batten P, Dayal R, Tate S	**6.2/05**	1985	Brodifacoum: Excretion and Tissue Distribution in the Rat Following Oral Administration at Several Dose Levels. ICI Central Toxicology Laboratory, Report No: CTL/P/1308. GLP, unpublished. [C2.7/02].	Y	Syngenta
Bratt H, Batten P, Mainwaring G, Tate S	**6.2/08**	1986	R170431 and Brodifacoum: Comparative Excretion and Tissue Distribution in the Rat. ICI Central Toxicology Laboratory, Report No: CTL/P/1346. GLP, unpublished. [C2.7/04].	Y	Syngenta
Briggs, G.G	**3.9/02**	1981	Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors and the parachor. J. Agric. Food Chem., **29**. pp.1050-1059.		
Buckle A	**5/02**	2004	Brodifacoum, Resistance to the Anticoagulants and Resistance Management. Not GLP, unpublished. [BR-959-0149]	Y	Syngenta
Callander	**6.6.1/01**	1984	Brodifacoum - An Evalution in the Salmonella Mutagenicity Assay. ICI Central Toxicology Laboratory Report No: CTL/P/949. GLP, unpublished. [C2.6/06].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company** **Report No.** **GLP or not** **(Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Chambers JG and Snowdon PJ	**2.10**	2004	Study to determine potential exposure to operators during simulated use of anticoagulant rodenticide baits. Synergy Laboratories Limited, Study Number SYN/1302. GLP, unpublished. [BR-959-0151].	Y	Syngenta as part of CEFIC/EBPF Rodenticides Data Development Group (at 15th February this comprised of BASF, Bayer, Liphatec, Rentokil, Sorex and Syngenta check names against MoU)
Confidentila data	**6.3.1/04**	1977	PP581 Subacute Feeding Study in Beagle Dogs. Huntingdon Research Centre, Report No: ICI/127/76809. Not GLP, unpublished. [C2.2/01].	Y	Syngenta
Craig WB	**3.5/02; 4.2 (c)/02**	2000	Brodifacoum - Physico-Chemical Testing with Brodifacoum: Water Solubility. Inveresk Research Report No: 18799. GLP, unpublished. [BR-959-0079].	Y	Syngenta
Craig W J	**7.4.1.3**	2003	The Growth Inhibition of the alga Selenastrum capricornutum by BRODIFACOUM Technical. Chemex Environmental International Ltd. Report - ENV5801/120140	Y	Activa / PelGar Brodifacoum and Difenacoum Task Force
Craig W J	**7.4.1.2**	2003	The Toxicity to Daphnia magna of BRODIFACOUM Technical. Chemex Environmental International Ltd report - ENV5802/120140	Y	Activa / PelGar Brodifacoum and Difenacoum Task Force
Confidential Data	**6.6.3/01**	1984	Brodifacoum: Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells. ICI Central Toxicology Laboratory, Report No: CTL/P/975. GLP, unpublished. [C2.6/08].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Davidson AJ	**2.8; 4.1/01**	2000	Brodifacoum - Product Chemistry of Brodifacoum: Analytical Profile of 5 Batches. Inveresk Research Laboratory Report Number: 18909. GLP, unpublished. [BR-959-0084].	Y	Syngenta
Davies DJ	**6.2/09**	2003	Klerat Pellets: In Vitro Absorption Through Human Epidermis. Syngenta CTL Report No: CTL/JV1757. GLP, unpublished. [BR-959-0131].	Y	Syngenta
Desmares-Koopmans M.J.E.	**7.4.1.4/01**	2001	Activated Sludge Respiration Inhibition Test with BRODIFACOUM (Contact Time: 30 Minutes). NOTOX B.V., Report No. 328793. GLP, unpublished. [BR-959-0097].	Y	Syngenta
Confidential Data	**6.1.1/01**	1993	Brodifacoum: Acute Oral Toxicity. ICI Central Toxicology Laboratory, CTL/P/3918. GLP, unpublished. [C2.1/20].	Y	Syngenta
Confidential Data	**6.13/01**	1985	Acute toxicity of brodifacoum to sheep. New Zealand Journal of Experimental Agriculture 13, 23 - 25, RIC0615. Not GLP, published. [C2.1/26].	N	
Confidential Data	**6.13/02**	1981a	The Oral Toxicity of Brodifacoum to Rabbits. New Zealand Journal of Experimental Agriculture 9, 23 - 25, RIC0585. Not GLP, published. [C2.1/22].	N	

