

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Coumatetralyl

EC Number: 227-424-0

CAS Number: 5836-29-3

Index Number: 607-059-00-7

**Contact details for dossier submitter: CA biocides Denmark,
Danish EPA, mst@mst.dk**

Version number: 02

Date: 11.10.2011

CONTENTS

Part A.

1	PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING.....	6
1.1	SUBSTANCE IDENTITY.....	6
1.2	HARMONISED CLASSIFICATION AND LABELLING PROPOSAL.....	6
1.3	PROPOSED HARMONISED CLASSIFICATION AND LABELLING BASED ON CLP REGULATION AND/OR DSD CRITERIA.....	8
2	BACKGROUND TO THE CLH PROPOSAL	12
2.1	HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING.....	12
2.2	SHORT SUMMARY OF THE SCIENTIFIC JUSTIFICATION FOR THE CLH PROPOSAL.....	12
2.3	CURRENT HARMONISED CLASSIFICATION AND LABELLING	12
2.3.1	<i>Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation:.....</i>	<i>12</i>
2.3.2	<i>Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation</i>	<i>12</i>
2.4	CURRENT SELF-CLASSIFICATION AND LABELLING	12
3	JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL	13
	SCIENTIFIC EVALUATION OF THE DATA	14
1	IDENTITY OF THE SUBSTANCE	14
1.1	NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE	14
4.10	PHYSICO-CHEMICAL PROPERTIES.....	15
2	MANUFACTURE AND USES.....	19
2.11	MANUFACTURE	19
2.12	IDENTIFIED USES.....	19
4.11	MODE OF ACTION	19
3	CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES.....	20
3.1.1	<i>Conclusions on classification and labelling on physico-chemical properties.....</i>	<i>20</i>
4	HUMAN HEALTH HAZARD ASSESSMENT.....	20
4.1	TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION).....	20
4.1.1	<i>Non-human information.....</i>	<i>20</i>
4.1.2	<i>Human information.....</i>	<i>21</i>
4.1.3	<i>Summary and discussion on toxicokinetics</i>	<i>21</i>
4.2	ACUTE TOXICITY	23
	Acute toxicity: oral.....	24
	Acute toxicity: dermal.....	24
	Acute toxicity: inhalation.....	24
4.2.1	<i>Conclusion on classification and labelling.....</i>	<i>25</i>
4.3	SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT SE).....	25
4.4	IRRITATION.....	25
4.4.1	<i>Skin irritation.....</i>	<i>25</i>
4.4.2	<i>Eye irritation.....</i>	<i>26</i>
4.4.3	<i>Respiratory tract irritation.....</i>	<i>26</i>
4.5	CORROSIVITY	26
	Conclusion on classification for corrosivity.....	26
4.6	SENSITISATION	26
4.6.1	<i>Skin sensitistaion.....</i>	<i>26</i>
	Conclusion on classification and labelling for skin sensitising potential	27

4.6.2	<i>Respiratory sensitisation</i>	27
	Conclusion of classification and labelling.....	27
4.7	REPEATED DOSE TOXICITY	27
4.7.1	<i>Non-human information</i>	27
4.7.2	<i>Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD</i>	30
4.7.3	<i>Conclusion on the classification and labelling of repeated dose toxicity findings relevant for classification according to DSD</i>	30
4.8	SPECIFIC TARGET ORGAN TOXICITY (CLP REGULATION) – REPEATED EXPOSURE (STOT RE)	31
4.8.1	<i>Summary and discussion of repeated dose toxicity finding relevant for classification as STOT RE according to CLP Regulation</i>	31
4.8.2	<i>Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE</i>	31
4.8.3	<i>Conclusions on classification and labelling for repeated dose toxicity (STOT RE)</i>	31
4.9	GERM CELL MUTAGENICITY (MUTAGENICITY)	32
4.9.1	<i>In-vitro genotoxicity</i>	32
4.9.2	<i>In vivo genotoxicity</i>	33
4.9.3	<i>Human information</i>	34
4.9.4	<i>Other relevant information</i>	34
4.9.5	<i>Summary and discussion of mutagenicity</i>	34
4.9.6	<i>Conclusion on classification and labelling</i>	34
4.10	CARCINOGENICITY	35
4.10.1	<i>Non-human information</i>	35
4.10.2	<i>Human information</i>	35
4.10.3	<i>Other relevant information</i>	35
4.10.4	<i>Conclusion on classification and labelling</i>	35
4.11	REPRODUCTIVE TOXICITY	35
4.11.1	<i>Effects on fertility</i>	36
4.11.1.1	Non-human information.....	36
4.11.1.2	Human information.....	37
4.11.2	<i>Developmental toxicity</i>	37
4.11.2.1	Non-human information.....	37
4.11.2.2	Human data	37
4.11.2.3	Other relevant information.....	37
4.11.3	<i>Summary and discussion of reproductive toxicity</i>	40
4.11.3.1	Fertility	40
4.11.3.2	Developmental toxicity	40
4.11.3.3	Effects on or via lactation	41
4.11.4	4.11.5 <i>Comparison with criteria</i>	41
4.11.4.2	Fertility	41
4.11.4.3	Development	41
4.11.4.4	Effects on or via lactation	43
4.11.5	<i>Conclusions on classification and labelling</i>	43
4.12	OTHER EFFECTS	43
4.12.1	<i>Non-human information</i>	43
4.12.1.1	Neurotoxicity	43
4.12.1.2	Immunotoxicity.....	43
4.12.1.3	Specific investigations: other studies	43
4.12.2	<i>Conclusions on classification and labelling</i>	44
5	ENVIRONMENTAL HAZARD ASSESSMENT	45
5.1	DEGRADATION	45
5.1.1	<i>Stability</i>	45
5.1.2	<i>Biodegradation</i>	46
Biotic degradation.....		46
5.1.3	<i>Summary and discussion of degradation</i>	47
5.2	ENVIRONMENTAL DISTRIBUTION	48
5.2.1	<i>Adsorption/Desorption</i>	48
5.2.2	<i>Volatilisation</i>	49
5.2.3	<i>Distribution modelling</i>	49

5.3	AQUATIC BIOACCUMULATION.....	49
5.3.1	<i>Aquatic bioaccumulation</i>	49
5.3.2	<i>Summary and discussion of aquatic bioaccumulation</i>	50
5.4	AQUATIC TOXICITY	50
5.4.1	<i>Fish</i>	50
5.4.1.1	Short-term toxicity to fish	50
5.4.1.2	Long-term toxicity to fish	51
5.4.2	<i>Aquatic invertebrates</i>	52
5.4.2.1	Short-term toxicity to aquatic invertebrates	52
5.4.2.2	Acute toxicity to invertebrates	52
5.4.2.3	Long-term toxicity to aquatic invertebrates	52
5.4.3	<i>Algae and aquatic plants</i>	53
5.4.3.1	Growth inhibition on algae.....	53
5.4.4	<i>Other aquatic organisms (including sediment)</i>	54
5.4.4.1	Inhibition of microbial activity (aquatic)	54
5.5	COMPARISON WITH CRITERIA FOR ENVIRONMENTAL HAZARDS (SECTIONS 5.1 – 5.4)	55
5.6	CONCLUSIONS ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS (SECTIONS 5.1 – 5.4)	55
6	OTHER INFORMATION	56
7	REFERENCES	56
8	ANNEXES	63
	ANNEX 1: CONFIDENTIAL INFORMATION ON IDENTITY OF THE SUBSTANCE,	
	ANNEX 2: IDENTITY AND PHYSICO-CHEMICAL PROPERTIES OF THE SUBSTANCE.	
	ANNEX 3: STUDY SUMMARIES RELATED TO HUMAN HEALTH EFFECTS OF THE SUBSTANCE.	
	ANNEX 4: STUDY SUMMARIES RELATED TO ENVIRONMENTAL EFFECTS AND FATE OF THE SUBSTANCE.....	

