

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

Substance Name:

BRODIFACOUM

EC Number: 259-980-5 (EINECS)

CAS Number: 56073-10-0

Index Number: 607-172-00-1

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	<i>Brodifacoum</i>
EC number:	259-980-5 (EINECS)
CAS number:	56073-10-0
Annex VI Index number:	
Degree of purity:	≥ 95.0% w/w (including both <i>cis</i> and <i>trans</i> isomers)
Impurities:	Confidential information (please refer to the separate confidential Annex to this CLH report). Based on the available information, none are of toxicological or environmental concern.

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	Directive 67/548/EEC (Dangerous Substances Directive; DSD)
Current entry in Annex VI, CLP Regulation	Acute Tox. 1; H310 Acute Tox. 2*; H300 STOT RE.1; H372 Aquatic Acute 1; H400 Aquatic Chronic 1; H410	T+; R27/28 T; R48/24/25 N; R50/53
Current proposal for consideration by RAC	Repr. 1B; H360D Acute Tox. 1; H300 Acute Tox. 1; H330 Skin Sens 1; H317	Repr. Cat. 2; R61 T+; R26 T; R48/23 Xi; R 43

	<p>Aquatic Acute 1; H400 Aquatic Chronic 1; H410 <i>M-factor Acute =10</i> <i>M-factor Chronic =10</i></p> <p><i>Suggested specific conc.limits:</i></p> <p>C ≥0,25%; Acute Tox1 H300 0.025%≤C<0.25%; Acute Tox 3 H301 0.0025%≤C<0.025% Acute Tox 4 H302</p> <p>C ≥0,25% Acute Tox 1H310 0.025%≤C<0.25%; Acute Tox 3 H311 0.0025%≤C<0.025% Acute Tox 4 H312</p> <p>C ≥0,25% Acute Tox 2 H330 0.025%≤C<0.25%; Acute Tox 3 H331 0.0025%≤C<0.025% Acute Tox 4 H332</p> <p>C ≥ 0.25 % STOT RE 1 H372 0,025 % ≤ C <0.25 % STOT RE 2 H373</p>	<p><i>Suggested specific conc.limits:</i></p> <p>C≥2.5%: T+, N; R26/27/28-48/23/24/25-50/53 0.25%≤C<2.5%: 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; 20/21/22</p>
<p>Resulting harmonised classification (future entry in Annex VI, CLP Regulation)</p>	<p>Repr. 1B; H360D Acute Tox. 1; H300 Acute Tox. 1; H310 Acute Tox. 1 H330 STOT RE.1; H372 Skin Sens 1; H317</p> <p>Aquatic Acute 1; H400 Aquatic Chronic 1; H410 <i>M-factor Acute =10</i> <i>M-factor chronic =10</i></p> <p><i>Suggested specific conc.limits:</i></p> <p>C ≥0,25%; Acute Tox1 H300 0.025%≤C<0.25%; Acute Tox 3 H301 0.0025%≤C<0.025% Acute Tox 4 H302</p> <p>C ≥0,25% Acute Tox 1H310 0.025%≤C<0.25%; Acute Tox 3 H311 0.0025%≤C<0.025% Acute Tox 4 H312</p> <p>C ≥0,25% Acute Tox 2 H330 0.025%≤C<0.25%; Acute Tox 3 H331 0.0025%≤C<0.025% Acute Tox 4 H332</p> <p>C ≥ 0.25 % STOT RE 1 H372 0,025 % ≤ C <0.25 % STOT RE 2 H373</p>	<p>Repr. Cat. 2; R61 T+; R26/27/28 T; R48/23/24/25 R43 N; R50/53</p> <p><i>Specific conc. limits:</i></p> <p>C≥2.5%: T+, N; R26/27/28-48/23/24/25-50/53 0.25%≤C<2.5%: 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; 20/21/22</p>

* Minimum classification for a category is indicated by the reference * in the column 'Classification' in Table 3.1, CLP.

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

The present proposal for harmonized Classification and Labelling applies to the substance *Brodifacoum* as proposed for inclusion in Annex I to Directive 98/8/EC, following evaluation of data from two different Applicants (Syngenta and Activa/PelGar, hereafter A and B, respectively) by RMS Italy.

Evaluation of technical equivalence of *Brodifacoum* produced by A and B has been also accomplished, in compliance with the TNsG on the assessment of technical equivalence of substances regulated under Directive 98/8/EC (adopted at the 29th CA Meeting, 28-30 May 2008). Both Tier I evaluation and Tier II evaluation have been carried out in order to assess the technical equivalence of the two *Brodifacoum* sources, which proved to be technically equivalent. Confidential information on isomeric composition and impurity profile is available separately for either Applicant in the confidential Annex to this CLH report based on the Confidential Annex to the Competent Authority Reports prepared by RMS Italy for the purpose of *Brodifacoum* inclusion in Annex I to Directive 98/8/EC.

Proposed classification based on Regulation EC 1272/2008 (CLP):

Physical/chemical properties: None.

Health hazards: Acute Tox. 1 H300; Acute Tox. 1 H310; Acute Tox. 1 H330;
STOT RE 1 H372
Repr. 1B H360D*
Skin Sens 1 H317

Environment: Aquatic acute 1 H400; Aquatic chronic 1 H410

Proposed classification based on Directive 67/548/EEC:

Physical/chemical properties: None.

Health hazards: Repr. Cat. 2; R61*
T+; R26/27/28
T; R48/23/24/25
Xi; R 43

Environment: N; R50/53

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

Proposed labelling based on Directive 67/548/EEC:

Symbol: T+; N
Risk phrases: R26/27/28, R43, R48/23/24/25, R61, R50/53
Safety phrases: S1/2, S36/37, S45, S60, S61

Proposed labelling 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

H400: Very toxic to aquatic life

H410: Very toxic to aquatic life with long lasting effects

The table 3 indicates the current harmonised classification in Annex VI CLP Regulation and the proposed classification.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification ¹⁾	Reason for no classification ²⁾
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral	H 300 Acute Tox 1	C \geq 0,25%; Acute Tox1 H300 0.025% \leq C<0.25%; Acute Tox 3 H301 0.0025% \leq C<0.025% Acute Tox 4 H302	H 300	
	Acute toxicity - dermal	H 310 Acute Tox 1	C \geq 0,25% Acute Tox 1H310 0.025% \leq C<0.25%; Acute Tox 3 H311 0.0025% \leq C<0.025% Acute Tox 4 H312	H 310	
	Acute toxicity – inhalation (Podwer)	H 330 Acute Tox 2	C \geq 0,25% Acute Tox 2 H330 0.025% \leq C<0.25%; Acute Tox 3 H331 0.0025% \leq C<0.025% Acute Tox 4 H332		
3.2.	Skin corrosion / irritation				
3.3.	Serious eye damage / eye irritation				
3.4.	Respiratory sensitisation				
3.4.	Skin sensitisation	H 317			
3.5.	Germ cell mutagenicity				
3.6.	Carcinogenicity				
3.7.	Reproductive toxicity	H 360			

3.8.	Specific target organ toxicity –single exposure				
3.9.	Specific target organ toxicity –repeated exposure	STOT RE H 372	$C \geq 0.25\%$ STOT RE 1 H372 $0,025\% \leq C < 0.25\%$ STOT RE 2 H373	STOT RE H 372	
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment	H 400 H410	<i>M-factor Acute =10</i> <i>M-factor Chronic =10</i>	H 400 H 410	
5.1.	Hazardous to the ozone layer		//		

¹⁾Including specific concentration limits (SCLs) and M-factors

²⁾Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Danger
 Symbol: GHS06, GHS08, GHS07, GHS09

Hazard statements: 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
 H400: Very toxic to aquatic life
 H410: Very toxic to aquatic life with long lasting effects

Precautionary statements: As precautionary statements are not included in Annex VI of Regulation EC 1272/2008, no proposal is made.

Proposed notes assigned to an entry: On the 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) and Regulation EC 1272/2008.

The currently proposed classification according to the DSD criteria and CLP criteria, except Acute Tox. 2 H 300 (CLP); R 26 (DSD) Acute Tox. 1 H330 (CLP) R 43 (DSD) Skin Sens 1 H 317 (CLP), R 48/23 (DSD) and Repr. Cat.2 R61 (DSD); H 360D (CLP).

The proposed have been discussed and agreed by the EU Technical Committee of Classification and Labelling (TC C&L) of Dangerous Substances at their meeting in May 2007.

The proposed specific concentration limits according to Directive 67/548/EEC have been discussed under DSD in the biocide program under directive 98/8/EC.

For skin sensitisation and for toxicity to reproduction, the general concentration limit was proposed to be applied.

Specific concentration limits (SCL_s) for acute and repeated dose toxicity were not agreed, although the method to be used to set SCL_s for acute toxicity (DSD) of any of the 2nd generation anticoagulants under discussion was agreed at the TC C&L May 2007 meeting.

Newly SCL_s calculated according to regulation EC 1272/2008 using the formulae presented in the guidance on CLP.

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

The classification for human health effects is still under discussion (since May 2007). A provisional classification with R61 was decided in November 2006 by the TC C&L, 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.

Note: Specific concentration limits (SCL's) for acute and repeated dose toxicity and for environment were agreed by TC C&L (Technical Committee on Classification and Labelling) in May 2007. For toxicity to reproduction, the general concentration limit (Dir 1999/45/EC) of 0.5% was proposed to be applied; the general concentration limit is included here in order to maintain a common manner of expression with documents produced under biocides legislation.

Proposed specific concentration limits based on Regulation EC 1272/2008:

$C \geq 0.1\%$ STOT RE 1

$0.01\% \leq C < 0.1\%$ STOT RE 2

As setting specific concentration limits for acute toxicity is not applicable according to CLP regulation, no values are set.

As regards classification concerning environmental endpoints, R phrases will not be used any longer under CLP but the corresponding information is to be communicated using M factors.