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Confidential Data	**6.13/08**	1981 b	The Acute Oral Toxicity of the Anticoagulant Brodifacoum to Dogs. New Zealand Journal of Experimental Agriculture 9, 147 - 149, RIC0586. Not GLP, published. [C2.1/23].	N	
Grimes J and Fink R	**7.5.3.1.2/01**	1979a	Forty day LC50 - Laughing Gull, Technical Brodifacoum, Final Report. Wildlife International Ltd Report No: 123-125. Not GLP, unpublished. [G2.1/02].	Y	Syngenta
Grimes J and Fink R	**7.5.3.1.2/02**	1979 b	Forty day LC50 - Laughing Gull, Technical Brodifacoum, Final Report. Wildlife International Ltd Report No: 123-126. Not GLP, unpublished. [G2.1/11].	Y	Syngenta
Confidential Data	**6.1.1/02**	1974a	Acute Oral Toxicity of WBA 8119 to Male Mice. Ward Blenkinsop and Company Limited, Agricultural Research, RIC0559. Not GLP, unpublished. [C2.1/04].	Y	Syngenta
Confidential Data	**6.3.1/05**	1974 b	Subacute Five Day Oral Toxicity of WBA 8119 to Male Rats. Ward Blenkinsop and Company Limited, Agricultural Research, Report No: RIC0564. Not GLP, unpublished. [C2.2/04].	Y	Syngenta
Confidential Data	**6.3.1/06**	1974c	The Subacute (5 Day) Oral Toxicity of WBA 8119 to Female Rats. Ward Blenkinsop and Company Limited, Agricultural Research, Report No: RIC0565. Not GLP, unpublished. [C2.2/05].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Confidential Data	**6.13/05**	1975a	Acute Oral Toxicity of WBA 8119 to Female Guinea Pig. Ward Blenkinsop and Company Limited, Agricultural Research, RIC0558. Not GLP, unpublished. [C2.1/03].	Y	Syngenta
Confidential Data	**6.13/09**	1975 b	Acute Oral Toxicity of WBA 8119 to Male Rabbit. Ward Blenkinsop and Company Limited, Agricultural Research, RIC055. Not GLP, unpublished. [C2.1/02].	Y	Syngenta
Confidential Data	**6.13/10**	1975c	Sub-acute (5-day) oral toxicity of Wba 8119 to female guinea pig. Ward Blenkinsop and Company, Report No: RIC0567. Not GLP, unpublished. [C2.2/07].	Y	Syngenta
Confidential Data	**6.3.1/02**	1978a	Five Day Subacute Oral Toxicity of WBA 8119 to Female Mice. Ward Blenkinsop and Company Limited, Agricultural Research, Report No: RIC0563. Not GLP, unpublished. [C2.2/03].	Y	Syngenta
Confidential Data	**6.3.1/03**	1978 b	The Subacute (5 day) Oral Toxicity of WBA 8119 to Male Homozygous Resistant Rats. Ward Blenkinsop and Company Limited, Agricultural Research, Report No: RIC0566. Not GLP, unpublished. [C2.2/06].	Y	Syngenta
Confidential Data	**6.3.1/01**	1978c	Subacute - Five Day Toxicity of WBA 8119 to Male Mice. Ward Blenkinsop and Company Limited, Agricultural Research, Report No: RIC0562. Not GLP, unpublished. [C2.2/02].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company** **Report No.** **GLP or not** **(Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Hall BE and Priestley I	**7.2.1/01**	1992	Brodifacoum: Metabolism in Soil Under Aerobic Conditions. Inveresk Research International Report No: 8795. GLP, unpublished. [F3.1/01]	Y	Syngenta
Hall M.G.	**4.2 (d)/01**	1997	Brodifacoum: Validation of the Methods for the Determination of Brodifacoum in Rat Liver and Plasma. Central Toxicology Laboratory Report No: CTL/M/258. GLP, unpublished. [Supp Series].	Y	Syngenta
confidential Data	**6.2/03**	1991	Determination Of The Residues And The Half-Life Of The Rodenticides Brodifacoum, Bromadiolone And Flocoumafen In The Livers Of Rats During 200 Days After Single Oral Doses Of Each At A Dose Level Of 0.2mg/kg. Huntingdon Research Centre Report No: HRC/LPA 158/891590. GLP, unpublished. [C2.7/03].	Y	Syngenta
Hegdal P L and Blaskiewicz R W	**7.5.6/03**	1981	Hazards to barn owls associated with the use of Talon (brodifacoum bait) for controlling rats and house mice. US Fish and Wildlife Service, Denver Wildlife Research Centre. Report number RIC0619. Not GLP, unpublished. [G2.4/03].	Y	Syngenta
Hill RW, Maddock BG, Hart B, Bowles PF	**7.4.1.1/01**	1976	PP581: Determination of the actue toxicity of PP581 to rainbow trout (*Salmo gairdneri)*. ICI Brixham Laboratory, Report No: BL/B/1758. Not GLP, unpublished. [G5.1/01].	Y	Syngenta
Confidential Data	**6.8.1/01**	1980a	Brodifacoum: Teratogenicity Study in the Rat. ICI Central Toxicology Laboratory Report No: CTL/P/437. GLP, unpublished. [C2.5/01].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Confidential Data	**6.8.1/02**	1980 b	Brodifacoum: Teratogenicity Study in the Rabbit. ICI Central Toxicology Laboratory Report No: CTL/P/459. GLP, unpublished. [C2.5/03].	Y	Syngenta
Hogg A	**7.1.3/01**	2002	Brodifacoum: Physico-Chemical Testing with Brodifacoum: Estimation of Adsorption Coefficient. Inveresk Research Report No: 21676. GLP, unpublished. [BR-959-0116].	Y	Syngenta
Confidential Data	**6.4.1/01**	1997	Brodifacoum: 6 Week Oral Toxicity Study In Dogs. Zeneca Central Toxicology Laboratory, Report No: CTL/P/5371. GLP, unpublished. [C2.2/09].	Y	Syngenta
Jaber MJ	**7.5.6/01**	1981	Secondary LC50 study of the toxicity of the anticoagulant brodifacoum to American Kestrels (Falco sparvarius). ICI Americas Inc. Report number: TMUE0017/B No GLP, unpublished. [G2.1/10].	Y	Syngenta
Jackson R and Hall BE	**7.2.3.2/01**	1992	Aged Soil Leaching of [^{14}C]-Brodifacoum. Inveresk Research International Report No: 8879. GLP, unpublished. [F3.2/02]	Y	Syngenta
Jackson R, Priestley I, Hall BE	**7.1.1.1.1/02**	1991	The Determination of the Hydrolytic Stability of [^{14}C]-Brodifacoum. Inveresk Research International Report Number 8330. GLP, unpublished. [F4.1/03].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Kelly CR and Clayton MA	**7.1.1.2.1/01**	2003	Brodifacoum – Determination of Ready Biodegradability by the Closed Bottle Test. Inveresk Research International, Report No: 21947. GLP, unpublished. [BR-959-0122]	Y	Syngenta
Confidential Data	**6.2/06**	1985	Brodifacoum: Residues in Rat Livers from a 90-Day Feeding Study. ICI Plant Protection Division, Report No: M3923B. GLP, unpublished. [C2.3/04].	Y	Syngenta
Knight B	**7.4.1.1/02**	2000a	Brodifacoum: Determination of Acute Toxicity to Rainbow Trout (96 h, Semi-Static, Limit Test). Inveresk Research Laboratory Report Number: 18997. GLP, unpublished. [BR-959-0080].	Y	Syngenta
Knight B	**7.4.1.2/01**	2000 b	Brodifacoum: Determination of Acute Toxicity to Daphnia (48 h, Static, Limit Test). Inveresk Research Report Number 19032. GLP, unpublished. [BR-959-0081].	Y	Syngenta
Knight B	**7.4.1.3/01**	2000c	Brodifacoum: Alga, Growth Inhibition Test (72 , Limit Test). Inveresk Research Laboratory Report Number: 19002. GLP, unpublished. [BR-959-0083].	Y	Syngenta
Koubek KG and Ussary JP	**4.2 (a)/01**	1979	An HPLC Method for the Determination of Brodifacoum in Soil. ICI Americas Inc Report Method No: TMU0423/A. Not GLP, unpublished. [F2.1/04].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company** **Report No.** **GLP or not** **(Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Confidential Data	**6.2/02; 6.8.1/03**	1992	Brodifacoum: Blood Kinetics in the Pregnant Rat. ICI Central Toxicology Laboratory Report No: CTL/P/3818. GLP, unpublished. [C2.5/04].	Y	Sygenta
Linder T	**7.5.3.1.3**	2005	Avian Reproduction Study with Difenacoum in the Japanese Quail (Coturnix coturnix japonica). Genesis Laboratories, Inc., Report no. 04012 Unpublished [DF-7.5.3.1.3-0392]	Y	Sorex Limited
Confidential Data	**6.6.2/01**	1990	Brodifacoum: An Evaluation in the In Vitro Cytogenetic Assay in Human Lymphocytes. ICI Central Toxicology Laboratory Report No: CTL/P/3109. GLP, unpublished. [C2.6/04].	Y	Syngenta
Mather, J I, and Tapp, J F.	**7.4.1.4/02**	1988	Brodifacoum: Determination of the toxicity to Pseudomonas putida. ICI Brixham Laboratory Report Number : BL/B/3447. GLP, unpublished. [G7.1/01].	Y	Syngenta
Mathis SMG, Benner JP and Skidmore MW	**7.1.1.1.1/01**	1995	Brodifacoum: Aqueous Hydrolysis in pH 5, pH 7 and pH 9 Solutions at 25^{o}C. Zeneca Agrochemicals Report Number RJ1927B. GLP, unpublished. [F4.1/01].	Y	Syngenta
Confidential Data	**6.1.2/01**	1991	Brodifacoum Technical: Acute Dermal Toxicity to the Rat. ICI Central Toxicology Laboratory, CTL/P/3595. GLP, unpublished. [C2.1/19].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Mellano D	**6.6.2/02**	1984a	In Vitro Study of Chromosome Aberration Induced by the Test Article Brodifacoum in Cultured Human Lymphocytes. Istituto Di Ricerche Biomediche Antione Marxer SpA, Report No: CTL/C/1258. [C2.6/05].	Y	Syngenta
Mellano D	**6.6.3/02**	1984 b	Study of the capacity of the test article brodifacoum to induce unscheduled DNA synthesis in cultured hela cells (autoradiographic method). Istituto Di Ricerche Biomediche "Antione Marxer" SpA (Italy) Experiment No. M 672. ICI Report No: CTL/C/1257. GLP, unpublished. [C2.6/03].	Y	Syngenta
Morris K D and Akhavein A A,	**7.5.7.1.2/02**	1978	Talon: Secondary toxicity of brodifacoum to foxes, (North Carolina). ICI Americas Inc. Report Series TMUD1998/B. Not GLP, unpublished. [G3.3/04].	Y	Syngenta
Morris K D and Kaukeinen D E,	**7.5.6/04**	1980	Talon: Rodent baiting sites of the Barn Owl Secondary hazard study. ICI Americas Inc. Report Series TMUD3335/B. Not GLP, unpublished. [G2.4/04].	Y	Syngenta
Morris K D and Kaukeinen D E,	**7.5.7.1.2/01**	1978	Talon: Secondary toxicity of brodifacoum to dogs (Beagles), (North Carolina). ICI Americas Inc. Report Series TMUD1997/B. Not GLP, unpublished. [G3.3/03].	Y	Syngenta
Newby SE and White BG	**7.2.3.1/01**	1979	Brodifacouom: Adsorption and Desorption in soils measured under laboratory conditions. ICI Plant Protection Division Report No. TMJ 1764 B. Not GLP, unpublished. [F3.2/03].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company** **Report No.** **GLP or not** **(Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
O'Bryan SM and Constable DJC	**4.2 (d)/02**	1991	Quantification of Brodifacoum in Plasma and Liver Tissue by HPLC. J Anal. Tox.,1991, **15**, Number 3, pp 144-147. Published. [C5.1/03].	N	
Osborn D	**7.5.6/02**	1986	Safety evaluation of Agrochemicals: R170431 and PP581; Sub-acute oral toxicity to Carrion Crows. Institute of Terrestrial Ecology (Natural Environmental Research Council), Report number: ICI/NERC F6/95/129. No GLP, unpublished. [G2.1/15].	Y	Syngenta
Confidential Data	**6.1.1/03**	1978a	Brodifacoum (PP581): Acute Oral and Acute Dermal Toxicity. ICI Central Toxicology Laboratory, CTL/P/413. Not GLP, unpublished. [C2.1/11].	Y	Syngenta
Confidential Data	**6.1.4/01**	1978 b	Brodifacoum: Skin and Eye Irritation. ICI Central Toxicology Laboratory, CTL/P/404. Not GLP, unpublished. [C2.1/10].	Y	Syngenta
Confidential Data	**6.1.5/02**	1979	PP581: Acute Oral Toxicity and Skin Sensitisation. ICI Central Toxicology Laboratory, CTL/P/260. Not GLP, unpublished. [C2.1/12].	Y	Syngenta
Confidential Data	**6.13/06**	1975	WBA 8119: Acute Oral Toxicity. ICI Central Toxicology Laboratory, CTL/P/216. Not GLP, unpublished. [C2.1/13].	Y	Syngenta
Confidential Data	**6.1.3/01**	1993	Brodifacoum: 4-Hour Acute Inhalation Toxicity Study in the Rat. ZENECA Central Toxicology Laboratory, CTL/P/4065. GLP, unpublished. [C2.1/21].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Confidential Data	**6.13/07**	1985	R170431 and PP581 Acute Oral Toxicity to Cats. Huntingdon Research Centre Report No: ISN 34A/85458. Not GLP, unpublished. [C2.1/17].	Y	Syngenta
Confidential Data	**6.1.5/01**	1996	Brodifacoum: Skin Sensitisation to the Guinea Pig. ICI Central Toxicology Laboratory, CTL/P/5105. GLP, unpublished. [C2.1/29].	Y	Syngenta
Confidential Data	**6.13/04**	1976	The Oral Toxicity of WB 8119 to the Domestic Pig. Huntindon Research Centre, Report No: SRX 2/7670. Not GLP, unpublished. [C2.1/24].	Y	Syngenta
Ross DB, Roberts NL and Cameron DM	**7.5.3.1.1/02**	1977a	The Acute Oral Toxicity (LD_{50}) of Brodifacoum to the Japanese Quail. Huntingdon Research Centre Report No: ICI 122 WL/77599. Not GLP, unpublished. [G2.1/13]	Y	Syngenta
Ross DB, Roberts NL and Cameron DM	**7.5.3.1.1/03**	1977 b	The Acute Oral Toxicity (LD_{50}) to the Chicken. Huntingdon Research Centre Report No: ICI ICI 122WL/77600. Not GLP, unpublished. [G2.1/16].	Y	Syngenta
Confidential Data	**6.13/03**	1977c	The Acute Oral Toxicity (LD50) of pp581 to the Chicken. Huntingdon Research Centre, Report No: ICI 122WL/77600. Not GLP, unpublished. [G2.1/16].	Y	Syngenta
Ross DB, Roberts NL and Fairley C	**7.5.3.1.1/01**	1980	The Acute Oral Toxicity (LD_{50}) of Brodifacoum to the Mallard Duck. Huntingdon Research Centre Report No: ICI 308 WL/791275. Not GLP, unpublished. [G2.1/07]	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company Report No.** **GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Rowland K	**6.12/01**	2004	Biological Monitoring of Rodenticide Workers at Pentagon Fine Chemicals Limited and Sorex Limited. Report prepared for Sorex. Not GLP, unpublished. [BR-959-0136]	Y	Syngenta
Sanderson DJ and Austin DJ	**4.2 (c)/01**	1990	The Determination of Residues of Brodifacoum (ICIA0581) and Difenacoum (ICIA0580) in Potable Water. ICI Agrochemicals Report Method No: 173. Not GLP, unpublished. [F2.2/03].	Y	Syngenta
Sheldon T, Richardson C R, Shaw J,	**6.6.4/01**	1984	An Evaluation of Brodifacoum in the Mouse Micronucleus Test. ICI Central Toxicology Laboratory, Report No: CTL/P/1006. GLP, unpublished. [C2.6/07].	Y	Syngenta
Staniland, J	**7.5.1.2**	2005	The toxicity to Eisenia foetida foetida of Brodifacoum. Chemex Environmental International Ltd. Ref:ENV7010/120140	Y	Activa / PelGar Brodifacoum and Difenacoum Task Force
Confidential Data	**6.2/01**	1996	[^{14}C]-Brodifacoum: Metabolism in the rat. Corning Hazleton (Europe), Report No: 88/126-1011. GLP, unpublished. [C2.7/06].	Y	Syngenta
Trueman RW	**6.6.1/02**	1979	An Examination of Brodifacoum for Potential Carcinogenicity Using Two in vitro Assays of Potential Carcinogenicity. ICI Central Toxicology Laboratory Report No: CTL/R/481. Not GLP, unpublished. [C2.6/01].	Y	Syngenta