PART A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance identity

Table 1: Substance identity

Substance name:	<i>Coumatetralyl</i>
EC number:	<i>227-424-0</i>
CAS number:	<i>5836-29-3</i>
Annex VI Index number:	<i>607-059-00-7</i>
Degree of purity:	<i>min. 980 mg/kg</i>
Impurities:	<i>Information on impurities is presented in the Confidential part of the CA-report.</i>

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 Chronic 3; H412	T+; R27/28; T; R48/24/25 and R52/53
Current proposal for consideration by RAC¹	Repr. 1A; H360D Acute Tox 2; H330 Acute Tox 3; H311 STOT RE 1; H372 (<i>blood coagulation</i>) Aquatic Chronic 1; H410	Repr. Cat 1; R61 T+; R26; T; R24 (instead of T+;R27); T; R48/23[/24/25] R52/53
Proposal for specific concentration limits²	$C \geq 0.2\%$: STOT RE 1; H372 (<i>blood coagulation</i>) $0.02\% \leq C < 0.2\%$: STOT RE 2; H373 (<i>blood coagulation</i>)	$C \geq 0.1$: T; 48/23/24/25 $0.01\% \leq C < 0.1\%$: Xn; R48/20/21/22

	Setting SCL for Repr. 1A; H360D should be considered. Aquatic Chronic 1; H410 M-factor: 10	
Precautionary statements/ S-phrases	P201 P308 +P313 P320 P273 P391 P405 P501 Additional statement on the specific antidote: <u>vitamin K</u> , should be given.	S53 S45 S61
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Repr. 1A; H360D Acute Tox 2; H300 Acute Tox 2; H330 Acute Tox 3; H311 STOT RE 1; H372 Aquatic Chronic 1; H410 <u>SCL:</u> [Discussion on SCL for reprotox_H360D] $\geq 0.2\%$: STOT RE 1; H372 (<i>blood coagulation</i>) and $0.02\% \leq C < 0.2\%$: STOT RE 2; H373 (<i>blood coagulation</i>) M-factor: 10	Repr. Cat 1; R61 T+; R26/28; T; R24 T; R48/23/24/25 R52/53 <u>SCL:</u> $C \geq 25\%$: T+; R61-24-26/28-48/23/24/25-52-53 $7\% \leq C < 25\%$: T+; R61-21-26/28-48/23/24/25 $3\% \leq C < 7\%$: T; R61-21-23/25-48/23/24/25 $1\% \leq C < 3\%$: T; R61-23/25-48/23/24/25 $0.5\% \leq C < 1\%$: T; R61-20/22-48/23/24/25 $0.1\% \leq C < 0.5\%$: T; R20/22-48/23/24/25 $0.01\% \leq C < 0.1\%$: Xn; R48/20/21/22

¹ The classification proposal for all end-points except for Reproductive Toxicity, Developmental (Repr.1A, H360D and Repr. Cat1;R61 respectively) was agreed by the Member States at the TC C&L meeting in May 2007.

² The calculation method for the proposed specific lower concentration limits for T; R48/23/24/25 according to Directive 67/548/EC was agreed by the TC C&L in 2007. Setting specific concentration limits according to the CLP regulation was not discussed by the TC C&L.

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

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	None	-	None	Conclusive data but not sufficient for classification
2.2.	Flammable gases	n.a.	-	-	-
2.3.	Flammable aerosols	n.a.	-	-	-
2.4.	Oxidising gases	None	-	None	Conclusive data but not sufficient for classification
2.5.	Gases under pressure	n.a.	-	-	-
2.6.	Flammable liquids	n.a.	-	-	-
2.7.	Flammable solids	None	-	None	Conclusive data but not sufficient for classification
2.8.	Self-reactive substances and mixtures	None	-	None	-
2.9.	Pyrophoric liquids	n.a.	-	-	-
2.10.	Pyrophoric solids	None	-	None	-
2.11.	Self-heating substances and mixtures	None	-	None	-
2.12.	Substances and mixtures which in contact with water emit flammable gases	None	-	None	-
2.13.	Oxidising liquids	n.a.	-	-	-
2.14.	Oxidising solids	None	-	None	Conclusive data but not sufficient for classification
2.15.	Organic peroxides	n.a.	-	-	-
2.16.	Substance and mixtures corrosive to metals	None	-	None	-
3.1.	Acute toxicity - oral	Acute Tox 2, H300	n.a.	Acute Tox. 1 H300	-
	Acute toxicity - dermal	Acute Tox 3; H311	-	Acute Tox. 2 H310	-
	Acute toxicity - inhalation	Acute Tox 2; H330	-	none	-
3.2.	Skin corrosion / irritation	None	-	-	Conclusive data but not sufficient for classification

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification ¹⁾	Reason for no classification ²⁾
3.3.	Serious eye damage / eye irritation	None		none	Conclusive data but not sufficient for classification
3.4.	Respiratory sensitisation	None		none	-
3.4.	Skin sensitisation	None		-	Conclusive data but not sufficient for classification
3.5.	Germ cell mutagenicity	None		-	Conclusive data but not sufficient for classification
3.6.	Carcinogenicity	None		-	Data lacking
3.7.	Reproductive toxicity	Repr. 1A; H360D	To be discussed.	none	-
3.8.	Specific target organ toxicity –single exposure	None		none	-
3.9.	Specific target organ toxicity – repeated exposure	STOT RE1; H372	C ≥ 0.2%: STOT RE1; H372; 0.02% ≤ C < 0.2 %: STOT RE2; H373	STOT RE 1	-
3.10.	Aspiration hazard	None		none	-
4.1.	Hazardous to the aquatic environment	Aquatic Chronic 1; H410	M-factor: 10	Aquatic Chronic 3; H412	-
5.1.	Hazardous to the ozone layer	None			Data lacking

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

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

Labelling: Signal word:

Danger

Hazard statements:

H360D: May damage the unborn child

H300: Fatal if swallowed

H311: Toxic in contact with skin

H330: Fatal if inhaled

H372: Causes damage to organs through prolonged or repeated exposure

H410: Very toxic to aquatic life with long lasting effects

Precautionary statements:

P201; P 273; P308 +P313; P320; P391; P405; P501

Additional statement on the specific antidote: vitamin K, should be given.