Rationale for specific concentration limits according to Regulation EC 1272/2008:

$$SCL_{Cat1} = \frac{ED}{GV1} \cdot 100\% = \frac{0.01 \text{ mg / kg bw / day}}{10 \text{ mg / kg bw / day}} \cdot 100\% = 0.1\%$$

$$SCL_{Cat2} = \frac{ED}{GV2} \cdot 100\% = \frac{0.01 \text{ mg / kg bw / day}}{100 \text{ mg / kg bw / day}} \cdot 100\% = 0.01\%$$

ED - Effective Dose: LOAEL 0.01 mg/kg bw/day based on threefold-fourfold increase in prothrombin time after oral application (dog, 42-day range finding study)

GV1 - Guidance Value 1: 10 mg/kg bw/day

GV2 - Guidance Value 2: 100 mg/kg bw/day

A consensus between limit values

- 1) originating from discussions under Directive 67/548/EEC and
- 2) calculated according to CLP formulae has not been found. Getting the numerical values in harmony does not seem feasible.

The conclusions from the Directive and the Regulation also do not match.

- According to SCL's agreed on under Directive 67/548/EEC, a typical product containing 50 ppm or 75 ppm (0.0050% or 0.0075%) of difenacoum will be classified as Xn; R20/21/22 and labelled with the "Harmful" symbol as the concentration falls in the concentration range $0.0025\% \leq C < 0.025\%$.
- According to the limit values calculated according to Regulation EC 1272/2008, the respective concentrations do not trigger any labelling requirement since the concentrations are lower than the potential SCL of 0.01% for category 2 classification of STOT, repeated exposure.

From a hazard communication point of view, the existence of a warning label on the packagings of products containing *brodifacoum* is extremely important. The preparations containing *brodifacoum* are intended to kill rodents and are potentially fatal to humans. *Brodifacoum* and the other second generation anticoagulants are intended to kill after a single dosing and it can be expected that the ingestion of even only one bait can cause a casualty in the human population. This hazard should not be overlooked.

The administrator should strive for a consistent set of specific concentration limits and one trigger for the labelling obligation. However, determining consistent limit values seems difficult.

On these grounds, setting specific concentration limits seems not to be the most effective way of protecting the public in this case. Instead, a novel 'Special rule for labelling and packaging of certain substances and mixtures' stating "Rodenticide for pest control. Keep out of reach of children." is hereby proposed. This should be introduced in Annex II to Regulation EC 1272/2008 for use in rodenticide packagings where applicable.

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification ¹⁾	Reason for no classification ²⁾
Explosiveness				
Oxidising properties				
Flammability				
Other physico-chemical properties <i>[Add rows when relevant]</i>				
Thermal stability				
Acute toxicity	T+R26/27/28	C ≥ 0.25% T+ R26/27/28 0.025% ≤ C < 0.25% T R23/24/25 0.0025% ≤ C < 0.025% Xn R20/21/22	T+ R 27/28	
Acute toxicity – irreversible damage after single exposure				
Repeated dose toxicity	T+R 48/23/24/25	C ≥ 0.25% T 48/23/24/25 0.025% ≤ C < 0.25% Xn 48/20/21/22	T 48/24/25	
Irritation / Corrosion				
Sensitisation	Xi R 43			
Carcinogenicity				
Mutagenicity – Genetic toxicity				
Toxicity to reproduction – fertility	T R 61			
Toxicity to reproduction – development				
Toxicity to reproduction – breastfed babies. Effects on or via lactation				
Environment	N R 50-53	C ≥ 2.5% N R50/53 0.25 ≤ C < 2.5% N R51/53 0.025% ≤ C < 0.25% R52/53	N R 50-53	

¹⁾ Including SCLs²⁾ Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Very Toxic; Dangerous for the environmental
R-phrases: R 26/27/28-48/23/24/25-43-61-50-53
S-phrases: S 1 /2-36/37-45-60-61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

2.2 Short summary of the scientific justification for the CLH proposal

On the 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) and Regulation EC 1272/2008.

The currently proposed classification according to the DSD criteria and CLP criteria, except Acute Tox. 2 H 300 (CLP); R 26 (DSD) Acute Tox. 1 H330 (CLP) R 43 (DSD) Skin Sens 1 H 317 (CLP), R 48/23 (DSD) and Repr. Cat.2 R61 (DSD); H 360D (CLP). The proposed have been discussed and agreed by the EU Technical Committee of Classification and Labelling (TC C&L) of Dangerous Substances at their meeting in May 2007.

The proposed specific concentration limits according to Directive 67/548/EEC have been discussed under DSD in the biocide program under directive 98/8/EC.

For skin sensitisation and for toxicity to reproduction, the general concentration limit was proposed to be applied.

Specific concentration limits (SCL_s) for acute and repeated dose toxicity were not agreed, although the method to be used to set SCL_s for acute toxicity (DSD) of any of the 2nd generation anticoagulants under discussion was agreed at the TC C&L May 2007 meeting.

Newly SCL_s calculated according to regulation EC 1272/2008 using the formulae presented in the guidance on CLP.

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

The classification for human health effects is still under discussion (since May 2007). A provisional classification with R61 was decided in November 2006 by the TC C&L, 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 provisionally classification for reprotoxicity was not confirmed as the TC C&L decided to await further results from studies on anticoagulant rodenticides, before finalising the discussion on reprotoxicity. Specific concentration limits for *Brodifacoum* were agreed upon as proposed.

2.3 Current harmonised classification and labelling

Repr. Cat. 2; R61;T+; R26; T; R48/23; R43; Repr. Cat. 2; R61; N; R50/53

Suggested specific conc.limits:

$C \geq 2.5\%$: T+, N; R26/27/28-48/23/24/25-50/53

$0.25\% \leq C < 2.5\%$: T+, N; R26/27/28-48/23/24/25-51/53

$0.025\% \leq C < 0.25\%$: T; R23/24/25-48/20/21/22-52/53

$0.0025\% \leq C < 0.025\%$: Xn; 20/21/22

Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

T+; R27/28T; R48/24/25; N; R50/53

2.3.1 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

2.4 Current self-classification and labelling

UnKnown

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

UnKnown.

2.4.2 Current self-classification and labelling based on DSD criteria

No

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

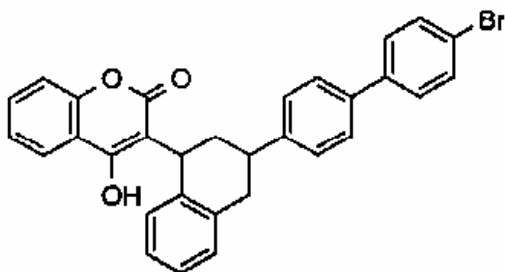
Table 5: Substance identity

EC number:	
EC name:	4-hydroxy-3-(3-(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl)coumarin (EINECS)
CAS number (EC inventory):	
CAS number:	56073-10-0
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-
IUPAC name:	3-[3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin
CLP Annex VI Index number:	607-172-00-1
Molecular formula:	C ₃₁ H ₂₃ BrO ₃
Molecular weight range:	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)

Structural formula:



Brodifacoum consists of a mixture of *cis/trans*-isomers. Full details on the isomeric composition are confidential information and have been made available in a separate confidential Annex to this CLH report (based on the Confidential Annex to either Competent Authority Report prepared by RMS Italy for the purpose of *Brodifacoum* inclusion in Annex I to Directive 98/8/EC).

According to the isomeric composition of *Brodifacoum* as reported therein, following the terminology under REACH and CLP *Brodifacoum* should be considered as a multi-constituent substance, since both the *cis*-isomer and the *trans*-isomer fall in the range 10 up to 80% w/w. Consequently, *Brodifacoum* should be named as a reaction mass of the two main constituents as described under isomeric composition below. Nevertheless, part 1.1.1.4 of Annex VI of EC 1272/2008 (CLP) states that whenever possible plant protection products and biocides are designated by their ISO names. As a result, in this proposal preference is given to the use of the ISO name *Brodifacoum*, along with *4-hydroxy-3-(3-(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl)coumarin* as the International Chemical Identifier for inclusion in Annex VI to EC 1272/2008.

1.2 Composition of the substance

The present proposal for harmonized Classification and Labelling applies to Brodifacoum as proposed for inclusion in Annex I to Directive 98/8/EC, following evaluation of data from two different Applicants (Syngenta and Activa/PelGar, hereafter A and B, respectively) by RMS Italy.

Evaluation of technical equivalence of Brodifacoum produced by A and B has been also accomplished, in compliance with the TNsG on the assessment of technical equivalence of substances regulated under Directive 98/8/EC (adopted at the 29th CA Meeting, 28-30 May 2008). Both Tier I evaluation and Tier II evaluation have been carried out in order to assess the technical equivalence of the two Brodifacoum sources, which proved to be technically equivalent.

Confidential information on isomeric composition and impurity profile is available separately for either Applicant in the confidential Annex to this CLH report based on the Confidential Annex to either Competent Authority Report prepared by RMS Italy for the purpose of Brodifacoum inclusion in Annex I to Directive 98/8/EC.

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Brodifacoum EC n°259-980-5	>= 95% (w/w)		

Current Annex VI entry:

Purity/Impurities/Additives

The minimum purity of 95% w/w is supported by the analytical data (5-batch analysis) and has been used in most toxicity and ecotoxicity tests presented by Applicant A for the purpose of *Brodifacoum* inclusion in Annex I to Directive 98/8/EC. A higher minimum purity of 99.2% w/w is supported by the analytical data (5-batch analysis) and has been used in most toxicity and ecotoxicity studies available in the *Brodifacoum* Dossier of Applicant B for the same purpose. Both specifications have been accepted by RMS Italy and, therefore, the minimum purity of 95.0% w/w shall apply for *Brodifacoum*.