Author	**Doc IIIA Section No/ Ref No**	**Year**	**Title** **Source/ Company Report No.** **GLP or not** **(Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Trueman RW	**6.6.3/03**	1979	An Examination of Brodifacoum for Potential Carcinogenicity Using Two in vitro Assays of Potential Carcinogenicity. ICI Central Toxicology Laboratory Report No: CTL/R/481. Not GLP, unpublished. [C2.6/01].	Y	Syngenta
WHO	**6.12/03**	1995	Environmental Health Criteria 175 – Anticoagulant Rodenticides. International Programme on Chemical Safety ISBN 9241571756. Not GLP, published. [BR-952-0141]	N	
WHO (World Health Organisation publication)	**5/01**	1995	Environmental Health Criteria 175 - Anticoagulant Rodenticides. International Programme on Chemical Safety.	N	
Wollerton C, Husband R	**3.1.1/01; 3.2/01; 3.4.1/01; 3.4.2/01; 3.4.3/01; 3.4.4/01; 3.5/01**	1991a	Pure Brodifacoum: Physico-Chemical Data File. ICI Agrochemicals Report No: RJ0959B. GLP, unpublished. [B2.1/02].	Y	Syngenta
Wollerton C, Husband R	**3.1.1/02; 3.1.2/01; 3.3.1/01; 3.3.2/01; 3.10/01**	1991 b	Brodifacoum TGAI: Physico-Chemical Data File. ICI Agrochemicals Report No: RJ0960B. GLP, unpublished. [B2.1/01]	Y	Syngenta
Wollerton C, Husband R	**3.9/01**	1990	Brodifacoum: Octanol-Water Partition Coefficient. ICI Agrochemicals Report No: RJ0913B. GLP, unpublished. [B2.1/05].	Y	Syngenta