Proposed notes assigned to an entry: none

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification ¹⁾	Reason for no classification ²⁾
Explosiveness	none	-	-	Data conclusive but not sufficient for classification
Oxidising properties	none	-	-	Data conclusive but not sufficient for classification
Flammability	none	-	-	Data conclusive but not sufficient for classification
Other physico-chemical properties <i>[Add rows when relevant]</i>	none	-	-	Data conclusive but not sufficient for classification
Thermal stability	none	-	-	Data conclusive but not sufficient for classification
Acute toxicity	T+:R26/28; T:R24	C_≥7%	T+; R27/28;	-
Acute toxicity – irreversible damage after single exposure	none	-	-	Data conclusive but not sufficient for classification
Repeated dose toxicity	T: R48/23/24/25 Xn: R48/20/21/22	C_≥0.1% 0.01%≤C<0.1%	T; R48/24/25	-
Irritation / Corrosion	none	-	-	Data conclusive but not sufficient for classification
Sensitisation	none	-	-	Data conclusive but not sufficient for classification
Carcinogenicity	none	-	-	Data lacking
Mutagenicity – Genetic toxicity	none	-	-	Data conclusive but not sufficient for classification
Toxicity to reproduction – fertility	none	-	-	Data conclusive but not sufficient for classification
Toxicity to reproduction – development	Repr 1; R61	-	-	-
Toxicity to reproduction – breastfed babies. Effects on or via lactation	none	-	-	Data lacking
Environment	R52/53	-	R52/53	-

¹⁾ Including SCLs

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

Labelling: Indication of danger: **T+**

R-phrases: R61-24-26/28-48/23/24/25-52/53
S-phrases: S53-45-61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Coumatetralyl was classified in 24th ATP to dir 67/548/EC.

2.2 Short summary of the scientific justification for the CLH proposal.

Coumatetralyl is an anticoagulant rodenticide. The CLH proposal is based on the information of the CA report under directive 98/8/EC, and the discussion and conclusions of the TC C&L group in 2006 and 2007. All end-points of the proposal except the classification for developmental toxicity and the setting of specific concentration limits were agreed by the TC C&L as referred in the Follow-up sheet V (FUV) from the meeting of May 2007. However, additional criteria introduced with the 2nd ATP to the CLP regulation relating to aquatic toxicity classification trigger reevaluation of this end-point.

2.3 Current harmonised classification and labelling

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

Hazard Class and Category Code(s):

Acute Tox. 1
Acute Tox. 2
STOT RE 1
Aquatic
Chronic 3

Pictogram, Signal Word Code(s):

GHS06
GHS08

Hazard statement code(s):

H310
H300
H372
H412

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

Classification (Hazard class and R-phrases):

T+; R27/28
T; R48/24/25
R52-53

Labelling (Symbols of Danger, R- and S phrases):

T+
R: 27/28-48/24/25-52/53
S: (1/2-)28-36/37-45-61

2.4 Current self-classification and labelling

Not relevant, as substance was included in Annex I to directive 67/548/EC and is thus included in Annex VI, tables 3.1 and 3.2 of CLP Regulation.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The substance is a biocide, regulated under dir 98/8/EC, and must therefore be classified at Community Level (cf. art. 36(3) of CLP Regulation). The existing classification is proposed to be amended with respect to acute toxicity, repeated dose toxicity, reproductive toxicity (development) and chronic aquatic toxicity. No changes are proposed to the existing classification on physico-chemical properties.

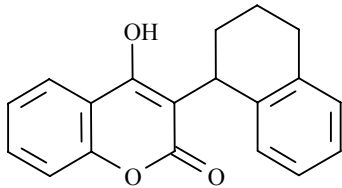
PART B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity and purity

EINECS-No.	227-424-0
Chemical name	3-(alpha-tetralyl)-4-hydroxycoumarin
CAS-No.	5836-29-3
CAS name:	2H-1-Benzopyran-2-one, 4-hydroxy-3-(1, 2, 3, 4-tetrahydro-1-naphthalenyl)-
Other No. (CIPAC, ELINCS)	CIPAC No.: 189
IUPAC Name	IUPAC name: 4-hydroxy-3-(1, 2, 3, 4-tetrahydronaphthalen-1-yl)-2H-chromen-2-one
Common name, Synonym	Coumatetralyl ENE 11183 b (Manufacturer's development code number), Racumin®
Molecular formula	C ₁₉ H ₁₆ O ₃
Structural formula	
Molecular weight (g/mol)	292.3
Purity	≥98,8%
Impurities, additives in the active substance	The specification and details of impurities of the coumatetralyl as placed on the market are presented in the attached confidential annex on impurities.. The impurities are not considered toxicologically significant. The purities of the batches tested in the toxicological and environmental studies are of 98.8-99.8%, with is the specification.

4.10 Physico-chemical properties

In this section summaries and evaluation of data for which robust study summaries are presented in the annex: “CLH report coumatetralyl RSS CAR identity-phys chem” which is reproduced from the final CAR report under the review programme under the biocides directive (98/8/EC are reported, as far as possible in summary tables. Due to an interim period agreement, the robust study summaries are not available in IUCLID.

A summary of the physico-chemical properties of coumatetralyl is given in table 1.3.

Table 1.3 Physico-chemical properties of coumatetralyl

Study	Method	Purity/ Specification	Result	Reference	Section in CA-report
Physical state	Data based on visual or other sensual assessment at room temperature	99.96 % / ≥ 98 %	Solid, crystalline powder	Stöcker, 2001	A3.3.1
Colour	Data based on visual or other sensual assessment at room temperature	99.96 % / ≥ 98 %	White to yellow-grey	Stöcker, 2001	A3.3.2
Odour	Data based on visual or other sensual assessment at room temperature	99.96 % / ≥ 98 %	Characteristic, slight	Stöcker, 2001	A3.3.3
Melting point	Directive 92/69/EC, A.1 (DTA-system)	98.8 % / ≥ 98 %	168.8 °C	Jungheim, 2000	A3.1.1
Boiling point	Directive 92/69/EC, A.2 (DTA-system)	98.8 % / ≥ 98 %	No boiling point up to the composition of the test substance	Jungheim, 2000	A3.1.2

Study	Method	Purity/ Specification	Result	Reference	Section in CA-report
Relative density	Directive 92/69/EC, A.3 (displacement method)	98.8 % / \geq 98 %	1.328 at 20 °C	Jungheim, 2000	A3.1.3
Bulk density			Approx. 1 kg/l	Bayer AG, 1999 (MSDS)	
Vapour pressure	Directive 92/69/EC, A.4 (vapour pressure balance method)	98.8 % / \geq 98 %	< 1.0E-05 hPa (20 °C)	Olf, 2000	A3.2
Surface tension	OECD guideline 115, Directive 92/69/EC, A.5 (ring method)	98.8 % / \geq 98 %	73.08 mN/m at 20.1 °C and 4.383 mg/L (90% saturation) The test substance is not surface active.	Olf, 2001	A3.13
Water solubility	Directive 92/69/EC, A.6 (flask method)	98.9 % / \geq 98 %	at 20 °C:4.40E-03 g/l pH 5.1 (pH 5:4.78E-03 g/l, pH 7: 4.60E-01 g/l,pH 9: 4.65 g/l)	Erstling and Jungheim, 2002a	A3.5
Partition coefficient n-octanol/water	Directive 92/69/EC, A.8 (shaking method)	98.9 % / \geq 98 %	Results at 23 °C demineralised water: Log P _{ow} (pH 5.8) = 2.9 (buffer solutions: log P _{ow} (pH 5) = 3.4, log P _{ow} (pH 7) = 1.5, log P _{ow} (pH 9) = -0.1)	Erstling and Jungheim, 2002b	A3.9
Henry's Law constant	Calculation		At 20°C : K < 6.64.10 ⁻² Pa.m ³ .mol ⁻¹	Stöcker, 2004	A3.2.1