No upper limit has been specified by either Applicant, but when results from the 5-batch analyses are treated statistically and expressed as mean \pm 3xSD, a maximum purity of 100% shall apply for *Brodifacoum*.

Brodifacoum does not contain impurities that would be of toxicological or environmental concern. *Brodifacoum* does not contain additives, either. Full details on impurities and their content are regarded as confidential and can be found in the confidential Annex to this CLH report based on the Confidential Annex of either Competent Authority Report prepared by RMS Italy for the purpose of *Brodifacoum* inclusion in Annex I to Directive 98/8/EC.

Table 7: Impurities (non-confidential information)

Not relevant for the classification.

Current Annex VI entry:

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

Current Annex VI entry:

1.2.1 Composition of test material

1.3 Physico-chemical properties

The data summarized below are obtained from the Competent Authority Reports prepared by RMS Italy for the purpose of Brodifacoum inclusion in Annex I to Directive 98/8/EC, following evaluation of the physico-chemical studies submitted from both Applicant A and Applicant B. Values in many endpoints are highly or reasonably similar and the reasons for deviations can be usually regarded as experimental.

Brodifacoum does not exhibit hazardous physico-chemical properties. Brodifacoum is thermally stable. Brodifacoum is not highly flammable and it shows no self-ignition below the melting point. Brodifacoum has not oxidizing or explosive properties, either. Brodifacoum does not show signs of reaction with container materials.

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa (Purity)	A: Fine powdery solid; colour: cream (92.5% w/w) B: White to off-white fine powder (99.7% w/w)	IUCLID 5 section: 4.1	
Melting/freezing point (purity) [method]	A: 232 °C with decomposition (98.7% w/w) [capillary method] B: Brodifacoum was observed to darken and decompose at 235.8 °C (100% w/w) [capillary method]	IUCLID 5 section: 4.2	
Boiling point	A: Not applicable B: Not determinable	IUCLID 5 section: 4.3	
Relative density (purity) [method]	A: 1.42 g/cm ³ (density) at 25 °C (92.5% w/w) [pycnometer method] B: D204 = 1.530 (>99% w/w) [pycnometer method]	IUCLID 5 section: 4.4 density	
Vapour pressure (purity) [method]	A: << 10E-6 Pa (20 °C) (98.7% w/w) [gas saturation method] B: 2.6E-22 Pa at 20°C 1.9E-21 Pa at 25°C (99.7% w/w) [estimated by the VP]	IUCLID 5 section: 4.6	

[method]	curve – experimental data by VP balance method]		
Surface tension	A: Not applicable (solubility < 1 mg/l) B: Not applicable (solubility < 1 mg/l)	IUCLID 5 section: 4.10	
Water solubility (purity) [method] (purity) [method]	A: pH 5.2: 3.83E-3 mg/l at 20 °C pH 7.4: 0.24 mg/l at 20 °C pH 9.3: 10 mg/l at 20 °C (98.7% w/w) [generator column method] B: pH 5: ≤ 3.17E-6 g/l at 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]	IUCLID 5 section: 4.8	
Partition coefficient n-octanol/water	A: 8.5 [calculated by clogp Algorithm of Hansch and Leo] 6.12 [estimated from measured Koc] B: 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)	IUCLID 5 section: 4.7 partition coefficient	

(purity) [method]	(99.7% w/w) [HPLC method]		
Flash point	A: Not applicable (solid) B: Not applicable (solid)	IUCLID 5 section: 4.11	
Flammability (purity) [method] (purity) [method]	A: Not highly flammable (>99%) [EC A.10 - preliminary test] B: Not highly flammable (>99%) [EC A.10 - preliminary test]	IUCLID 5 section: 4.13	
Explosive properties	A: Not explosive on the basis of the structural formula and oxygen balance B: Not explosive based on structure and experience in use	IUCLID 5 section: 4.14	
Self-ignition temperature (purity) [method]	A: No data B: No auto-ignition was observed below the melting temperature (99.7%) [EC A.16]	IUCLID 5 section: 4.12	
Oxidising properties	A: Not oxidising on the basis of the structural formula B: Not oxidising based on structure and experience in use	IUCLID 5 section: 4.15	
Granulometry	A: No data	IUCLID 5 section: 4.5	

(purity) [method]	B: Proportion of test material having an inhalable particle size: less than 100 µm = 14.8% (sieve); less than 10.0 µm = 0.998% (cascade impactor); less than 5.5 µm = 8.14E-02 % (cascade impactor) (*) (99.7%) [OECD 110]		
Stability in organic solvents and identity of relevant degradation products	A: Not required B: --	IUCLID 5 section: 4.17	
Dissociation constant	A: 4.5 [PETE database calculation/estimation] B: 4.50 [QSAR estimation by ACD/I-Lab Web service]	IUCLID 5 section: 4.21	
Viscosity	A: Not applicable (solid) B: Not applicable (solid)	IUCLID 5 section: 4.22	

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for the classification.

2.2 Identified uses

Not relevant for the classification.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
//			
//			
//			
//			

3.1 *[Insert hazard class when relevant and repeat section if needed]*

3.1.1 Summary and discussion of :

- *Explosivity*: based on structural formula and experience in use, *Brodifacoum* does not show explosive properties. No classification is required;

- *Flammability*: *Brodifacoum* has proved to be not highly flammable. No auto-ignition was observed below the melting temperature. No classification is required.

- *Oxidising potential*: based on structural formula and experience in use, *Brodifacoum* does not show explosive properties. No classification is required.

3.1.2 Comparison with criteria

No data.

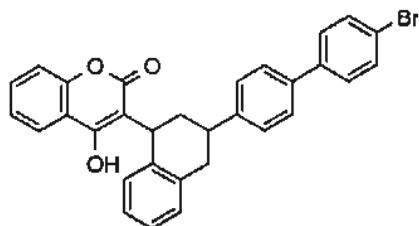
3.1.3 Conclusions on classification and labelling

Brodifacoum does not exhibit hazardous physico-chemical properties. *Brodifacoum* is thermally stable. *Brodifacoum* is not highly flammable and it shows no self-ignition below the melting point. *Brodifacoum* has not oxidizing or explosive properties, either. *Brodifacoum* shows no signs of reaction with container materials.

4 HUMAN HEALTH HAZARD ASSESSMENT

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 rodenticides 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.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Oral Absorption

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.

To support the experimental data on *Brodifacoum* itself, read across to data from some related 2nd generation anticoagulants (i.e. *Difenacoum*, *Flocoumafén*) can be also applied, based on bridging studies demonstrating the similarity in physico-chemical and toxicological properties of these class

of substances sharing the same mode of action. 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.

Inhalation Absorption

For the inhalation route no data are available. Based on the physico-chemical characteristic of the compound, a 100% absorption is considered.

Dermal Absorption

As long as dermal absorption is concerned, *Brodifacoum* is expected to be slowly absorbed through the skin, due to the lipophilicity of the molecule, allowing passive transport through the membrane. *Brodifacoum* dermal absorption was assessed by using a formulation (ready-for-use pellet bait) containing 0.0048% *Brodifacoum* w/w tested *in vitro* on human skin samples. In the study 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 corresponding to the LOQ in the receptor fluid and in the epidermis after tape stripping, which can be considered as systemically available material. This value can be considered as a worst case, also taking into account that the exposure period exceeds the usual time (*i.e.* 8 hours) of professional handling.

To support these data and to cover the risk characterization depending on the type of formulation (including ready-for-use pellet bait or grains and wax block bait or paste), 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 characterization depending on the type of formulation, that is 3% (pellets and grains) or 0.047% (wax block bait).

On the basis of the available study and reading across from data on other 2nd generation anticoagulant rodenticides, two different values could be used for risk characterization, depending on the type of formulation, that is 5% (pellets and grains) or 0.047% (wax block bait).

Distribution

After oral absorption *Brodifacoum* is widely distributed and bioaccumulates in the liver with minor concentrations in the kidney. Indeed, 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.

Metabolism

Brodifacoum was only partially metabolized: 31.3% and 19.6% of the residues in the carcass and liver, respectively, was unchanged *Brodifacoum*. Two metabolites more polar than the parent compound were detected in the bile, the major one being identified as the glucuronide. The toxicologically relevant chemical species is the parent compound.

Excretion

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 \cong 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.

Potential for accumulation

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 (half-life in the liver was calculated in the range of 282–350 days).

Analyses of the rat livers from the 90 day feeding study, indicate a non-linear accumulation of *Brodifacoum* vs. dose and time.

4.1.2 Human information

Not evaluated in this dossier.

4.1.3 Summary and discussion on toxicokinetics

Summary of toxicokinetic parameters of Brodifacoum in rats

Absorption	Oral: Almost complete oral absorption (>75-100%) Inhalation: No data are available. 100% assumed as default value Dermal: 5% pellets and grains – 0.05% wax block bait.
Distribution	Widely distributed. High potential for bioaccumulation in the liver
Metabolism	Limited (parent compound as toxicologically relevant compound)
Excretion	Very slow (11 – 14% equally distributed urine and faeces in 10 days)

An almost complete oral absorption (range >75-100%) can be considered, on the basis of the amount of radioactivity recovered in the excreta and retained in the tissues and in comparison with structurally and toxicologically similar 2nd generation anticoagulants. 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.

As long as dermal absorption is concerned, on the basis of the available study and reading across from data on other 2nd generation anticoagulant rodenticides, two different values could be used for risk characterization depending on the type of formulation, that is 5% (pellets and grains) or 0.047% (wax block bait).