B.

List of studies for Active Substance

The studies for the active substance considered as confidential information are given in the Doc I_not public access_Appendix III.

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
ACD/I Laboratory	A3.6	2004	ACD/I Lab web service. ACD/pKa calculation	Y	Public domain
Bachmann KA and Sullivan TJ	A6.2(4)	1983	Dispositional and Pharmacodynamic Characteristics of Brodifacoum in Warfarin-Sensitive Rats *Pharmacology*, 27, 281-288	N	Public domain
Boermans HJ, Johnstone I, Black WD and Murphy M	A6.2(7)	1991	Clinical Signs, Laboratory Changes and Toxicokinetics of Brodifacoum in Horses *Canadian Journal Vet Res*, 55, 21-27	N	Public domain
Breckenridge AM, Cholerton S, Hart JAD, Park BK and Scott AK	A6.2(1)	1985	A Study of the Relationship Between the Pharmacokinetics and the Pharmacodynamics of the 4-Hydroxycoumarin Anticoagulants Warfarin, Difenacoum and Brodifacoum in the Rabbit. *British Journal of Pharmacology*, 84, 81-91	N	Public domain
Brunton CFA, Macdonald DW and Buckle AP	A5	1993	Behavioural Resistance Towards Poison Baits in Brown Rats *Behavioural Processes*	N	Public domain
Confidential Data	A7.4.1.1	2003a	The Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) of Brodifacoum Technical Confidential Data, Report No. ENV5803/120140 GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A7.4.1.2	2003b	The Toxicity to *Daphnia magna* of Brodifacoum Technical Confidential Data, Report No. ENV5802/120140 GLP, Unpublished	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Confidential Data	A7.4.1.3	2003c	The Growth Inhibition of the alga *Selenastrum capricornutum* by Brodifacoum Technical Confidential Data, Report No. ENV5801/120140 GLP, Unpublished	Y	Activa Pelgar Task Force
Davanzo F, Faraoni, L, Pirina, A, Sesana, F and Pannacciulli, E	A6.12.3	2001	Brodifacoum: Information about and toxicity of anticoagulant rat poisons: Case Histories from Milan Poisons Centre 1996-1999. Servizio di Anestesia e Rianimazione Centro Antiveleni	N	Public domain
Donovan JW, Ballard JO, Murphy MJ	A6.2(9) A6.12.7	1990	Brodifacoum Therapy With Activated Charcoal: Effect on Elimination Kinetics *Vet Human Toxicology*, 32, 350	N	Public domain
Drake RM	A3.1.1 A3.1.2	2003a	Determination of the Melting Point and Boiling Point of Brodifacoum Technical Chemex Environmental International Ltd., Report No. ENV5808/120140 GLP, Unpublished	Y	Activa Pelgar Task Force
Drake RM	A3.10	2005a	Determination of the Thermal Stability of Breakdown Products of Brodifacoum Chemex Environmental International Ltd. Report No. ENV7062/120140 Unpublished	Y	Activa Pelgar Task Force
Drake RM	A7.1.1.1.2	2004a	Determination of the Direct Photolysis Rate in Water by Sunlight of Brodifacoum Chemex Environmental International Ltd., Report No. ENV6768/120140	Y	Activa Pelgar Task Force Syngenta
Drake RM	A7.1.1.2.1	2003b	Determination of the Ready Biodegradability of Brodifacoum Technical Chemex Environmental International Ltd., Report No. ENV5807/120140 GLP, Unpublished	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Drake RM	A7.1.1.2.2	2005b	Determination of the Inherent Biodegradability of Brodifacoum Chemex Environmental International Ltd., Report No. ENV7146/120140	Y	Activa Pelgar Task Force
Drake RM	A7.1.2.1.2	2005c	Determination of the Anaerobic Biodegradability of Brodifacoum Chemex Environmental International Ltd., Report No. ENV7145/120140	Y	Activa Pelgar Task Force
Drake RM	A7.1.3(1)	2005d	The Estimation of the Adsorption Coefficient (K_{oc}) of Brodifacoum Chemex Environmental International Ltd., Report No. ENV7008/120140	Y	Activa Pelgar Task Force
Confidential Data	A6.6.3	2004	Brodifacoum – L5178Y TK+/- Mouse Lymphoma Assay Confidential Data. 1558/004 GLP, Unpublished	Y	Activa Pelgar Task Force
Fabbrini R	A3.2(1)	1997a	Brodifacoum – Determination of the Vapour Pressure ChemService S.r.l, Report No. CH-14/96-C-BDF GLP, Unpublished	Y	Activa Pelgar Task Force
Fabbrini R	A3.2.1(1)	1997b	Brodifacoum – Adsorption/Desorption: Adsorption Coefficient (Koc), Volatility: Henry's Law Constant (H) ChemService S.r.l, Report No. 1 GLP, Unpublished	Y	Activa Pelgar Task Force
Fabbrini R	A3.5(1)	1997c	Brodifacoum – Determination of the Water Solubility ChemService S.r.l, Report No. CH-14/96-A-BDF GLP, Unpublished	Y	Activa Pelgar Task Force
Fabbrini R	A3.9(1)	1997d	Brodifacoum – Determination of the Partition Coefficient ChemService S.r.l, Report No. CH-14/96-B-BDF GLP, Unpublished	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Fabbrini R	A7.1.1.1.1	1997e	Brodifacoum – Determination of Abiotic Degradation Hydrolysis as a Function of pH. ChemService S.r.l, Report No.CH-15/96-B-BDF GLP, Unpublished	Y	Activa Pelgar Task Force
Garofani S	A3.1.3	2001a	Brodifacoum – Determination of the Relative Density ChemService S.r.l, Report No. CH-158/2000 GLP, Unpublished	Y	Activa Pelgar Task Force
Garofani S	A3.4(1)	2001b	Draft: Brodifacoum UV/Vis, MS, IR and NMR Spectra ChemService S.r.l, Report No. CH-157/2000 GLP, Unpublished	Y	Activa Pelgar Task Force
Garofani S	A3.4(2)	2001c	Final: Brodifacoum UV/Vis, MS, IR and NMR Spectra ChemService S.r.l, Report No. CH-133/2001 GLP, Unpublished	Y	Activa Pelgar Task Force
Garofani S	A4.2(d)	2007	Protocol: Validation of the Analytical Method for the Determination of Brodifacoum Residues in Serum Blood Samples ChemService S.r.l,, Study Protocol No. CH-283-2007		Activa Pelgar Task Force
Garofani S	A3.11(1)	2001d	Determination of the flammability Chemservice S.r.l, Report number CH-159/2000 GLP, Unpublished	Y	Activa Pelgar Task Force Syngenta
Confidential Data	A7.5.3.1.1	2005	Acute Oral Toxicity of Brodifacoum Technical of Japanese Quail (*Coturnix coturnix japonica*) Confidential Data, Report No. 04/903-115FU	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Gill JE, Kerins GM and MacNicoll AD	A5	1992	Inheritance of Low Grade Brodifacoum Resistance in the Norway Rat *Journal of Wildlife Management*, 56 (4), 809-816	N	Public domain
Godfrey MER, Laas FJ and Rammell CG	A6.2(10) A6.13	1985	Acute Toxicity of Brodifacoum to Sheep *New Zealand Journal of Experimental Agriculture*, 13, 23-25	N	Public domain
Greaves JH, Shepherd DS and Quy R	A5	1982	Field trials of Second-Generation Anticoagulants Against Difenacoum-Resistant Norway Rat Populations *Journal of Hygiene*, 89, 295-301	N	Public domain
Huckle KR, Hutson DH, Logan CJ, Morrison BJ and Warburton PA	A6.2(2i)	1989a	The Fate of the Rodenticide Flocoumafen in the Rat: Retention and Elimination of a Single Oral Dose *Pesticide Science*, 25, 297-312	N	Public domain
Huckle KR, Hutson DH, Warburton PA	A6.2(2ii)	1988	Elimination and Accumulation of the Rodenticide Flocoumafen in Rats Following Repeated Oral Administration *Xenobiotica*, 18, 1465-1479	N	Public domain
Huckle KR, Morrison BJ, Warburton PA	A6.2(2iii)	1989b	The Percutaneous Fate of the Rodenticide Flocoumafen in the Rat: Role of Non-Biliary Intestinal Excretion *Xenobiotica*, 19, 63-74	N	Public domain
Humphries RE, Meeham AP and Sibly RM	A5	1992	The Characteristics and History of Behavioural Resistance in Inner-city House Mice in the UK In: Borrecco JE and Marsh RE (eds.) *15th Vertebrate Pest Conference.* University of California, Davis, pp. 161-164	N	Public domain
Laas FJ, Forss DA and Godfrey MER	A6.2(5)	1985	Retention of Brodifacoum in Sheep Tissues and Excretion in Faeces *New Zealand Journal of Agricultural Research*, 28, 357-359	N	Public domain