Study	Method	Purity/ Specification	Result	Reference	Section in CA-report
Flash-point	Directive 92/69/EC, A.9	98.8 % / \geq 98 %	The test substance is a solid. The requested test according to EC method A.9 was not necessary. This test guideline is only applicable to liquid materials.	Heitkamp, 2001	A3.12
Flammability	Directive 92/69/EC, A.10	98.8 % / \geq 98 %	The test substance is not highly flammable.	Heitkamp, 2001	A3.11
Evolution of flammable gases when contact with water	Directive 92/69/EC, A.12	98.8 % / \geq 98 %	The test substance does not liberate gases in hazardous amounts upon contact with water.	Heitkamp, 2001	A3.11
Pyrophoric properties	Directive 92/69/EC, A.13	98.8 % / \geq 98 %	The EC method A.13 was omitted as the test substance did not deliver indications of pyrophoric properties during the realisation of tests as defined in EC methods A.10 and A.12.	Heitkamp, 2001	A3.11
Explosive properties	Directive 92/69/EC, A.14	98.8 % / \geq 98 %	The test substance has no explosive properties	Heitkamp, 2001	A3.15
Self-ignition temperature (Auto-flammability)	Directive 92/69/EC, A.16	98.8 % / \geq 98 %	No self-ignition up to the melting point at 168.8°C	Heitkamp, 2001	A3.11
Oxidizing properties	Directive 92/69/EC, A.17	98.8 % / \geq 98 %	The test substance has no oxidising properties	Smeykal, 2006	A3.16
Granulometry	No data submitted				

Study	Method	Purity/ Specification	Result	Reference	Section in CA-report
Solubility in organic solvents	Comparable to OECD-Guideline 105	98.8 % / \geq 98 %	Results at 20 °C: 2-Propanol: 16.4 g/l, Dichloromethane: 44.3 g/l Xylene: 2.7 g/l, Polyethylenglycol: 37.9 g/l Acetone: 25.4 g/l, Ethylacetate: 11.8 g/l, Acetonitrile: 6.8 g/l, Dimethylsulfoxide: >250 g/l Cyclohexanone: 80.9 g/l Toluene: 3.9 g/l	Jungheim, 2001	A3.7
Thermal stability	Directive 92/69/EC, A.1 (Test was conformed using Differential-and Isothermal Step-Thermal Analysis (DTA and ISTA))	98.8 % / \geq 98 %	Exothermal decomposition starts at 195 °C	Jungheim, 2000	A3.10
Dissociation constant	In accordance with OECD 112	98.8 % / \geq 98 %	pK-value in water/acetone = 5.3	Jungheim, 2001	A3.6
Viscosity			Not applicable, active substance is a solid		A3.14
Reactivity towards container material	Coumatetralyl has been produced by Bayer since 1957. For at least 25 years the active substance has been packaged in an LDPE sack enclosed in a steel drum. Based upon this experience, recommended container materials are plastic materials e.g. PE or high-grade steel. Aluminium, unprotected steel or iron are not suitable for container material.			Böcker, 2004	A3.17

2 MANUFACTURE AND USES

2.11 Manufacture

No data available in the CA-report under 98/8/EC review programme

2.12 Identified uses

Coumatetralyl is a biocidal active substance used in products to control rodents, especially rats. It is included on Annex I to the biocides directive for use in PT 14, rodenticide.

4.11 Mode of action

Coumatetralyl is classified as a first-generation anticoagulant rodenticide. Anticoagulant rodenticides are vitamin K antagonists, thereby inhibiting coagulation of the blood and making the walls of the blood vessels permeable. The mode of action of coumatetralyl was described by Andrews (1999):

The main site of action is the liver and the main effect consists in inhibition of blood clotting by interference with the hepatic synthesis of the vitamin K-dependent clotting factors II, VII, IX and X which effectively inhibits de-novo synthesis of vitamin K₁, thereby interrupting cellular recycling of vitamin K₁. Vitamin K₁ in its hydroquinone form is an essential co-factor for the synthesis of functional clotting factors. The function of vitamin K₁ is the post translational transformation of the precursor protein to respective functional clotting factors by γ -carboxylation of their glutamic acid moieties, which in turn, enhances the binding of Ca⁺⁺ by chelating phosphate on the phospholipids, thus accelerating, and providing a template for, the blood clotting mechanism. Concomitant with the γ -carboxylation of glutamic acid residues to form clotting factors, an epoxidation reaction occurs, converting the active form of vitamin K₁, the hydroquinone, to vitamin K₁ 2, 3-epoxide, which in turn is returned to vitamin K₁ quinone by vitamin K₁ 2, 3-epoxide reductase, which in turn has to be reduced to vitamin K₁ hydroquinone, thus forming the vitamin K₁ cycle. The regeneration of vitamin K₁ quinone from vitamin K₁ 2, 3-epoxide is the step inhibited by coumatetralyl.

First-generation anticoagulant rodenticides as coumatetralyl require a few days until the onset of clinical symptoms. Typical symptoms are general weakness, anorexia, blood in faeces or urine, nasal bleeding.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

3.1.1 Conclusions on classification and labelling on physico-chemical properties

Based on the results of the available data, no classification for physico-chemical properties is proposed.

No classification for physico-chemical properties was agreed by the TC CL 2007.

No classification according to the CLP regulation is necessary.

4 HUMAN HEALTH HAZARD ASSESSMENT

In this section summaries and evaluation of data for which robust study summaries are presented in the annex: “CLH report coumatetralyl RSS CAR toxicology” which is reproduced from the final CAR report under the review programme under the biocides directive (98/8/EC are reported, as far as possible in summary tables. Due to an interim period agreement, the robust study summaries are not available in IUCLID.

The data highlighted by the use of a **grey background in the tables** are so-called **key studies**. Results from such studies are the basis for risk assessment. Supplementary studies give additional information for the risk assessment. Key studies have a high reliability, while other studies can be used as supporting evidence and in view of an overall weight of evidence approach. Unless otherwise stated, all studies were conducted according to internationally accepted guidelines and principles for good laboratory practice (GLP). The text related to the table highlights the data used for the risk assessment. These data will in most cases also be the ones relevant for classification.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Table 4.1 gives an overview of the available studies on toxicokinetics of coumatetralyl in the rat.