4.2 ACUTE TOXICITY

Table 11 Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Oral OECD TG 423	< 5 mg/kg bw (female)		Szakonyi (2004) Doc IIA Activa Pelgar
Oral No guideline reported Similar to TG401	0.40 mg/kg bw (male)		Hadler (1974) Doc III A Section 6.1.1a Syngenta
Inhalation OECD TG 403	3.05 mg/m ³ (female)		Parr-Dobrzanski (1993) Doc III A Section 6.1.3 Syngenta
Dermal OECD 402	7.48 mg/kg bw (female)		Szakonyi (2004) Doc III A Section 6.1.2a Activa Pelgar
Dermal OECD 402	3.16 mg/kg bw (female)		McCall and Leah (1991) Doc III A Section 6.1.2 Syngenta

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Acute oral toxicity studies, considered as key studies for classification purposes, are summarized in table 4.2.1.1 and 11.

In the rat study (Szakonyi, 2004) the acute oral LD₅₀ value of *Brodifacoum* (technical grade) proved to be below 5 mg/kg body weight, with clinical signs such as decreased activity, lateral position, decreased righting reflex, decreased grip and limb tone, paleness, piloerection, dyspnoea and bleeding from the nose observed starting from five days after treatment. One rat died immediately after onset of symptoms; one died two days after the first symptoms. The third one died without any clinical signs. At necropsy effects were consistent with the well-known anticoagulant effect. In the mouse study (Hadler, 1974) all the animals dosed with 0.2 mg/kg or less survived until the end of the study. In the top three dose groups (0.5, 1.0 and 2.0 mg/kg) deaths occurred between days 4 and 12. Necropsy of mice found dead during the study showed massive internal hemorrhage, in line with the anticoagulant action of *Brodifacoum*. The oral LD₅₀ in the male mouse was determined to be 0.4 mg/kg.

Table 4.2.1-1: Oral acute toxicity

Route	Method Guideline	Species	Dose levels duration of exposure	Value LD ₅₀	Reference
Oral	OECD TG 423	Rat	5 mg/kg	< 5 mg/kg bw (female)	Szakonyi (2004) Doc III Section 6.1.1a A Activa Pelgar
Oral	No guideline reported Similar to TG401	Mice	0.1, 0.2, 0.5, 1.0, and 2.0 mg/kg	0.40 mg/kg bw (male)	Hadler (1974) Doc IIIA Section 6.1.1 Syngenta

4.2.1.2 Acute toxicity: inhalation

One acute inhalation toxicity study with rats is available and is listed in table 4.2.1.2 and 11.

In the Parr-Dobrzanski study (1993) during exposure and immediately after exposure, clinical abnormalities generally associated with restraint (stains around the snout, wet fur, hunched posture and piloerection) were seen in all groups. Symptoms of toxicity included subcutaneous hemorrhage of the head and thorax, signs of bleeding from hind limbs and snout, decreased activity, increased respiratory depth, reduced respiratory rate and shaking. A small initial bodyweight loss was seen in animals from all exposure groups, probably due to the use of restraint during exposure. All surviving animals gained weight throughout the remainder of the study. The delayed clinical effects, post-mortem findings and late deaths are all indicative of hemorrhage which are typical of exposure to anticoagulant rodenticides. The lack of any significant clinical effects and the lack of gross abnormalities at necropsy in those animals surviving to termination, demonstrates a rapid recovery from exposure to non-lethal concentrations of the test material. On other end-points the principle of read-across has been applied. For this reason, data obtained with structurally related compounds with the same mechanism of action (*i.e.* 2nd generation anticoagulants) were considered. On this basis it is expected that the substance is highly toxic after inhalation.

Table 4.2.1-2: Inhalation acute toxicity

Route	Method/ Guideline	Species	Exposure Concentrations (mg/m ³)	Duration of Exposure	Value LC ₅₀	Reference
Inhalation	OECD TG 403	Rat	0.82, 1.88, 4.96	4 hours (nose only)	3.05 mg/m ³ (female)	Parr- Dobrzanski (1993) Doc IIIA Section 6.1.3 Syngenta

4.2.1.3 Acute toxicity: dermal

Two acute dermal toxicity studies with rats are available and are summarized in table 4.2.1.3 and 11.

In the rat study by Szakonyi (2004) the dermal LD₅₀ is 7.5 mg/kg bw. No dermal changes were found after 24 hours exposure. Clinical symptoms (decreased activity, tremor, lateral position, squatting position, paleness, dyspnoea, piloerection, sanguineous fur around the eyes) appeared 5 and 6 days after treatment in one animal treated at 6 mg/kg group and in all animals of 18 mg/kg group. Mortality occurred between days 5 and 9. In animals found dead, bleeding and hematoma in various organs and tissues, clay colored liver were observed.

In a second study (McCall and Leah, 1991) the dermal LD₅₀ is determined to be 3.16 mg/kg bw. Animals treated with a single dermal application of 1 mg/kg showed no significant signs of toxicity or skin irritation considered to be compound related. All mortalities in higher dosage groups occurred between days 5–11. The animals found dead or sacrificed during the study showed signs of extreme toxicity (pallor, bleeding/bruising, breathing abnormalities) immediately prior to death. There were no signs of skin irritation in any of the animals and no significant signs of toxicity in the surviving male. Post-mortem examination revealed internal hemorrhaging in the animals which died or were killed *in extremis*.

Table 4.2.1-3 Dermal acute toxicity

Route	Method Guideline	Species	Dose levels duration of exposure (mg/kg)	Value LD ₅₀	Reference
Dermal	OECD 402	Rat	2, 6, 18	7.48 mg/kg bw (female)	Szakonyi (2004) Doc III A Section 6.1.2a Activa Pelgar
Dermal	OECD 402	Rat	1, 10, 500	3.16 mg/kg bw (female)	McCall and Leah (1991) Doc IIIA Section 6.1.4

					Syngenta
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4.2.1.4 Acute toxicity: other routes

Neurotoxicity

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

4.2.4 Human information

4.2.3 Summary and discussion of acute toxicity

On the basis of the available information *Brodifacoum* is very toxic after oral administration and also via the dermal and inhalation routes. Death was the result of internal haemorrhage.

Brodifacoum was already evaluated at the written procedure for Plant Protection Products in September 2004. It was the agreed to classify Brodifacoum with T+; R 26/27/28. This classification was confirmed at the May 2007 Meeting.

4.2.4 Comparison with criteria

4.2.5 Conclusions on classification and labelling

Classification proposals according to Directive 67/548/EEC: *Brodifacoum* is very toxic after oral administration ($0.4 \text{ mg/kg bw} < \text{LD}_{50} \leq 5 \text{ mg/kg bw}$) and also via the dermal ($3.16 \text{ mg/kg bw} < \text{LD}_{50} \leq 7.5 \text{ mg/kg bw}$) and inhalation routes ($\text{LC}_{50} = 3.05 \text{ mg/m}^3$). 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. (Indication of danger: Very Toxic; T+: R-phrases: R 26/27/28).

Classification proposals according to Regulation EC 1272/2008: Acute Tox. 1 H330; Acute Tox. 1 H310; Acute Tox. 1 H300.

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

4.3.2 Comparison with criteria

4.3.3 Conclusions on classification and labelling

4.4 Irritation

4.4.1 Skin irritation

Table12: Skin Irritation

Species	Method	Average score 24, 48, 72 h		Reversibility yes/no	Result	Reference Doc III
		Erythema	Oedema			
Rabbit	EPA GL 5 13 77	0.41 (0.5)	0.17 (0.33)	yes	Non irritant according to the score	Parkinson (1978) Doc IIIA Section 6.1.4 Syngenta
Rabbit	OECD 404	0	0	Not relevant	Not irritant	Stahl (2004) Doc IIIA Section 6.1.4 (1) Activa Pelgar

4.4.1.1 Non-human information

4.4.1.2 Human information

4.4.1.3 Summary and discussion of skin irritation

Two skin irritation studies with rats are available and are reported in table 12.

In the Parkinson study (1978) slight signs of irritation were observed at all but one of the application sites at the end of the 24 hour exposure period. All the sites affected showed slight erythema, while two of the intact areas had slight oedema and three of the abraded areas had slight or moderate oedema. The mean skin irritation scores (24 and 72 hours) after application of the test substance *Brodifacoum*, were 0.41 and 0.50 for erythema (intact and abraded skin respectively), and 0.17 and 0.33 for oedema (intact and abraded skin respectively). *Brodifacoum* was concluded to be a slight irritant to rabbit skin, but no classification is required according to the score.

In the rabbit study by Sthal (2004) no primary irritation signs, such as erythema and oedema, occurred during the observation period: therefore an average score of zero was given at each time period. During the study the general state and behaviour of animals were normal. According to EEC directive 2001/59/EEC, the test item has not been classified as irritating for the skin.

4.4.1.4 Comparison with criteria

4.4.1.5 Conclusions on classification and labelling

No classification.

4.4.2 Eye irritation

Table 13 Summary table of relevant eye irritation studies

Species	Method	Average Score				Reversibility yes/no	Result	Reference Doc III
		Cornea	Iris	Conjunctiva				
				Redness	Chemosis			
Rabbit	EPA GL 5 13 77	0/0		0/0	0.67/0	Yes	Non irritant according to the score	Parkinson (1978) Doc IIIA Section 6.1.4 Syngenta
Rabbit	OECD 405	0/0	0/0	0/0	0/0	Yes	Not irritant	Hirka (2004) Doc III A Section 6.1.4 (2) Activa Pelgar

4.4.2.1 Non-human information

4.4.2.2 Human information

4.4.2.3 Summary and discussion of eye irritation

Two eye irritation toxicity studies with rats are available and are reported in table 13.

In the Parkinson study (1978) the mean total score according to the EPA guideline (max 110) for unwashed eyes was 8 (1 – 2 h), 2 (24 h), 1 (48 h) and 1 (72 h) and the mean total score for washed eyes was 6 (1 – 2 h), 2 (24 h), 1 (48 h) and 1 (72 h). All eyes (both washed and unwashed) appeared normal at the end of the seven day observation period. *Brodifacoum* was concluded to be a very mild irritant to both washed and unwashed rabbit eyes, but no classification is required according to the score.