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Londyn M	A4.1(1) A4.1(2) A4.1(3)	2001	Brodifacoum Five-Batch Analysis Pliva – Lachema a.s., Report No. 01/07/001/PLG GLP, Unpublished	Y	Activa Pelgar Task Force
Lund M	A5	1984	Resistance to the Second-Generation Anticoagulant Rodenticides In: Clark DO (ed.) *11th Vertebrate Pest Conference*, University of California, Davis, pp. 89-94	N	Public domain
MacNicoll AD and Gill JE	A5	1987	The occurrence and significance of rodenticide resistance in the UK In : Lawson, T. J. (ed.) *Stored Products Pest Control. British Crop Protection Council Monograph No. 37*. BCPC Publications, Thorton Heath, UK, 89-95	N	Public domain
Confidential Data	A6.1.1(2)	1996a	Brodifacoum – Acute Oral Toxicity in Rats of a 0.25% Concentrate Confidential Data, Report No. CIT/14095 TAR GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.1.2(2)	1996b	Brodifacoum – Acute Dermal Toxicity in Rats of a 0.25% Concentrate Confidential Data, Report No. CIT/14096 TAR GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.1.4(3)	1996c	Brodifacoum – Acute Dermal Irritation in Rabbits of a 0.25% Concentrate Confidential Data, Report No. CIT/14094 TAL GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.1.4(4)	1996d	Brodifacoum – Acute Eye Irritation in Rabbits of a 2.5% Concentrate Confidential Data, Report No. CIT/14093 TAL GLP, Unpublished	Y	Activa Pelgar Task Force

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Confidential Data	A6.1.5(1)	1996e	Brodifacoum – Skin Sensitization in Guinea Pigs of a 2.5% Concentrate Confidential Data, Report No. CIT/14097 TSG GLP, Unpublished	Y	Activa Pelgar Task Force
Martinez MP	A4.2(c)	2005	Brodifacoum Technical – Validation of the Analytical Method for the Determination of the Residues in Dinking, Ground and Surface Waters ChemService S.r.l, Report No. CH-289/2005 GLP, Unpublished	Y	Activa Pelgar Task Force Syngenta
Misenheimer TM and Suttie JW	A5	1990	Warfarin Resistance in a Chicago Strain of Eats *Biochemical Pharmacology,* 40 (9), 2079-2084	N	Public domain
Morlacchini M	A4.2(a)	2005	Residues Determination of Brodifacoum, Difenacoum and Bromadiolone in Soil CERZOO, Report No. CZ/05/002/ACTIVA/SOIL GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.4.1(1)	1995a	Brodifacoum 90-day Feeding Study in the Rat Confidential Data, Report No. MLS/10020 GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.8.1(1)	1995b	Brodifacoum – Development Toxicity to the Rat Confidential Data., Report No. MLS/10025 GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.8.1(2)	1995c	Brodifacoum – Development Toxicity to the Rabbit Confidential Data, Report No. MLS/10019 GLP, Unpublished	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Parmar G, Bratt H, Moore R and Batten PL	A6.2(3)	1985	Evidence for Common Binding Site *in vivo* for the Retention of Anticoagulants in Rat Liver *Human Toxicology*, 6, 431-432	N	Public domain
Quy RJ, Cowan DP, Haynes P, Inglis IR and Swinney T	A.5	1992b	The Influence of Stored Food on the Effectiveness of Farm Rat Control British Crop Protection Conference, *Pests and Diseases*, 4A-3, pp. 291-300	N	Public domain
Quy RJ, Shepherd DS and Inglis IR	A5	1992a	Bait Avoidance and Effectiveness of Anticoagulant Rodenticides Against Warfarin- and Difenacoum-Resistant Populations of Norway Rats *Crop Protection*, 11, 14-20	N	Public domain
Rammell CG, Hoogenboom JJL, Cotter M, Williams JM and Bell J	A7.5.7.1.1	1984	Brodifacoum Residues in Target and Non-Target Animals Following Rabbit Poisoning Trials *New Zealand Journal of Experimental Agriculture*, 12, 107-111	N	Public domain
Ray AC, Murphy MJ, DuVall MD and Reagor JC	A6.2(11)	1989	Determination of Brodifacoum and Bromadiolone Residues in Rodent and Canine Liver *American Journal of Veterinary Research*, 50 (4), 546-550	N	Public domain
Confidential Data	A7.4.3.3.1	2004b	The Bioconcentration Potential of Brodifacoum in Rainbow Trout (*Onocorhynchus mykiss*)Under Flow-Through Conditions Confidential Data, Report No. ENV6597/120140	Y	Activa Pelgar Task Force
Confidential Data	A3.13	2005a	Determination of the Surface Tension of Brodifacoum Confidential Data, Report No. ENV7164/120140 GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.1.5(2)	2006	Brodifacoum – Local Lymph Node Assay in the Mouse Confidential Data t No. 2109/0004 GLP, Unpublished	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Confidential Data	A7.5.3.1.3	2005	Avian Reproduction Toxicity Test of Brodifacoum Technical in the Japanese Quails (*Coturnix Coturnix Japonica*) Confidential Data, Report No. 03/778-206FU	Y	Activa Pelgar Task Force
Confidential Data	A6.1.4(1)	2004a	Acute Skin Irritation Study of Test Item Brodifacoum Technical in Rabbits Confidential Data, Report No. 04/903-006N GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A6.1.4(2)	2004b	Acute Eye Irritation Study of Test Item Brodifacoum Technical in Rabbits Confidential Data, Report No. 04/903-005N GLP, Unpublished	Y	Activa Pelgar Task Force
Staniland J	A3.7(1)	2005a	The Solubility of Brodifacoum in Organic Solvents Chemex Environmental International Ltd., Report No. ENV7058/120140 Unpublished	Y	Activa Pelgar Task Force
Staniland J	A7.4.1.4	2004	An Evaluation of the Effect of Brodifacoum Technical on the Respiration Rate of Activated Sludge Chemex Environmental International Ltd., Report No. ENV7009/120140	Y	Activa Pelgar Task Force
Staniland J	A7.5.1.2	2005b	The Toxitiy to *Eisenia foetida foetida* of Brodifacoum Chemex Environmental International Ltd., Report No. ENV7010/120140	Y	Activa Pelgar Task Force Syngenta
Confidential Data	A6.1.1(1)	2004a	Acute Oral Toxicty Study (Acute Toxic Class Method) of Test Item Brodifacoum Technical in Rats Confidential Data, Report No. 04/903-001P	Y	Activa Pelgar Task Force