Table 4.1: Toxicokinetic and metabolism studies with coumatetralyl in rats

Route	Method, Guideline	Test system	Label, Exposure	Dose level	Analysed parameters	Reference
Oral	Methods in accordance with the OECD 417 and the US-EPA, OPPTS 870.7485	Rat, Wistar, <u>Single dose:</u> m+f (1:1), 4/sex/group <u>Repeated dose:</u> m, 5/group	¹⁴ C ring labelled coumatetralyl , Single and repeated exposure	<u>Single application:</u> 0.1 mg/kg bw labelled active substance <u>Repeated application:</u> 0.1 mg/kg bw non-labelled substance on 14 consecutive days and a final dose at day 15	Absorption, distribution, elimination, metabolism	Anderson (1999)
<i>In vitro</i>	Determination of metabolite profile and quantitation of parent compounds in the microsomal fraction and cytoplasmic fraction	Rat, Wistar, Subcellular fraction of liver cells	¹⁴ C ring labelled coumatetralyl	1. Study on dependency of metabolism on various parameters: 0.8 – 6.4 µg/ml 2. Preparative incubation: 31.4 µg/ml	Metabolism	Anderson & Bornatsch (1998)

Route	Method, Guideline	Test system	Label, Exposure	Dose level	Analysed parameters	Reference
	of liver cells, No guideline available.					
Oral	Investigation of the persistence of coumatetralyl in sub-lethally poisoned rats, No guideline available.	Rat, f, 4 - 6/group Examined target organ: liver	Unlabelled coumatetralyl	Single dose of 4 mg/kg bw (sub-lethal)	Persistence	O'Connor et al. (2001)
Oral	Examination of the potency of coumatetralyl to bioaccumulate, No guideline available.	Rat, f, 6/group Examined target organ: liver	Unlabelled coumatetralyl	Repeated dose of 4 mg/kg bw (approx. LD15); three doses with intervals of 12 weeks	Accumulation	Eason et al. (2003)

The toxicokinetic properties of coumatetralyl have been investigated after single and repeated oral dosing in the rat; metabolism was additionally examined in vitro in rat liver cells.

4.1.2 Human information

No information was available.

4.1.3 Summary and discussion on toxicokinetics

Absorption:

The maximum relative concentration in blood plasma after a single oral dose was found 3 hours after administration in males and after 8 hours in females. An absorbed fraction of at least 75% and 86% of administered dose was calculated for males and females, respectively.

Distribution:

After single dosage to rats, 49 – 56% of applied radioactivity was retained in the body (gastrointestinal tract exclusive). After repeated dosage, 18% was retained. Coumatetralyl reaches relatively high concentrations in the liver and the skin. The largest fraction was found in liver (21–25% after single treatment and 7% after repeated dosing), followed by the skin (7-16% after a single dose and 4% of the dose after multiple dosing). All other organs retained less than 1% of the dose at sacrifice.

Excretion:

Excretion was slow in all tests and dependent on sex and on the number of applications (single dose or repeated dose). The primary route of excretion is via the urine and to a smaller extent via faeces. Single-dosed males excreted about 20% of the administered dose with the urine and about 20% with the faeces until sacrifice (7 days post administration). After repeated dosing the ratio shifted towards 44% renal and 33% faecal excretion until sacrifice, which could be an indication of enzyme induction during the 14-day pre-treatment. Single-dosed females excreted about 37% with the urine and about 12% with the faeces until sacrifice.

Excretion of coumatetralyl in the exhaled air was negligible, i.e. less than 0.60% of the administered dose. Plasma curve analysis revealed distinct effects of sex and dose on the elimination process. The toxicokinetic behaviour of radioactivity in the plasma could be characterized by a quick rise followed by a broad maximum and a steady and fairly slow decline. Male rats reached maximum plasma concentration about 3 hours post administration (t_{max}), and t_{max} for females was between 8 and 24 hours post administration. The

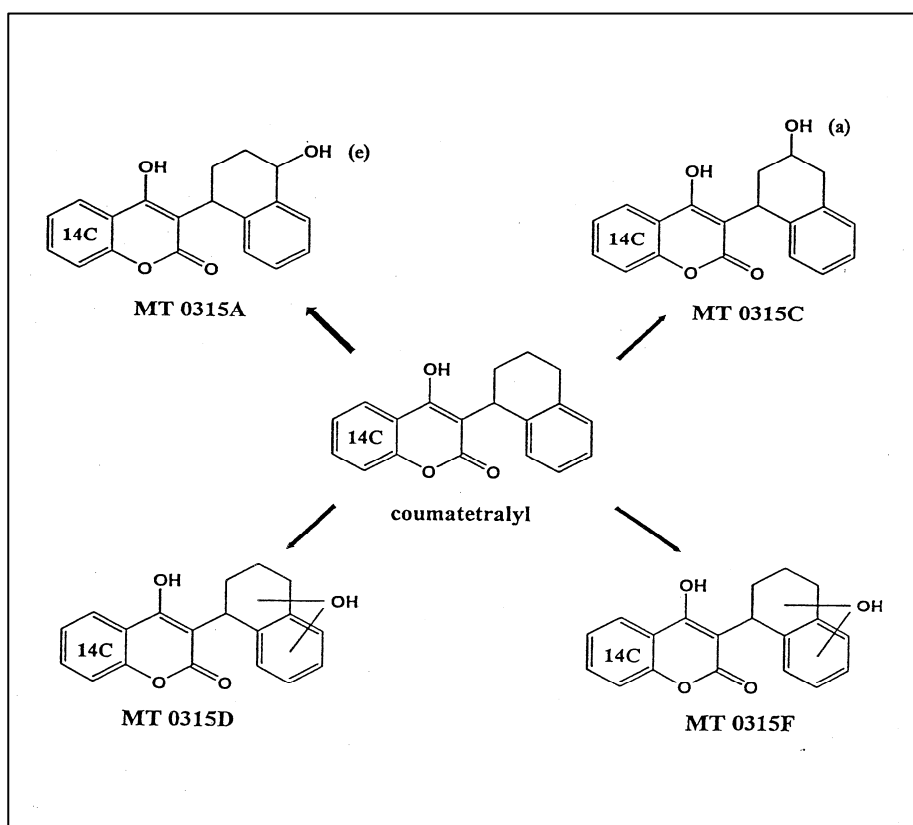
half-lives of the terminal phase after a single dose application were approximately 71 and 46 hours for male and female rats, respectively. After multiple dosing of males the half-life of the terminal phase was 36 hours. The total clearance (CL_{total}) was very low with approximately 0.02 ml/min/rat, the renal clearance (CL_R) ranged from 0.004 to 0.007 ml/min/rat. The theoretical volume of distribution under steady state conditions (V_{ss}) was also sex dependent: 54% of the body volume for male rats and 28% for females. The computed V_{ss} for pre-treated males was 18% of the body volume. The mean residence time (MRT), which is indicative for the "body burden", was approximately 98 and 70 hours after a single dose to male and female rats and 44 hours after multiple dosing, respectively.

In-vivo metabolism:

The molecule is extensively metabolised within the organism. Sex and dose had only minor effects on the metabolite profiles. The main pathway of biotransformation proceeded via hydroxylation of the tetrahydronaphthyl moiety. Four metabolites of coumatetralyl were identified in urine and faeces (Figure 1). The main metabolite MT 0315A accounted for up to 27% of the applied dose. Additionally, three isomers of the main metabolite (MT 0315C, MT 0315D, MT 0315F) were detected, all far below 10% of the dose. In urine two further metabolites (MT 0315B and MT 0315E) could be verified (both approx. 2%). Only traces of the dose in urine and faeces were unchanged coumatetralyl. The total rate of identification ranged from 23% (42% total radioactivity excreted) to 37% (77% total excreted) of administered dose.

An in-vitro metabolism study was conducted to determine the metabolite profile and to isolate and identify the main metabolites of coumatetralyl. All six metabolites from the rat in-vivo study were also found in-vitro.