In the study by Hirka (2004), after a single application of the test item into the eyes of the rabbit slight redness and slight to moderate increase discharge excretion were observed in the animals. Chemosis, corneal and iris alteration were not found during the study. 24 hours after treatment every animal was symptom-free. 72 hours after the treatment the study was terminated, since no primary irritation symptoms occurred. The observed symptoms can be evaluated as fully reversible alteration and the test item was concluded to be not irritating to the rabbit eyes.

4.4.2.4 Comparison with criteria**4.4.2.5 Conclusions on classification and labelling**

Brodifacoum does not fulfil the EU criteria for classification as a skin or eye irritant. No classification.

4.4.3 Respiratory tract irritation**4.4.3.1 Non-human information****4.4.3.2 Human information****4.4.3.3 Summary and discussion of respiratory tract irritation****4.4.3.4 Comparison with criteria****4.4.3.5 Conclusions on classification and labelling****4.5 Corrosivity****4.5.1 Non-human information****4.5.2 Human information****4.5.3 Summary and discussion of corrosivity****4.5.4 Comparison with criteria****4.5.5 Conclusions on classification and labelling****4.6 Sensitisation****4.6.1 Skin sensitisation****Table 4.6-1: Skin sensitisation**

Species	Method	Number of animals sensitized/total number of animals or Stimulation Index	Result	Reference Doc III
Guinea pig	OECD 406 (Test of Ritz and Buehler)	20/30	Skin sensitizer	Robinson (1996) Doc IIIA

				Section 6.1.5 Syngenta
Guinea pig	OECD 406 (Maximisation test, Magnusson & Kligman)	1/20 Historical positive control: 2,4-DNCB	Not sensitizer (test item : 0.25% of the active substance)	Manciaux(1996) Doc III A Section 6.1.5 (1) Activa Pelgar
Mouse	OECD 429 Local Lymph Node Assay	Stimulation Index less than 3 in all 4 groups	Not a skin sensitizer	Sanders (2006) Doc III A Section 6.1.5 (2) ActivaPelgar

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Guinea pig OECD 406 (Test of Ritz and Buehler)	Skin sensitizer		Robinson (1996) Doc IIIA Section 6.1.5 Syngenta
Guinea pig OECD 406 (Maximisation test, Magnusson & Kligman)	Not sensitizer (test item : 0.25% of the active substance)		Manciaux (1996) Doc III A Section 6.1.5 (1) Activa Pelgar
Mouse OECD 429 Local Lymph Node Assay	Not a skin sensitizer		Sanders (2006) Doc III A Section 6.1.5 (2) Activa Pelgar

4.6.1.1 Non-human information

4.6.1.2 Human information

4.6.1.3 Summary and discussion of skin sensitisation

In the Robinson study (1978) during the induction phase with the test substance, one test animal showed signs of severe toxicity and extensive bruising following the second induction and was humanely killed. The dose level for the third induction was therefore reduced to 0.1% w/v. There were no signs of irritation in any of the test or control animals during the induction phase. Following the challenge with a 0.1% w/v preparation of *Brodifacoum*, scattered mild redness or moderate and diffuse redness was seen in 8 of the 19 test animals. Scattered mild redness was seen in 3 of the 8 control animals (one doubtful reading excluded). The net percentage response was calculated to be 4%. Following challenge with a 0.05% w/v preparation of *Brodifacoum*, scattered

mild redness was seen in 7 of the 18 test animals (one doubtful reading excluded). There was no erythematous response in any of the control animals. The net percentage response was calculated to be 39%. *Brodifacoum* was considered to be a moderate skin sensitizer to the guinea pig under the conditions of the test.

In the Manciaux study (1996) the test item was a dilution (0.25%) of the active substance. During the pilot study, 2 mortalities by intradermal route were registered and the substance was well tolerated by cutaneous route. For induction 5% of *Brodifacoum* 0.25% in sterile isotonic saline was used; 50% of the test item was used for challenge. Positive control (75%) with 2,4-DCNB were run separately (historical control from the facility). During the test, 24h after challenge 1/20 animal was sensitized and 48h after challenge 1/20 animal was sensitized. The tested substance is not a skin sensitizer, but considering that the test item was a substantial dilution (0.25%) of the active substance, results cannot be extrapolated to *Brodifacoum*.

In the study conducted on mice (LLNA), the Stimulation Index (expressed as the mean radioactive incorporation for each treatment group divided by the mean radioactive incorporation of the vehicle control group) was less than 3 in all 4 groups, and therefore the result is considered negative. The test material was a non-sensitizer under the conditions of the test.

4.6.1.4 Comparison with criteria

4.6.1.5 Conclusions on classification and labelling

Although *Brodifacoum* showed no sensitizing potential in a LLNA study in mice, it was able to cause skin sensitization in a high number of guinea pig. Therefore, the overall results indicate for *Brodifacoum* a potential for skin sensitization, fulfilling the EU criteria for classification as a skin sensitizer.

Classification proposals according to Directive 67/548/EEC: *Brodifacoum* is considered skin sensitizer Xi R43, according to the criteria of Annex VI of Directive 67/548/EC.

Classification proposals according to Regulation EC 1272/2008: Skin Sens.1 H 317.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

4.6.2.2 Human information

4.6.2.3 Summary and discussion of respiratory sensitisation

4.6.2.4 Comparison with criteria

4.6.2.5 Conclusions on classification and labelling

4.7 Repeated dose toxicity

Table 17: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference
Oral OECD TG 408	Critical effect: increased blood coagulation time. NOAEL 1µg/kg bw/d		Batten (1984) Doc IIIA Section 6.4.1(09) Syngenta
Oral. Not reported. Similar to OECD 409	Critical effect: increased blood coagulation time. NOAEL 3µg/kg bw/d		Horner, 1997 Doc IIIA Section 6.4.1(03) Syngenta
Oral OECD TG 408	Critical effect: slight increase in clotting times indices. NOAEL 40 µg /kg/day		Morris, 1995 Doc III A Section 6.4 Activa Pelgar

Table 4.7

Route/ Method	Duration of study	Species Strain Sex no/group	Dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Oral Not reported Similar to OECD TG 408	90 days	Rat Wistar Male 10/group	0.02 and 0.08 ppm (corresponding to 1 and 4 µg/kg bw/day)	Critical effect: increased blood coagulation time	4 µg /kg bw/d	1µg/kg bw/d	Batten (1984) Doc IIIA Section 6.4.1(09) Syngenta
Oral Not reported, Similar to OECD TG 409	6 weeks	Dog Beagle Male (1) and female (1)	0.0001, 0.0003, 0.001, 0.003 or 0.01 mg/kgbw/day	Critical effect: increased blood coagulation time	10 µg /kg bw/day	3 µg /kg bw/day	Horner, 1997 Doc IIIA Section 6.4.1(03) Syngenta

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

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.

The study by Morris (1995) shows a higher NOAEL: at 80 µg/kg bw /day in male rats resulted in a slight increased incidence of haemorrhage in two animals and slight increase in clotting times indices. The clinical signs and toxicity are consistent with the mode of action of the rodenticide and its properties of anti-coagulant agent. Females showed no effects in the range of concentrations used. The NOAEL is established in 0.04 mg/kg/day.

There is no inconsistencies among the two studies, although the derived NOELs are different: indeed, the mode of action is the same, as well as the critical effect (altered blood coagulation mechanisms): the study by Batten addressed the measurement of very sensitive parameters related with the mode of action (i.e. increases in both the kaolin-cephalin time and the prothrombin time), and therefore were taken as earlier signs of *Brodifacoum* toxicity. The lowest NOEL is considered appropriate for risk characterization.

Repeated-dose oral studies in the dog show that at doses as low as 3 µg/kg/day in the dog, hemorrhagic effects begin to be seen after 6 weeks administration. The clinical signs, haematological and post mortem data were consistent with the mode of action of *Brodifacoum* and similar to what found in the rat, supporting the NOEL derived from the rat study, although the number of animal tested was quite limited.

4.7.1.2 Repeated dose toxicity: inhalation

No data on repeated inhalation toxicity have been submitted. However, the acute inhalation study (Parr-Dobrzanski, 1993) shows that *Brodifacoum* is acutely toxic by inhalation (LD₅₀ = 3.05 mg/m³). Based on the mode of action shown by *Brodifacoum* independently on the route of exposure, considering the inhalation absorption (100%) and the bioaccumulative nature of *Brodifacoum*, it can be expected that potential repeated exposure by inhalation will probably result in death by induction of a haemorrhagic syndrome. Therefore specific repeated dose inhalation studies would not provide any additional important information.

However, as indicated by data on the low vapour pressure (2.6×10^{-22} Pa at 20°C 1.9×10^{-21} Pa at 25°C) of *Brodifacoum*, on dustiness and particle size, the potential for inhalation is low and a repeated dose inhalation toxicity study to be carried out is also considered not justified.

4.7.1.3 Repeated dose toxicity: dermal

No data have been submitted on dermal repeated toxicity. On the basis of both physico-chemical properties and mode of action of *Brodifacoum* and the results of the acute dermal toxicity

study (McCall J C and Leah A M, 199; rat LD₅₀ = 3.16 mg/kg bw), it can be anticipated that subchronic effect due to prolonged skin contact should not be disregarded. Although the dermal absorption is limited, the bioaccumulative nature of *Brodifacoum* is such that repeated dermal administration is likely to cause severe toxic effects at doses lower than those resulting in death following a single dose. Death would be caused by the pharmacological action of the molecule, inducing fatal haemorrhage, the mode of action being similar independently on the route of administration. Therefore specific repeat dose dermal studies would not provide any additional important information to that obtained in repeated dose studies by the oral route.