Author(s)	**Section No / Reference No**	**Year**	**Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished**	**Data Protection Claimed (Yes/No)**	**Owner**
Confidential Data	A6.1.2(1)	2004b	Acute Dermal Toxicity Study of Test Item Brodifacoum Technical in Rats Confidential Data, Report No. 04/903-002P	Y	Activa Pelgar Task Force
Confidential Data	A6.8.2	2004c	Brodifacoum – Two-Generation Reproduction Toxicity Study of Test Item Brodifacoum Technical in Rats Confidential Data, Report 03/737-202P GLP, Unpublished	Y	Activa Pelgar Task Force
Thompson PW	A6.6.1	2002	Brodifacoum – Reverse Mutation Assay "Ames Test", Using *Salmonella typhimurium* SafePharm Laboratories Ltd., Report No. 1558/006 GLP, Unpublished	Y	Activa Pelgar Task Force
Tremain SP	A3.3.1 A3.3.2 A3.11(2)	2007	Brodifacoum: Determination of physico-chemical properties. SafePharm Laboratories Ltd., Report No. 2109/0006 GLP, Unpublished	Y	Activa Pelgar Task Force
Turnbull G	A4.2(d) A4.3 A6.15.1	2005	Validation of Analytical Methodology to Determine Rodenticides in Food Matrices Central Science Laboratory, Report No. PGD-180 GLP, Unpublished	Y	Activa Pelgar Task Force
Confidential Data	A5	1997a	Efficacy Overview: Vertox™ Rolled Oats, A Rodenticide Formulation, Containing 50ppm Brodifacoum, for the Control of Rats and Mice Confidential Data., Report No. EO/VRO/09-97 Unpublished	Y	Activa Pelgar Task Force

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Weitzel JN, Sadowski JA, Furie BC, Moroose R, Kim H, Mount ME, Murphy MJ and Furie B	A6.2(8) A6.12.2	1990	Surreptitious Ingestion of a Long-Acting Vitamin K Antagonist/Rodenticide, Brodifacoum – Clinical and Metabolic Studies of Three Cases *Blood*, 76(12), 2555-2559	N	Public domain
White DF and Mullee DM	A3.2(2) A3.2.1(2) A3.5(2) A3.7(2) A3.9(2)	2006	Brodifacoum – Determination of Physico-chemical Properties SafePharm Laboratories Ltd., Report No. 2109/0002 GLP, Unpublished	Y	Activa Pelgar Task Force
Woody BJ, Murphy MS, Ray AC and Green RA	A6.2(6)	1992	Coagulopathic Effects and Therapy of Brodifacoum Toxicosis in Dogs *Journal of Veterinary Internal Medicine*, 6, 23-28	N	Public domain
Woolley AJ and Mullee DM	A3.3.1(a)	2007	Determination of Dustability and Particle Size Distribution SafePharm Laboratories Ltd., Report No. 2109/0003	Y	Activa Pelgar Task Force
Worthington M	A7.3.1	2007	Estimation of Indirect Photolysis in Air SafePharm Laboratories Ltd.	Y	Activa Pelgar Task Force
Wright NP	A6.6.2	2003	Brodifacoum – Chromosome Aberration Test in Human Lymphocytes *in vitro.* SafePharm Laboratories Ltd., Report No. 1558/003 GLP, Unpublished	Y	Activa Pelgar Task Force

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Doc. IIIB

Author	Doc IIIB Section No/ Ref No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
Anon	**2.2/01**	-	Component 9 Safety Data Sheet. Ragus Sugars Manufacturing Limited. Not GLP, published.	N	
Anon	**2.2/02**	1994	Component 5 Safety Data Sheet. Orsan France. No GLP, published.	N	
Anon	**4.1/01**	1998	Sorex method 102: The determination of the active substances within rodenticidal baits. Sorex Limited. Not GLP, unpublished.	Y	Syngenta
Anon	**2.2/03**	2000	Component 11 Safety Data Sheet. Henry Bell & Co (Grantham) Limited. Not GLP, published.	N	
Anon	**2.2/04**	2001a	Component 3 Safety Data Sheet. Macfarlan Smith Limited. Not GLP, published.	N	
Anon	**2.2/05**	2001 b	Component 7 Safety Data Sheet. Lyondell Chemie Nederland, B.V. Not GLP, published.	N	
Anon	**2.2/06**	2002a	Component 2 Safety Data Sheet. Imerys Minerals Limited. Not GLP, published.	N	
Anon	**2.2/07**	2002 b	Component 8 Safety Data Sheet. Albion Colours Limited. Not GLP, published.	N	
Anon	**2.2/08**	2002c	Component 10 Safety Data Sheet. Crestchem Limited. Not GLP, published.	N	
Anon	**2.2/09**	2003a	Component 4 Safety Data Sheet. Stahl Industrial Colorants S.A.S. Not GLP, (published.	N	
Anon	**2.2/10**	2003 b	Component 6 Safety Data Sheet. Dow Chemical Company Limited. Not GLP, published.	N	