Figure 1: Proposed metabolism of coumatetralyl



Mode of action:

Anticoagulant rodenticides are vitamin K antagonists. The mode of action of coumatetralyl was described as follows:

The main site of action is the liver and the main effect consists in inhibition of blood clotting by interference with the hepatic synthesis of the vitamin K-dependent clotting factors II, VII, IX and X which effectively

inhibits de-novo synthesis of vitamin K₁, thereby interrupting cellular recycling of vitamin K₁. Vitamin K₁ in its hydroquinone form is an essential co-factor for the synthesis of functional clotting factors. The function of vitamin K₁ is the post translational transformation of the precursor protein to respective functional clotting factors by γ -carboxylation of their glutamic acid moieties, which in turn, enhances the binding of Ca⁺⁺ by chelating phosphate on the phospholipids, thus accelerating, and providing a template for, the blood clotting mechanism. Concomitant with the γ -carboxylation of glutamic acid residues to form clotting factors, an epoxidation reaction occurs, converting the active form of vitamin K₁, the hydroquinone, to vitamin K₁ 2, 3-epoxide, which in turn is returned to vitamin K₁ quinone by vitamin K₁ 2, 3-epoxide reductase, which in turn has to be reduced to vitamin K₁ hydroquinone, thus forming the vitamin K₁ cycle. The regeneration of vitamin K₁ quinone from vitamin K₁ 2, 3-epoxide is the step inhibited by coumatetralyl.

First-generation anticoagulant rodenticides as coumatetralyl require a few days until the onset of clinical symptoms. Typical symptoms are general weakness, anorexia, blood in faeces or urine, nasal bleeding.

There are no convulsions, squealing or other sounds connected with the poisoning process. The target animal seems to die with no apparently painful symptoms.

4.2 Acute toxicity

Table 4.2: Acute toxicity of coumatetralyl

Route	Method, Guideline	Species, Strain, Sex, No/group	Dose levels, duration of exposure	Value LD50/LC50	Reference
Oral	OECD 401, US-EPA, Subdivision F, 81-1	Rat, Wistar, m+f (1:1), 5/sex/group	1 to 500 mg/kg bw (m+f), single oral dose	30/15 mg/kg bw (m/f)	Bomann (1992a)
Oral	No guideline, No GLP	Rat		< 20 mg/kg bw (m+f)	Herrmann (1973)
Oral	No guideline, No GLP	Rat		5 - 25 mg/kg bw (m+f)	Kimmerle (1958)
Oral	No guideline, No GLP	Mouse		2000 – 4000 mg/kg bw (m)	Herrmann (1973)
Oral	No guideline, No GLP	Guinea pig		approx. 250 mg/kg bw	Kimmerle (1958)
Oral	OECD 401, US-EPA, Subdivision F, 81-1	Rabbit, New Zealand, m+f (1:1), 5/sex/group	50 to 500 mg/kg bw (m), 50 to 750 mg/kg bw (f), single oral dose	> 500 mg/kg bw (m), > 750 mg/kg bw (f)	Bomann (1992b)
Oral	No guideline, No GLP	Rabbit		Death occurred at 10 mg/kg bw and above	Kimmerle (1958)
Oral	No guideline, No GLP	Cat		Death occurred at 50 mg/kg bw and above	Kimmerle (1958)
Oral	No guideline, No GLP	Dog		approx. 35 mg/kg bw	Herrmann (1960)
Dermal	OECD 402, US-EPA, Subdivision F, 81-2	Rats, Wistar, m+f (1:1), 5/sex/group	50 - 2000 mg/kg bw, 24 hours, one single dermal application	258 mg/kg bw (f) 100 mg/kg bw <LD ₅₀ (m) < 500 mg/kg bw	Bomann (1992c)
Dermal	No guideline, No GLP	Rat, m	4 hours	25 – 50 mg/kg bw	Kimmerle (1970a)

Route	Method, Guideline	Species, Strain, Sex, No/group	Dose levels, duration of exposure	Value LD50/LC50	Reference
Dermal	No guideline, No GLP	Rat, m	4 hours	61.9 mg/kg bw	Kimmerle (1970b)
Dermal	No guideline, No GLP	Rat, f	7 days	approx. 5 mg/kg bw	Kimmerle (1970a)
Inhalation	Comparable to OECD 403 No GLP	Rat, Wistar, m+f (1:1), 10/sex/group, additionally groups with 20 f dosed with 145.0 or 184.0 mg/m ³	30 - 202 mg/m³ 4 hours, (head and nose) MMAD not specified.	0.063 mg/l/4h) (m), (0.039 mg/l/4h) (f),	Pauluhn (1982)
Inhalation	Comparable to OECD 403 No GLP	Mouse, NMRI, m 20/group	53 - 117 mg/m ³ 4 hours	approx. 54 mg/m ³ /4h (equiv. to 0.054 mg/l/4h) (m)	Pauluhn (1982)
Waiver for acute toxicity studies in rat by inhalation					

From Doc. III-A6.1.1, 6.1.2 and 6.1.3

Acute toxicity: oral

Coumatetralyl is highly toxic by acute oral exposure. The rat appears to be the most sensitive species with LD₅₀ values for coumatetralyl of 30 and 15 mg/kg bw for males and females, respectively in a guideline study (Bomann, 1992a).

: The oral LD₅₀ values in rabbits is of > 500 mg/kg bw for males and >750 mg/kg for females based on a guideline study (Bomann, 1992b). Other mammalian species (mouse, guinea pig, dog and cat) are less susceptible to single oral doses of coumatetralyl.

Based on the available IUCLID data and none guideline compliant studies, the sensitivity of different species to the oral toxicity of coumatetralyl seems to be in declining order: rat/dog/cat/rabbit/mouse/guinea pig. However it is not known if the data are fully comparable.

Acute toxicity: dermal

The LD₅₀ values from a guideline study in rats were 100 - 500 mg/kg bw for males and 258 mg/kg bw for females (Bomann, 1992c). The lowest value is supported by the results from three non-guideline studies.

Acute toxicity: inhalation

No acute and short-term inhalation guideline-studies are available. The acute toxicity by inhalation was investigated in rats and in the mouse in an unpublished test reported in IUCLID (Pauluhn, 1982). The study was not considered as reliable to establish a precise LC₅₀ value because of major methodological and reporting deficiencies with the current guideline. However, despite its deficiencies, the study can be used as supportive for classification/labelling of coumatetralyl. The study indicates an LC₅₀ in rats of 0.063 mg/l/4h (males) and 0.039 mg/l/4h (females) while the mouse LC₅₀ is reported to be 0.054mg/l/4h. The applicant proposed classification according the Directive 67/548/EEC as T; R25 and submitted a justification for non-performance of the study for acute and short-term studies by inhalation for coumatetralyl.

4.2.1 Conclusion on classification and labelling

Based on the data supporting the dossier for coumatetralyl, in relation to the criteria on Annex VI to directive 67/548, the following classification for acute toxicity according to Directive 67/548/EEC is proposed: T+; - R26/28 very toxic by inhalation and if swallowed T; R24: Toxic in contact with skin. The corresponding labelling is T+; R24-26/28. This classification was agreed by the TC CL group in November 2006.

According to the available data and the criteria of Regulation no. 1272/2008, coumatetralyl should be classified as Acute Tox 2, H300: Fatal if swallowed, Acute Tox 3; H311 Toxic in contact with skin and Acute Tox 2; H330: Fatal if inhaled. Labelling will be Signal Word: Danger and Hazard Statements H300, H330 and H311.

This classification was agreed by the TC CL group in May 2007.