4.7.1.4 Repeated dose toxicity: other routes

4.7.1.5 Human information

4.7.1.6 Other relevant information

4.7.1.7 Summary and discussion of repeated dose toxicity

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 both in rats and dog is in the range 1–40 µg/kg/day (the lowest values identified with sensitive end-points, such as increases in both the kaolin-cephalin time and the prothrombin time, related to the mode of action, thus considered as early diagnostic signs). Based on results from the acute dermal and inhalation toxicity studies, route-to-route extrapolation, consistently with the decision adopted for other second generation anticoagulants, it is justified to assume serious damages associated to prolonged exposure through dermal and inhalation routes also.

Brodifacoum was already evaluated at the written procedure for Plant Protection Products in September 2004. It was the agreed to classify *Brodifacoum* with T; R 48/23/24/25. This classification was confirmed at the May 2007 Meeting.

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

Classification proposal according to Directive 67/548/EEC: *Brodifacoum* is classified 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”:

C≥0.25%: T 48/23/24/25

0.025%≤C<0.25%: Xn 48/20/21/22

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

Classification proposal according to Regulation EC 1272/2008: STOT RE 1 H372:

$C \geq 0.25 \%$ STOT RE 1 H372;

$0,025 \% \leq C < 0.25 \%$ STOT RE 2 H373

4.9 Germ cell mutagenicity (Mutagenicity):

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies:

Method	Results	Remarks	Reference
Ames test	<i>Vitro</i> – - (+S9) - (-S9)	Non toxic and non mutagenic	Thompson P W, 2002 Doc III A Section 6.6.1 Activa Pelgar
Maron and Ames (1983)	<i>Vitro:</i> - ve (+S9) - ve (-S9)	Cytotoxic for strain TA1538 (-S9) at concentrations above 40 µg/plate; and TA100 (-S9 and +S9) at concentrations above 200µg/plate	Doc III A Section 6.6.1 Syngenta
Gene mutation	<i>Vitro</i> - (+S9) - (-S9)	Non toxic and non clastogenic	Durward R, 2004 Doc III A Section 6.6.3 Activa Pelgar
Mammalian Cell Gene Mutation Tests	<i>Vitro:</i> - ve (+S9) - ve (-S9)	Cytotoxic at concentrations greater than 112.5µg/ml. The addition of auxiliary metabolic activation (S9 mix) appeared to slightly decrease the toxicity	Doc. III A Section 6.6.3 Syngenta
Chromosomal aberration	<i>Vitro</i> - (+S9) - (-S9)	Non toxic and Non Mutagenic	Wright N P, 2003 Doc IIIA Section 6.6.2 Activa Pelgar
OECD 473 (1983)	<i>Vitro:</i> - ve (+S9) - ve (-S9)	Cytotoxic at 500 and 1000 µg/ml and precipitation of the test substance	Doc III A Section Syngenta
Mammalian cell transformation assay of Styles (1977): Styles J A (1977), Brit J Cancer, 36, 58	<i>Vitro</i> Not tested (+S) - ve (-S9)	Increasing cell mortality with increasing dose, with LC ₅₀ determined to be 20 µg/ml	Doc III A Section 6.6.3 Syngenta
J E Cleaver (1977) - Handbook of Mutagenicity Test Procedures, B. Kilbey <i>et al</i> eds., Elsevier, Amsterdam 19-4B; Abbondandolo <i>et al</i> (Roma 1979) - Mutagenesi ambientale, Metodiche di analisi ed. CNR 223-236; Benigni <i>et al.</i> , Mutation Res. 103 (1982) 385-390; Ames B N, McCann J, Yamasaki E, Mut. Res. 31 (1975) 347-364; Snedecor C W, Statistical Methods, Iowa State College Press, Ames, 5th Edition, 1956.	<i>Vitro:</i> - ve (+S9) - ve (-S9)	No statistically significant increases in the incorporation of tritiated thymidine in cultured human Hela cells, either in the presence of absence of metabolic activation up to a dosage concentration of 1000µg/ml. Cytotoxicity was indicated at the higher dose levels (100 and 1000µg/ml) by an inhibition of S-phase	Doc III A Section 6.6.3 Syngenta
OECD 474 Sheldon <i>et All.</i> (1984)	<i>Vivo</i> No statistically significant increase in incidence of micronuclei was seen with		Doc III A Section 6.6.4

	<i>Brodifacoum</i> at any dose level or sampling time, even though the dose levels were equivalent to 80% and 50% of the MLD/7.		Syngenta
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Table 4.9: *In vitro*

Test system Method Guideline	organism/ strain(s)	Concentra_ tions tested	Result		Remark	Reference
			+ S9	- S9		
			+/-/±	+/-/±		
Ames test	<i>S. Typhimurium</i> TA 98,100,102, 1535, 1537	0,0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1500, 5000	—	—	Non toxic and non mutagenic	Thompson P W, 2002 Doc IIIA Section 6.6.1 Activa Pelgar
Maron and Ames (1983)	<i>Salmonella</i> <i>Typhimurium</i> : TA 1535, TA 1537,TA 98, TA 100, TA 1538	0.064 – 5000 µg/plate	-ve	-ve	Cytotoxic for strain TA1538 (-S9) at concentrations above 40 µg/plate; and TA100 (-S9 and +S9) at concentrations above 200µg/plate	Doc.III A Section 6.6.1 Syngenta
Gene mutation	Mouse lymphoma	0, 3.13, 6.25, 12.5, 25, 37.5 and 50 µg/ml	—	—	Non toxic and non clastogenic	Durward R, 2004 Doc III A Section 6.6.3 Activa Pelgar
Section 4 Genetic Toxicology, 476. <i>In Vitro</i> Mammalian Cell Gene Mutation Tests	Mouse lymphoma cell line L5178Y (-3.7.2C) (TK +/-)	3.9 - 150 µg/ml in cell suspension	-ve	-ve	Cytotoxic at concentrations greater than 112.5µg/ml. The addition of auxiliary metabolic activation (S9 mix) appeared to slightly decrease the toxicity	Doc. III A Section 6.6.3 Syngenta
Chromosomal aberration	human lymphocytes <i>in vitro</i>	0, 18.75, 37.5, 75, 150, 225 and 300 µg/ml	—	—	Non toxic and Non Mutagenic	Wright N P, 2003 Doc III A Section 6.6.2 Activa Pelgar
OECD 473 (1983)	Human lymphocytes	5 – 1000	-ve	-ve	Cytotoxic at 500 and 1000 µg/ml and precipitation of	Doc.III A

	(male and female)	µg/ml			the test substance	Section 6.6.2 Syngenta
Mammalian cell transformation assay of Styles (1977): Styles J A (1977), Brit J Cancer, 36, 558	Baby Hamster Kidney Fibroblasts (BHK21/C13)	0.12 - 1200 µg/ml	Not tested	-ve	Increasing cell mortality with increasing dose, with LC ₅₀ determined to be 20 µg/ml	Doc. III A Section 6.6.3 Syngenta
J E Cleaver (1977) - Handbook of Mutagenicity Test Procedures, B. Kilbey <i>et al</i> eds., Elsevier, Amsterdam 19-4B; Abbondandolo <i>et al</i> (Roma 1979) - Mutagenesi ambientale, Metodiche di analisi ed. CNR 223-236; Benigni <i>et al.</i> , Mutation Res. 103 (1982) 385-390; Ames B N, McCann J, Yamasaki E, Mut. Res. 31 (1975) 347-364; Snedecor C W, <i>Statistical Methods</i> , Iowa State College Press, Ames, 5th Edition, 1956.	Hela cells (human)	1, 10, 100 and 1000 µg/ml	-ve	-ve	No statistically significant increases in the incorporation of tritiated thymidine in cultured human Hela cells, either in the presence of absence of metabolic activation up to a dosage concentration of 1000µg/ml. Cytotoxicity was indicated at the higher dose levels (100 and 1000µg/ml) by an inhibition of S-phase	Doc. III A Section 6.6.3 Syngenta

Table 4.9.1: In vivo

Type of test Method/ Guideline Reference	Species Strain Sex no/group	frequency of application	sampling times	dose levels	Results	Remarks	Reference
OECD 474 Sheldon et All. (1984)	<i>Mus domesticus</i> (mouse) C57BL/6J male and female 5 + 5	Once	24, 48, 72 hours after treatment	0.187 and 0.30 mg/kg	No statistically significant increase in incidence of micronuclei was seen with <i>Brodifacoum</i> at any dose level or sampling time, even though the dose levels were equivalent to 80% and 50% of the MLD/7.		Doc. III A Section 6.6.4 Syngenta

4.9.1 Non-human information**4.9.1.1 In vitro data****4.9.1.2 In vivo data****4.9.2 Human information****4.9.3 Other relevant information****4.9.4 Summary and discussion of mutagenicity**

Brodifacoum was tested in *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537, TA 1538, with and without S9-mix, up to 5000 mg/plate, with negative results in all bacterial strain. 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 substance resulted negative up to cytotoxic concentration in the *in vitro* mammalian chromosome aberration test in human lymphocytes (50% mitotic inhibition at the maximum dosage tested). An *in vivo* mouse micronucleus test gave negative results. Therefore a genotoxic potential of *Brodifacoum* can be ruled out.

4.9.5 Comparison with criteria**4.9.6 Conclusions on classification and labelling**

None.

4.10 Carcinogenicity

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

4.10.1.2 Carcinogenicity: inhalation

4.10.1.3 Carcinogenicity: dermal

4.10.2 Human information

4.10.3 Other relevant information

4.10.4 Summary and discussion of carcinogenicity

As for the chronic toxicity studies, carcinogenicity studies were not considered to be technically feasible and necessary due to the specific action of *Brodifacoum* on the test/target species. The anticoagulant action is the sole pharmacological action of the materials. Short-term studies where vitamin K has been co-administered have not shown any other toxic effects at doses that would have otherwise been lethal. However, administration of vitamin K is not practical for long-term studies in rodents. The absence of carcinogenic potential is supported by the fact that mutagenicity studies on *Brodifacoum* are negative. The likely mechanisms of carcinogenicity are limited to those resulting from effects such as hepatic hypertrophy, or irritancy, and short-term studies show that there are no responses of that nature. It is reasonable to conclude that *Brodifacoum* has no carcinogenic potential. Repeated toxicity studies with second generation anticoagulants cannot be carried out for more than a few weeks due to the accumulative nature and high toxicity of *Brodifacoum*.