Author	Doc IIIB Section No/ Ref No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
Anon	**8/01**	2003c	Klerat Pellets Safety Data Sheet. Sorex Limited. Not GLP, published.	N	Syngenta
Anon	**2.2/11**	2004	Brodifacoum Technical Material (Component 1) Safety Data Sheet. Sorex Limited.Not GLP, published.	N	
Beavers JB and Fink R	**7.6.1/01**	1978a	Forty-Day Dietary LC50 - Bobwhite Quail, Technical Brodifacoum, Final Report. Wildlife International Ltd Report No: 123-127, December 1978. Not GLP, unpublished. [G2.1/04].	Y	Sygnenta
Beavers JB and Fink R	**7.6.1/02**	1978 b	Forty-Day Dietary LC50 - Mallard Ducks, Technical Brodifacoum, Final Report. Wildlife International Ltd Report No: 123-128, December 1978. Not GLP, unpublished. [G2.1/03].	Y	Syngenta
British Pest Control Association,	**5.4/01**	2001	Guidelines for the safe use of anticoagulant rodenticides by professional users. Not GLP, published. [PT-958-1225].	N	
Buckle A	**5.10.2/01**	1993a	Field efficacy trials of 'Klerat' Pellets against Norway rats infesting farm buildings in Surrey and Sussex. Trial sites: Lower Lodge Farm, Allfields Farm, Langhurst Outbuildings and Great Slifehurst. Zeneca Agrochemicals. Report number TMF/4460/B. Not GLP, unpublished. [H4.2/10].	Y	Syngenta
Buckle A	**5.10.2/05**	1993 b	Field efficacy trial of 'Klerat' Pellets against House mice in farm buildings on an agricultural holding on the Welsh border. Trial sites: Drenewydd Farm, Shropshire. Zeneca Agrochemicals. Report number TMF/4458/B. Not GLP, unpublished. [H4.2/09].	Y	Syngenta

Author	Doc IIIB Section No/ Ref No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
Buckle A	**5.10.2/07**	2004a	Field tests of brodifacoum: Rationale for using field trial results from the USA to support efficacy assessment for the Biocidal Products Directive (98/8/EC). Syngenta Limited. Not GLP, unpublished. [BR-959-0152].	Y	Syngenta
Buckle A	**5.11.2/01**	2004 b	Buckle A, 2004. Brodifacoum, Resistance to the Anticoagulants and Resistance Management. Syngenta Limited. Not GLP, unpublished. [BR-959-0149].	Y	Syngenta
Butcher SM	**3.7/02**	1994	'Klerat' (Brodifacoum): Quality Control Storage Stability Evaluation over Four Years. Zeneca Agrochemicals, Report series TMF4526B. Not GLP, unpublished.[B3.1/18].	Y	Syngenta
Chambers JG and Snowdon PJ	**6.6/01**	2004	Study to determine potential exposure to operators during simulated use of anticoagulant rodenticide baits. Synergy Laboratories Limited, Study Number SYN/1302, January 2003. GLP, unpublished. [BR-959-0151].	Y	Syngenta as part of CEFIC/EBPF Rodenticides Data Development Group (at 15th February this comprised of BASF, Bayer, Liphatec, Rentokil, Sorex and Syngenta check names against MoU)
Davies DJ	**6.4/01**	2003	Klerat Pellets: In Vitro Absorption Through Human Epidermis. Syngenta CTL, CTL/JV1757/REGULATORY/REPORT, 20th November 2003. GLP, unpublished. [BR-959-0131].	Y	Syngenta

Author	Doc IIIB Section No/ Ref No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
Getty C and Wilkinson W	**7.7.1.1/01**	1978	Brodifacoum: Toxicity of the liquid concentrate, pelleted bait and technical material to first instar Daphnia magna. ICI Plant Protection Division, Report number RJ0046B. Not GLP, unpublished. [G6.1/02].	Y	Syngenta
Hegdal P L and Blaskiewicz R W	**7.8.7.1/01**	1981	Hazards to barn owls associated with the use of Talon (brodifacoum bait) for controlling rats and house mice. US Fish and Wildlife Service, Denver Wildlife Research Centre. Report number RIC0619. Not GLP, unpublished. [G2.4/03].	Y	Syngenta
Johnson IR	**6.1.1/01**	1999	Brodifacoum 0.05g/kg RB formulation: Acute oral toxicity study in rats. Central Toxicology Laboratory, Report Number: CTL/P/6373. GLP, unpublished. [C3.1/16].	Y	Syngenta
Kaukeinen DE	**5.10.2/02**	1978a	Talon: Control of Norway rats in a poultry house by interior and exterior baiting. ICI Americas Inc Report number: TMUD1995/B (Revised). Not GLP, unpublished.	Y	Syngenta
Kaukeinen DE	**5.10.2/03**	1978 b	Kaukeinen DE, 1978. Talon: Control of Norway rats in a poultry using bait stations. ICI Americas Inc. Report number: TMUD2117/B. Not GLP, unpublished.	Y	Syngenta
Kaukeinen DE	**5.10.2/04**	1978c	Talon: Exterior control of Norway rats in an anticoagulant resistant area of Chicago by burrow baiting. ICI Americas Inc. Report number: TMUD2467/B. Not GLP, unpublished.	Y	Syngenta
Kaukeinen DE	**5.10.2/06**	1978 d	Kaukeinen DE, 1978. Talon: Interior control of Norway rats and House mice in a barn. ICI Americas Inc Report number: TMUD2113/B Not GLP, unpublished.	Y	Syngenta

Author	**Doc IIIB Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Kennedy SH	**7.8.7.2/03**	1985	Brodifacoum: Residues in Rat Livers from a 90-Day Feeding Study*****. ICI Plant Protection Division, Report No: M3923B. Not GLP, unpublished. [C2.3/04. (***** Batten P et al. (1984). 'Brodifacoum: 90-Day Feeding Study In Rats'. ICI Central Toxicology Laboratory, Report No: CTL/P/862. Not GLP, unpublished, [C2.3/03]).	Y	Syngenta
Lumsden AM	**3.7/01**	1999	Brodifacoum Pellets: Determination of long-term storage stability and physico-chemical characteristics. Safepharm Laboratories Limited. SPL Project number: 560/065, Zeneca WI No: 26916. GLP, unpublished.[B3.1/24].	Y	Syngenta
Morris K D and Akhavein A A	**7.8.1/02**	1978	Talon: Secondary toxicity of brodifacoum to foxes, (North Carolina). ICI Americas Inc. Report Series TMUD1998/B. Not GLP, unpublished. [G3.3/04].	Y	Syngenta
Morris K D and Kaukeinen D E	**7.8.1/01**	1978	Talon: Secondary toxicity of brodifacoum to dogs (Beagles), (North Carolina). ICI Americas Inc. Report Series TMUD1997/B. Not GLP, unpublished. [G3.3/03].	Y	Syngenta
Morris K D and Kaukeinen D E	**7.8.7.1/02**	1980	Talon: Rodent baiting sites of the Barn Owl Secondary hazard study. ICI Americas Inc. Report Series TMUD3335/B. Not GLP, unpublished. [G2.4/04].	Y	Syngenta