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

This end-point target organ toxicity after single exposure is considered covered by the section on acute toxicity (see point 4.2 above) and irritation (see point 4.4 below)

Conclusion: no classification is proposed for STOT SE.

4.4 Irritation

4.4.1 Skin irritation

Table 4.3: Skin irritation of coumatetralyl

Species	Method	Average score 24, 48, 72 h		Reversibility yes/no	Result	Reference
		Erythema	Oedema			
Rabbit	OECD 404, US-EPA (TSCA §798.4470, §798.4500 and Subdivision F, §81-4, § 81-5)	0.0	0.0	No	Not irritating	Renhof (2003a)
Rabbit	No Guideline No GLP	0.0 (intact skin) 0.4 (scarified skin)	0.0 (intact skin) 0.4 (scarified skin)		Not irritating	Bhide (1984a)

Skin irritation: Coumatetralyl was not irritating to the rabbit's skin in a guideline study (Renhof, 2003a).

Conclusion on classification for irritative effect to the skin:

No classification or labelling for skin irritation according to Regulation 1272/2008 or Directive 67/548/EEC is warranted. This conclusion was endorsed by the TC CL group in November 2006.

4.4.2 Eye irritation

Table 4.4: Eye irritation of coumatetralyl

Species	Method	Average score 24, 48, 72 h				Reversibility yes/no	Result	Reference
		Cornea	Iris	Conjunctiva				
				Redness	Chemosis			
Rabbit	OECD Guideline 405 GLP	0.0	0.0	0.0	0.0	yes	Not irritating	Renhof, (2003b)
Rabbit	No Guideline No GLP	0.0	0.0	0.0	0.0		Not irritating	Bhide (1984b)

Eye irritation: Coumatetralyl was not irritating to the rabbit's eye in study compliant to OECD guidelines (Renhof, 2003b).

Conclusion on classification for irritative effect to the eyes:

No classification or labelling for eye irritation according to Regulation 1272/2008 or Directive 67/548/EEC is warranted. This conclusion was endorsed by the TC CL group in November 2006.

4.4.3 Respiratory tract irritation

No information on irritative effects to the respiratory tract was reported.

Conclusion on classification for respiratory tract irritation

No classification or labelling for respiratory tract irritation is warranted for coumatetralyl. This conclusion was endorsed by the TC CL group in November 2006.

4.5 Corrosivity

This end-point is described under point 4.4.1 Skin irritation.

Conclusion on classification for corrosivity

No classification is proposed.

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 4.5: Skin sensitisation of coumatetralyl

Species	Method	Number of animals sensitized/total number of animals	Result	Reference
Guinea pig	Buehler Patch Test according to OECD 406	0/20 (24 h after challenge), 0/20 (48 h after challenge)	Negative; no skin-sensitising	Stropp (1998)

	and US-EPA, Suvdivision F, § 81-6		potential	
--	---	--	-----------	--

Skin sensitisation: not sensitising.

Due to coumatetralyl intrinsic anticoagulant properties and its toxicity, it was not possible to conduct a guinea-pig maximisation test under the current guidelines with application of irritating concentrations of the test substance.

A Magnusson and Kligman guinea-pig maximisation test was initiated in order to assess the sensitising potential of coumatetralyl. Five days following the intradermal injection of 5% of coumatetralyl in polyethylene glycol (PEG) 400 some animals showed clinical signs of toxicity. However, the test had to be terminated on day 6, as three animals out of ten died and the remaining animals were killed in a moribund state on that same day.

Therefore coumatetralyl potential to induce skin sensitisation was tested using the Buehler method (Stropp G., 1998). In this study a 50% coumatetralyl suspension in PEG 400 was used for the first induction. The challenge with a 25% coumatetralyl formulation did not induce any skin effect. It was concluded that under the conditions of the Buehler patch test and with respect to the evaluation criteria coumatetralyl exhibits no skin sensitisation potential.

The conductance of the Buehler test instead of an adjuvant test was scientifically explained by the toxicity of coumatetralyl in intradermal injections and the explanation is acceptable.

Conclusion on classification and labelling for skin sensitising potential

No classification/labelling of coumatetralyl for skin sensitisation according to Regulation 1272/2008 or Directive 67/548/EEC is warranted based on the result of a Buehler test by Stropp (1998). This conclusion was endorsed by the TC CL group in November 2006.

4.6.2 Respiratory sensitisation

No data were available indicating a potential of coumatetralyl to be a respiratory sensitizer.

Conclusion of classification and labelling

No classification for respiratory sensitisation is proposed for coumatetralyl.

The conclusions that no classification is warranted for sensitising effects were endorsed by the TC C&L group.

4.7 Repeated dose toxicity

4.7.1 Non-human information

Key studies shaded in grey in the table. Summaries of these studies can be found in the appended CAReport, section 6. Some studies were only filed by the applicant as IUCLID summaries. This is indicated in column 7 of the table. Reliability indicators are included in column 2.

Table 4.6 Short-term repeated dose, subchronic and chronic toxicity of coumatetralyl

Route	Duration of study, Method Study reliability.	Species, Strain, Sex, no/group	Dose levels, Frequency of application	Results	LOAEL /NOAEL	Reference RSS or only IUCLID summary available
Oral/ diet	3 weeks, Pilot feeding study according to OECD 407, No GLP. Valid with restrictions	Rat, Wistar, m+f 3 per sex/group	130 and 270 ppm Racumin® Tracking Powder 0.769% containing 1 or 2 ppm coumatetralyl	All animals died after administration of 2 ppm coumatetralyl and one male after feeding of 1 ppm. The clinical signs observed (paleness), prolongation of blood clotting time and internal haemorrhages are consistent with the pharmacological mechanism of coumatetralyl.	LOAEL ≈1 ppm. No NOAEL could be determined.	Andrews (1996) IUCLID only
Oral/ gavage	9 weeks, Pilot gavage study, No GLP. Valid with restrictions	Rat, Wistar, m+f, 3 -5 per sex/group	0, 0.01, 0.03, 0.05, 0.1, 0.12, 0.16 or 0.2 mg/kg bw, daily	Deaths occurred in males at 0.16 mg/kg bw/day and above and in females at 0.2 mg/kg bw/day. Blood clotting time in male rats were increased at 0.05 mg/kg bw/day (23 days of treatment) and in females at 0.1 mg/kg bw day (42 days of treatment).	LOAEL: 0.05 mg/kg bw/day in males NOAEL: 0.03 mg/kg bw/day	Andrews (1996) IUCLID only
Oral/ diet	112 days, OECD 408, US-EPA, Sub-division F, § 82-1 Valid,	Rat, Wistar, m+f (1:1), 10 per sex/group	0, 13, 40, 85, 170 ppm Racumin® Tracking Powder daily, containing 0.769 % (These dose levels correspond to 0, 0.0068, 0.0210, 0.0458, 0.0994 mg/kg coumatetralyl bw/day for males and 0, 0.0083, 0.0270, 0.0563, 0.1223 mg coumatetralyl/kg bw/day for females) purity: 0.769% a.s.	Mortality: 14/20 males and 5/20 female died at 170 ppm. <u>Haematology</u> : significantly decreased erythrocyte count in males at 170 ppm. Slight, but statistically significant increase in blood clotting time in males from 40 ppm and above. In females the clotting time values were significantly increased from 85 ppm and above, with at sporadic occurrence of a statistically significantly increased value at 40 ppm. <u>Clinical chemistry</u> : increased cholesterol values, decreased triglyceride values, decrease in total bilirubin from 85 ppm and above in both sexes were seen. <u>Pathology</u> : haemorrhages in many tissues and organs at 170 ppm <u>Histopathology</u> : Stimulated extramedullary haemopoiesis in the liver and the spleen as well as haemopoiesis in the bone marrow at 170 ppm. Hepatic centrolobular cytoplasmatic vacuolation, single	<u>LOAEL</u> : 40 ppm (equivalent to 0,0210/0.0270 mg/kg bw/day in males and females, respectively. <u>NOAEL</u> : 13 ppm equiv. to 0.0068/ 0.0083 mg coumatetralyl/kg bw/day (m/f), based on significantly increased blood clotting time and haemorrhage in males at 40 ppm.	Andrews & Romeike (1997)