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 *Brodifacoum* on the test/target species. However, the anticoagulant action is apparently the only pharmacological action of *Brodifacoum*. *Brodifacoum* 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 the Applicants for not-submission of carcinogenicity data was considered acceptable.

4.10.5 Comparison with criteria

4.10.6 Conclusions on classification and labelling

None.

4.11 Toxicity for reproduction

Table 20: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Fertility Oral OECD 416	NO(A)EL Parental (mg/kg/day): m 0.003, f 0.001; NO(A)EL F1 (mg/kg/day): m 0.003, f 0.003; NO(A)EL F2 (mg/kg/day): m 0.003, f 0.003;	Critical effect: High dose Parental, F1 and F2,, mid-dose parental females: haemorrhagic diathesis.	Szakonyi, 2004 Doc IIIA Section 6.8.2 Activa Pelgar
Developmental Oral gavage OECD 414	NO(A)EL maternal toxicity: 0.002 mg/kg bw/day NO(A)EL developmental toxicity: equal or higher than 0.005 mg/kg bw/day	Critical effect: Deaths with internal haemorrhages. No developmental effects (maternal toxicity)	Doc III A Section 6.8.1 Syngenta
Developmental Oral gavage OECD 414	NO(A)EL maternal toxicity: 0.002 mg/kg bw/day NO(A)EL developmental toxicity: Equal or higher than 0.004 mg/kg/day	Critical effect: Dams: Increase in Kaolin-cephalin and prothrombin time at 0.004 mg/kg/day. No developmental effects	Morris, 1995 Doc IIIA Section 6.8.1 (2) Activa Pelgar
Developmental Oral gavage OECD 414	NO(A)EL maternal toxicity: 0.001 mg/kg bw/day NO(A)EL developmental toxicity: Equal or higher than 0.020 mg/kg bw/day	Critical effect: Deaths with internal haemorrhages. No developmental effects (maternal toxicity)	Doc III A Section 6.8.1 Syngenta
Developmental Oral gavage OECD 414	NO(A)EL maternal toxicity: Equal or higher than 0.040 mg/kg bw /day NO(A)EL developmental toxicity: Equal or higher than 0.040 mg/kg bw /day	No maternal or developmental effects	Morris, 1995 Doc IIIA Section 6.8.1 (1) Activa Pelgar

4.11.1 Effects on fertility

No specific effects on fertility or reproductive performance effects were observed at doses eliciting general toxicity. Dose related induction of haemorrhagic diathesis was consistent with the anti-coagulant properties of the active substance. Female animals were more sensitive than the male animals in the Parental generation. The NOEL and LOEL were 0.001 and 0.003 mg/kg bw/day, respectively, based on parental toxicity associated to anticoagulant effect. Overall, parental animals were more sensitive than F1 and F2 animals.

4.11.1.1 Non-human information

4.11.1.2 Human information

No specific information on reproductive or developmental effects of *Brodifacoum*. *Warfarin* is an established human teratogen, sharing the same chemically active group as *Brodifacoum*.

4.11.2 Developmental toxicity

In a series of studies compliant with OECD 414 in rats and rabbits, there was no evidence of developmental effects up to the dose levels tested of 0.020 and 0.040 mg/kg bw for rat and rabbit, respectively. The specific anticoagulant effects of the compound were clearly shown in rats and rabbits, the latter appearing more sensitive.

4.11.2.1 Non-human information

4.11.2.2 Human information

4.11.3 Other relevant information

4.11.4 Summary and discussion of reproductive toxicity

The available studies provided no hint that *Brodifacoum* may elicit reproductive or developmental effects at dose levels at which the specific anticoagulant effects are not induced. However, the issue of human developmental hazard remains an open one. (tables 4.11 and 4.11.1) It is widely recognized that the conventional OECD Guideline 414 may have limitations in the detection of possible teratogenic effects of coumarin-related compounds. In particular, *Brodifacoum* has the same chemically active group as the recognized human teratogen *Warfarin* (classified as Repr. category 1). Taking into account the limitations of the current protocol, the potential species-specificity of effects and the structure-activity similarity with *Warfarin*, the EU approach towards anticoagulant rodenticides is a precautionary one. Specific areas of uncertainties as regards the comparison with *Warfarin* of 2nd generation anticoagulants concern the placental transfer, as well mode of action in developing tissues (extrahepatic vitamin K deficiency). Such areas of uncertainties make it difficult to rule out the developmental toxicity of 2nd generation anticoagulants and support a conservative read-across with *Warfarin*.

Accordingly, *Brodifacoum* should be classified for developmental toxicity with Repr. Cat. 2; R61.

Table 4.11 Effects on fertility

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	critical effect	NO(A)EL Parental (mg/kg/day)		NO(A)EL F1 (mg/kg/day)		NO(A)EL F2 (mg/kg/day)		Reference
						m	f	m	f	m	f	
Oral	OECD 416	Rat Wistar 25 /sex/group	2-generation	0,0.001,0.003 and 0.006 mg/kg bw/day	High dose Parental, F ₁ and F ₂ , mid- dose parental females: haemorrhagic diathesis	0.003	0.001	0.003	0.003	0.003	0.003	Szakonyi, 2004 Doc IIA Activa Pelgar

4.11.1 Developmental toxicity

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	Critical effects dams fetuses	NO(A)EL maternal toxicity	NO(A)EL developmental toxicity	Reference
Oral - gavage	OECD 414	Dutch Rabbit 15/group	Gestation days 6-18	0, 0.001, 0.002, 0.005 mg/kg bw/d	(maternal toxicity): deaths with internal haemorrhages. No developmental effects	0.002 mg/kg bw/day	Equal or higher than 0.005 mg/kg bw/day	Doc. IIIA 6.8.1 (Syngenta)
Oral - gavage	OECD 414	Rabbit, New Zealand White, 20/group	Gestation days 6-18	0, 0.001, 0.002, 0.004 mg/kg bw/day	Dams: Increase in Kaolin-cephalin and prothrombin time at 0.004 mg/kg/day. No developmental effects	0.002 mg/kg bw/day	Equal or higher than 0.004 mg/kg/day	Morris, 1995 Doc III A Section 6.8.1 (2) Activa Pelgar
Oral - gavage	OECD 414	Rat 20/group	Gestation day 6-15	0, 0.001, 0.010, 0.020 mg/kg bw/day	(maternal toxicity): deaths with internal haemorrhages. No developmental effects	0.001 mg/kg bw/day.	Equal or higher than 0.020 mg/kg bw/day.	Doc. IIIA 6.8.1 Syngenta
Oral	OECD 414	Pregnant Rat	Gestation day 6-15	0, 0.01,	No maternal or developmental	Equal or higher	Equal or higher than	Morris, 1995

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	Critical effects dams fetuses	NO(A)EL maternal toxicity	NO(A)EL developmental toxicity	Reference
		20/group		0.020, 0.040 mg/kg bw/day	effects	than 0.040 mg/kg bw/day	0.040 mg/kg bw/day	Doc III A Section 6.8.1 (1) Activa Pelgar

4.11.5 Comparison with criteria

4.11.6 Conclusions on classification and labelling

Classification proposal according to Directive 67/548/EEC: Toxic Repr. Cat. 2; R61* (*Based on the classification for developmental effect by read across to *Warfarin*).

Classification proposal according to Regulation EC 1272/2008: Toxic Repr. 1B H360D* (*Based on the classification for developmental effect by read across to *Warfarin*).

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

4.12.1.2 Immunotoxicity

4.12.1.3 Specific investigations: other studies

4.12.1.4 Human information

4.12.2 Summary and discussion

4.12.3 Comparison with criteria

4.12.4 Conclusions on classification and labelling

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 21: Summary of relevant information on degradation

Method	Results	Remarks	Reference
EC C.7, OECD 111	DT50: > 1 yr		R. Fabbrini
EC C.7, OECD 111	DT50: > 1 yr		Mathis SNG, Benner JP and Skidmore MW
OPPS 835-2210	Half-life [t1/2E]: < 1 d		R.M. Drake
OECD 301B	Incubation period: 28 days Degree[%]:0%		R.M. Drake
OECD 302	Incubation period: 56 days Degree[%]:2%		R.M. Drake
OECD (1992) 301D	Incubation period: 28 days Degree[%]:3.5%		Kelly C:R.Clayton
ISO 11734 and method 3 of ECETOC report no. 28	Incubation period: 56 days Degree[%]:0%		R.M. Drake
EPA Guidelines, 162-1 (October 1982).	DT50: 157		Hall BE and Priesley

5.1.1 Stability

Hydrolysis

Two hydrolysis studies are available and are reported in table 4.1.1-1. The studies indicated that Brodifacoum is hydrolytically stable at pH 4, 7 and 9; the hydrolytic half-life (DT50) is above one year at environmentally relevant pH.

Photolysis in water

Photolysis of Brodifacoum was fast with 38% removal in the first hour of exposure. Greater than 89% photolysis was noted to have occurred by around three hours. Furthermore, whatever the season, the half-life of Brodifacoum is less than one day. In the laboratory the substance completes photolysis. No degradation products were detected.

Photo-oxidation in air

The photo-oxidation of Brodifacoum in air has been estimated using AOPWIN. According to these calculations, Brodifacoum has a potential for rapid photo-oxidative degradation in air with a half-life of 6.61 h, considering COH 0.5 x 10⁶ molec/cm³ and the time 24 h.