Author	**Doc IIIB Section No/ Ref No**	**Year**	**Title Source/ Company Report No. GLP or not (Un)published**	**Data Protection Claimed (yes/no)**	**Owner**
Parkinson GR	**6.1.2/01**	1977a	PP581 Pellet formulation JFU5072: Acute Toxicity and Local Irritation. ICI Central Toxicology Laboratory, Report Number: CTL/P/385. Not GLP, unpublished. [C3.1/02].	Y	Syngenta
Parkinson GR	**6.2/01;** **6.2/03**	1977 b	PP581 Pellet formulation JFU5072: Acute Toxicity and Local Irritation. ICI Central Toxicology Laboratory, Report Number: CTL/P/385. Not GLP, unpublished. [C3.1/02].	Y	Syngenta
Parkinson GR	**6.2/02**	1978	Brodifacoum pellet formulation JFU5072: Eye irritation. ICI Central Toxicology Laboratory, Report Number: CTL/P/398. Not GLP, unpublished. [C3.1/03].	Y	Syngenta
Ross D B, Roberts N L and Phillips C N K	**7.8.7.2/01 ; 7.6.1/03**	1979	Assessment of the palatability of 'Talon' pellets containing 0.005% (50ppm) brodifacoum to the Ring-necked Pheasant. Huntingdon Research Centre Report number CTL/C/813. Not GLP, unpublished. [G2.3/04].	Y	Syngenta
Ross D B, Roberts, N L and Phillips C N K	**7.6.1/04; 7.8.7.2/02**	1979	Assessment of the palatability of 'Talon' pellets containing 0.005% (50ppm) brodifacoum to the Bobwhite Quail. Huntingdon Research Centre Report number CTL/C/812. Not GLP, unpublished. [G2.3/05].	Y	Syngenta
Stevens JEB and Arnold DJ	**7.1/01**	1982	Using read-across to Difenacoum study F3.2/03: Difenacoum: Leaching of Formulated Material in Soil Columns. ICI Plant Protection Division Report No: RJ 0266B. Not GLP, unpublished. [F3.2/03]	Y	Sorex Limited

Author	Doc IIIB Section No/ Ref No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
Vernall AJ and Culleton CL	**6.1.3/02**	1978	PP581 Pellet (JFU5072), PP581 0.25% Liquid Concentrate (JFU5074): 4 hour Acute Inhalation in Rats. ICI Central Toxicology Laboratory, Report Number: CTL/P/406. Not GLP, unpublished. [C3.1/07].	Y	Syngenta
WHO	**5.7/01**	1995	Environmental Health Criteria 175 – Anticoagulant Rodenticides. International Programme on Chemical Safety. Not GLP, published. [PT-952-0842].	N	
WHO	**5.8/01**	1995	Environmental Health Criteria 175 – Anticoagulant Rodenticides. International Programme on Chemical Safety. Not GLP, published. [PT-952-0842].	N	

B.

List of studies for Biocidal Product

The studies for the biocidal product considered as confidential information are given in the Doc I_not public access_Appendix III.

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Brunton CFA, Macdonald DW and Buckle AP	B5.11	1993	Behavioural Resistance Towards Poison Baits in Brown Rats *Behavioural Processes*	N	Public domain
Chambers JG and Snowdon PJ	B6.6(ii)	2004	Study to Determine Potential Exposure to Operators During Simulated Use of Anticoagulant Rodenticide Baits Synergy Laboratories Ltd., Report No. SYN/1302	Y	Activa Pelgar Task Force

Author(s)	**Section No / Reference No**	**Year**	**Title.** **Source (where different from company)** **Company, Report No.** **GLP (where relevant) / (Un)Unpublished**	**Data Protection Claimed (Yes/No)**	**Owner**
Drake RM	B4.1	2005e	Method Validation for the Determination of Brodifacoum in Pellet and Wax Block Baits Chemex Environmental International Ltd., Report No. ENV6414 GLP, Unpublished	Y	Activa Pelgar Task Force
Fox JM and Mullee DM	B3.1.1 B3.1.2 B3.1.3 B3.6	2007	Determination of Physico-chemical Properties SafePharm Laboratories Ltd., Report No. 2254/0037 GLP, Unpublished	Y	Activa Pelgar Task Force
Gill JE, Kerins GM and MacNicoll AD	B5.11	1992	Inheritance of Low Grade Brodifacoum Resistance in the Norway Rat *Journal of Wildlife Management*, 56 (4), 809-816	N	Public domain
Gray A, Eadsforth CV and Dutton AJ	B7.8.7.1(3)	1994	The Toxicity of Three Second-Generation Rodenticides to Barn Owls, *Pesticide Science*, 42, 179-184	N	Public Domain
Greaves JH, Shepherd DS and Quy R	B5.11	1982	Field trials of Second-Generation Anticoagulants Against Difenacoum-Resistant Norway Rat Populations *Journal of Hygiene,* 89, 295-301	N	Public domain
Humphries RE, Meeham AP and Sibly RM	B5.11	1992	The Characteristics and History of Behavioural Resistance in Inner-city House Mice in the UK In: Borrecco JE and Marsh RE (eds.) *15th Vertebrate Pest Conference.* University of California, Davis, pp. 161-164	N	Public domain
Kaukeinen DE	B7.8.7.1(1)	198	A Review of the Secondary Poisoning Hazard to Wildlife from the Use of Anticoagulant Rodenticides Biological Research Centre, ICI Americas Inc. Published	N	Public Domain

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Lund M	B5.11	1984	Resistance to the Second-Generation Anticoagulant Rodenticides In: Clark DO (ed.) *11th Vertebrate Pest Conference*, University of California, Davis, pp. 89-94	N	Public domain
MacNicoll AD and Gill JE	B5.11	1987	The occurrence and significance of rodenticide resistance in the UK In : Lawson, T. J. (ed.) *Stored Products Pest Control. British Crop Protection Council Monograph No. 37*. BCPC Publications, Thorton Heath, UK, 89-95	N	Public domain
Misenheimer TM and Suttie JW	B5.11	1990	Warfarin Resistance in a Chicago Strain of Eats *Biochemical Pharmacology*, 40 (9), 2079-2084	N	Public domain
Newton I and Wyl	B7.8.7.1(2)	198	Effects of New Rodenticides on Owls, Institute of Terresterial Ecology, Monks Wood Experimental Station Abbots Ripton, Huntingdon, Cambs PE17 2LS Published	N	Public Domain
Quy RJ, Cowan DP, Haynes P, Inglis IR and Swinney T	B5.11	1992b	The Influence of Stored Food on the Effectiveness of Farm Rat Control British Crop Protection Conference, *Pests and Diseases*, 4A-3, pp. 291-300	N	Public domain
Quy RJ, Shepherd DS and Inglis IR	B5.11	1992a	Bait Avoidance and Effectiveness of Anticoagulant Rodenticides Against Warfarin- and Difenacoum-Resistant Populations of Norway Rats *Crop Protection*, 11, 14-20	N	Public domain
Thomas KT	B3.7	1999	Storage Stability and Physical-Chemical Characteristics of a 0.005% w/w Wax Block Formulation of Brodifacoum School of Pure and Applied Biology, University of Wales Cardiff, Report 96021261 GLP, Unpublished	Y	Activa Pelgar Task Force

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/No)	Owner
Confidential Data	B5.10.2(1)	1997b	Field Trial Report To Determine the Efficacy of Vertox Wax Block Bait, containing 0.005% Brodifacoum, for the Control of an Infestation of Warfarin Resistant Norway Rats (*Rattus norvegicus*) on an Agricultural Holding (Bradhouse Farm, Hengoed, Oswestry, Shropshire, UK) Confidential Data, Report RFT/97/1932 Unpublished	Y	Activa Pelgar Task Force
Confidential Data	B5.10.2(2)	1997c	Field Trial Report To Determine the Efficacy of Vertox Wax Block Bait, Containing 0.005% Brodfiacoum, for the Control of an Infestation of Warfarin Resistant House Mice (*Mus domesticus*) on an agricultural holding (Drenewydd Farm, Straw Loft, Whittington, Shropshire, UK) Confidential Data, Report No. RFT/97/1933 Unpublished	Y	Activa Pelgar Task Force
Wyllie I, Newton I and Freestone P	B7.8.7.1(4)	1990	Rodenticide Residues in British Barn Owls *Environmental Pollution*, 68, 101-117	N	Public Domain