5.1.2 Biodegradation

Anaerobic biodegradation

Results from a study following test method ISO11734 on the anaerobic degradation of Brodifacoum are summarised in Table 4.1.2-2. No degradation was observed after 56 days of incubation. These test results indicated that Brodifacoum is not biodegradable under anaerobic conditions.

Degradation in soil

Brodifacoum is persistent in soil with DT50 value of 157 days. Mineralization rate is about 35.8% and the non-extractable bound residue is maximum 23.6% in one soil after 365 days.

5.1.2.1 Biodegradation estimation

No data.

5.1.2.2 Screening tests

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.

5.1.2.3 Simulation tests

Was not degraded in anaerobic condition.

5.1.3 Summary and discussion of degradation

Abiotic degradation

Brodifacoum showed to be hydrolytically stable under environmentally relevant conditions (DT50 > 1 year). Brodifacoum was found to be susceptible to photo-transformation in water (DT50 < 1 d) and photo-oxidation in air (DT50 = 0.275 d for reaction with OH-radicals).

Biodegradation in water

Brodifacoum is not readily or inherently or anaerobically biodegradable.

Degradation in soil

Brodifacoum is persistent in soil with a DT50 value of 157 days. Mineralization rate is about 35.8% and the non-extractable bound residue is maximum 23.6% in one soil after 365 days.

5.2 Environmental distribution

No data.

5.2.1 Adsorption/Desorption

Brodifacoum is immobile in soil (Koc > 9155 l/kg). Brodifacoum is not expected to contaminate groundwater.

5.2.2 Volatilisation

Brodifacoum has a low vapour pressure ($\ll 1 \times 10^{-6}$ Pa) and a Henry's Law constant of 2.18×10^{-3} Pa m³ mol⁻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 Brodifacoum is in a closed system. There are no releases to air of Brodifacoum from manufacturing, formulating, use or disposal phases.

5.2.3 Distribution modelling

No Data.

5.3 Aquatic Bioaccumulation

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The log K_{ow} of Brodifacoum has been experimentally determined to be 4.92 at pH 7 and 20°C. This value exceeds the guidance values for bioaccumulation for classification purposes according to Directive 67/548/EEC (log K_{ow} > 3) and Regulation EC 1272/2008 (log K_{ow} > 4).

5.3.1.2 Measured bioaccumulation data

No reliable experimental data are available for the bioaccumulation of Brodifacoum in fish.

5.3.2 Summary and discussion of aquatic bioaccumulation

The log K_{ow} of Brodifacoum has been experimentally determined to be 4.92 at pH 7 and 20°C.

An experimentally derived BCF value is not available.

The log K_{ow} value for Brodifacoum fulfils the criteria for bioaccumulation potential according to Directive 67/548/EEC and Regulation EC 1272/2008 as it exceeds the value of 3 and 4, respectively.

5.4 Aquatic toxicity

Table 23: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
OECD 203 (1992)	LC ₅₀ 0.042	Species: Rainbow trout	W. J Craig
OECD (1984) Guideline 202 Part 1	Results (mg a.s./l) EC ₀ : 0.07 EC ₅₀ : 0.25 EC ₁₀₀ : 0.92	Species: Daphnia magna	W. J Craig
OECD 201 (1984)	Results (mg a.s./l) NOE _r C: 0.01 E _b C ₅₀ : 0.016 E _r C ₅₀ ¹ : 0.04	Species: Selenastrum capricornutum (renamed Pseudokirkneriella sub capitata)	W. J Craig

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

One fully reliable GLP study with Rainbow trout, carried out following OECD 203, is available.

Seven fish were exposed under semistatic conditions to nominal concentration of Brodifacoum: 0 (control), DMF (control), 0.06, 0.13, 0.25, 0.5 and 1.0 mg a.s./l. Mean measured concentrations of old and new solutions (4 old and 4 fresh) were: 0.03, 0.06, 0.11, 0.23, 0.53 mg a.s./l and were used to express results. No mortality was recorded at the lowest concentration, while 100% fish died at 0.11 mg a.s./l. The 96h LC₅₀ was calculated equal to 0.042 mg a.s./l.

5.4.1.2 Long-term toxicity to fish

No data are available.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The results of an acute GLP study with Daphnia magna, carried out according to OECD 202, are available. Twenty daphnids (divided in 4 replicates) were exposed to nominal concentrations of Brodifacoum of 0 (control), DMF (control), 0.13, 0.25, 0.5, 1.0, 2.0 and 4.0 mg a.s./l. The measured mean concentrations of new and old test solutions were 0, 0.07, 0.12, 0.28, 0.63, 0.92 mg a.s./l, which were used to express the results. The calculated 48h EC₅₀ was 0.25 mg/l (0.20 – 0.31). No statistically significant effect were observed at 0.12 mg/l.

5.4.2.2 Long-term toxicity to aquatic invertebrates

No data are available.

5.4.3 Algae and aquatic plants

A 72h study with algae, carried out with *Selenastrum capricornutum* (renamed *Pseudokirkneriella subcapitata*) according OECD 201 and under GLP provisions, is available. Nominal test concentrations were 0 (control), DMF, 0.032, 0.056, 0.10, 0.18, 0.32 mg/l. The endpoints of the study have been recalculated on the basis of the geometric mean concentrations, hence: NOEC = 0.010 mg/l, EbC50 0.016 mg/l and ErC50 0.04 mg/l. The result for growth rate is that considered for risk assessment.

5.4.4 Other aquatic organisms (including sediment)

No data are available.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

No data are available

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Related to environment Brodifacoum LC50 is below 1 mg/L (the 96h LC50 Rainbow trout equal to 0.042 mg a.s./l; 48h EC50 *Daphnia magna* equal to 0.25 mg/l; static 72h ErC50 *Selenastrum capricornutum* equal to 0.04 mg/l) with proposal for specific concentration limits: $C_n \geq 2,5$ (DSD); M=10 (CLP) and the substance is not readily biodegradable. Classification proposal according to Directive 67/548/EEC.

6 OTHER INFORMATION

No data.

7 REFERENCES**REFERENCE LIST**

The studies considered as confidential information are available separately for either Applicant in the confidential Annex to this CLH report.

Applicant A

Author	CAR, 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
Berry D	6.18/01	2003	Brodifacoum: Global Evaluation of Toxicological and Metabolism Studies. Central Toxicology Laboratory Report No:	Y	Syngenta

Author	CAR, Doc. IIIA Section No/ Ref. No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
			CTL/03A274/OVERVIEW/REPORT. No GLP, unpublished.		
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.		Syngenta
Callander	6.6.1/01	1984	Brodifacoum - An Evaluation in the Salmonella Mutagenicity Assay. ICI Central Toxicology Laboratory Report No: CTL/P/949. GLP, unpublished. [C2.6/06].	Y	Syngenta

Author	CAR, 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	6.3.1/04	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	2000	Brodifacoum - Physico-Chemical Testing with Brodifacoum: Water Solubility. Inveresk Research Report No: 18799. GLP, unpublished. [BR-959-0079].	Y	Syngenta
Confidential data	7.4.1.3	2003	The Growth Inhibition of the alga <i>Selenastrum capricornutum</i> by BRODIFACOUM Technical. Confidential data. Report - ENV5801/120140	Y	Activa / PelGar Brodifacoum and Difenacoum Task Force
Confidential data	7.4.1.2	2003	The Toxicity to <i>Daphnia magna</i> of BRODIFACOUM Technical. Confidential data 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
Davidson AJ	2.8	2000	Brodifacoum - Product Chemistry of Brodifacoum: Analytical Profile of 5 Batches. Inveresk Research Laboratory Report Number: 18909.	Y	Syngenta

Author	CAR, Doc. IIIA Section No/ Ref. No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
			GLP, unpublished. [BR-959-0084].		
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
Confidential Data	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 <u>13</u> , 23 - 25, RIC0615. Not GLP, published. [C2.1/26].	N	
Confidential Data	6.13/02	1981 a	The Oral Toxicity of Brodifacoum to Rabbits. New Zealand Journal of Experimental Agriculture <u>9</u> , 23 - 25, RIC0585. Not GLP, published. [C2.1/22].	N	
Confidential Data	6.13/08	1981 b	The Acute Oral Toxicity of the Anticoagulant Brodifacoum to Dogs. New Zealand Journal of	N	

Author	CAR, Doc. IIIA Section No/ Ref. No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
			Experimental Agriculture 9, 147 - 149, RIC0586. Not GLP, published. [C2.1/23].		
Confidential Data	6.1.1/02	1974 a	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	1974 c	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
Confidential Data	6.13/05	1975 a	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	6.13/10	1975	Sub-acute (5-day) oral toxicity	Y	Syngenta

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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	1978 c	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
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
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	Y	Syngenta

Author	CAR, Doc. IIIA Section No/ Ref. No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
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Confidential Data	7.4.1.1/01	1976	PP581: Determination of the acute toxicity of PP581 to rainbow trout (<i>Salmo gairdneri</i>). ICI Brixham Laboratory, Report No: BL/B/1758. Not GLP, unpublished. [G5.1/01].	Y	Syngenta
Confidential Data	6.8.1/01	1980 a	Brodifacoum: Teratogenicity Study in the Rat. ICI Central Toxicology Laboratory Report No: CTL/P/437. GLP, unpublished. [C2.5/01].	Y	Syngenta
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Author	CAR, Doc. IIIA Section No/ Ref. No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
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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
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
Confidential Data	7.4.1.1/02	2000 a	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
Confidential Data	7.4.1.2/01	2000 b	Brodifacoum: Determination of Acute Toxicity to Daphnia (48 h, Static, Limit Test). Inveresk Research Report Number 19032.	Y	Syngenta

Author	CAR, Doc. IIIA Section No/ Ref. No	Year	Title Source/ Company Report No. GLP or not (Un)published	Data Protection Claimed (yes/no)	Owner
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Confidential Data	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
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8 ANNEXES

No data