Route	Duration of study, Method Study reliability.	Species, Strain, Sex, no/group	Dose levels, Frequency of application	Results	LOAEL /NOAEL	Reference RSS or only IUCLID summary available
				cell necrosis and centrolobular fatty changes in the high-dose animals, primarily in the males.		
Oral/ diet	1 or 3 days, Secondary poisoning study in dogs; poisoned rats served as chow (according to OEPP protocol) Valid with restrictions	Dog, Beagle, m+f, 5/group	Rats were fed for three days with 375 mg/kg coumatetralyl and were then prepared to chow for the dogs. One rat/day, as single dose or on three consecutive days.	<u>Single application:</u> Moderate increase of prothrombin time (2 of 5 animals), the value peaked at day 3 after exposure. <u>Repeated dose:</u> All dogs exhibited an increased prothrombin time; the value peaked at day 5 after study initiation. Prothrombin times returned to normal values rapidly thereafter.	No LOAEL/NOAEL set due to study protocol (unclear dosing)	Berny (1999) IUCLID only
Oral	Sub-chronic	dog	Study not performed. Waiver submitted.			Lautraite (2003b)
Oral	chronic	rodent	Study not performed. Waiver submitted.			Lautraite (2003b)

Sub-chronic oral toxicity study in rats:

A guideline feeding study over 16 weeks was performed in rats with a formulation of coumatetralyl, Racumin® 0.75% Tracking Powder (Andrews & Romeike, 1997). The study is acceptable as a subsequent submission of the composition of the formulation was provided by the applicant showing that none of the non-active components are expected to interact toxicologically with coumatetralyl.

Mortality in the high dose group (approx. 0.1 mg/kg bw/day) was 70% in males and 25% in females. No mortality was seen at any lower dose level. Animals that died on study showed direct or indirect signs of haemorrhages, i.e. either dark discoloration of stomach and/or intestinal contents, dark red discoloration of testes, lungs or the abdominal cavity, or pale liver, kidneys, lungs and spleen.

The effects seen in the subchronic study were directly or indirectly related to the well-known pharmacological effects of coumatetralyl on blood clotting. Effects observed were generally haemorrhages and pallor and reduced activity before the death of the animal. Blood clotting time was consistently (and statistically significantly) increased in both sexes at 85 ppm and above. A slight (5-10%) but statistically significant increase in blood clotting time was observed consistently in males fed 40 ppm at all time points except the last one. In females of the 40 ppm group, only one time point showed statistical significant prolonged clotting time. The effect on blood clotting time was dose dependent in both sexes.

Therefore, the statistically significant dose dependent effect on blood clotting in males at 40 ppm (0.021 mg/kg bw/day) and in both sexes from 85 ppm is regarded as adverse.. No measurement of the prothrombin levels (possibly more sensitive parameter) were performed, and no other study is available on subchronic or chronic toxicity of coumatetralyl. Therefore a conservative interpretation of the result of this study has been chosen.

The NOAEL is therefore set at 13 ppm equivalent to 0.0068 mg coumatetralyl/kg bw/day in males. Prolonged blood clotting time occurs at and above the dose level of 40 ppm, corresponding to 0.021 and

0.027 mg/kg bw/day in males and females, respectively. At this effect level, blood clotting function is impaired and this is considered a serious functional adverse effect on the blood.

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

The effects on blood clotting and haemorrhages seen in males in the oral subchronic study in the rat (Andrews & Romeike, 1997) at a dose level 0.021 mg/kg bw/day are regarded as serious functional impairment.

The criteria for classification with T; R48 include a guidance value of 50:10 = 5 mg/kg bw/day based on an oral rat subchronic study. Therefore, classification as T; R48/25 is relevant for coumatetralyl.

As the mechanism of toxicity of coumatetralyl (and other anticoagulant rodenticides), i.e. vitamin K1 antagonism, is independent of the route of exposure, classification with T; R48 is also relevant for the other routes the following classification/labelling for coumatetralyl is proposed for repeated dose toxicity according to Directive 67/548/EEC.

Specific concentration limits

No guidelines for setting specific concentration limits under the DSD for repeated dose toxicity are available. The proposed method for setting SCL was agreed by the TC C&L group in May 2007. The effect level (impaired blood clotting and haemorrhages) was 0.021 mg coumatetralyl/kg bw/day in male rats, based on a 16 week oral study. The ratio between this effect level and the cut-off level for T; R48/25 of 50 : 10 = 5 mg/kg bw/day is 238. The generic concentration limits for preparations containing a substance classified as T; 48 according to the DPD are 10% for T; R48 and 1% for Xn; R48.

Specific concentration limits can be calculated as 10% : 238 = 0.04% for T; R48 and 1% : 238 = 0.004% for Xn; R48. However, in order to avoid too many different levels specific concentration limits, it is proposed to use the orders of magnitude, in this case 2, in calculating a specific concentration limit. Subsequently, specific concentration limits of 10%:100 = 0.1% for T; R48/25 and 0.01% for Xn; R48/22 are proposed. The same concentration limits are proposed for the dermal and inhalation routes, as no specific data are available for these routes.

4.7.3 Conclusion on the classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

The following proposal for repeated exposure toxicity is proposed for coumatetralyl: T, R48/23/24/25: Toxic, danger of serious damage to health by prolonged exposure by inhalation, in contact with skin and if swallowed.

This classification proposal was endorsed by the TC C&L group in November 2006.

The proposed specific concentration limits for the end-point of repeated dose toxicity under the DSD are:

C > 0.1%: T; R48/24/25/26

0.01% < C < 0.1%: Xn; R48/20/21/22.

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

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

As described above under point 4.7 the effect level for the statistically significant increased blood clotting time and haemorrhages the repeated dose toxicity, is 0.021 mg/kg bw/day in male rat in a 16-week oral study (Andrews & Romeike, 1997), which is in accordance with current guidelines. The effect on blood coagulation time is regarded as a serious functional impairment of the coagulation process.

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

The effects seen in the oral rat repeated dose study are regarded to show the potential to produce a significant toxicity (blood clotting impairment) in humans following repeated exposure. The effect level of 0.021 mg/kg bw/day in the 16 week oral study in rats is significantly lower than the guidance value for classification as STOT RE Cat 1 of 10 mg/kg bw/day based on a 90 day study. Therefore classification of coumatetralyl as STOT RE Cat 1 is proposed.

As the mechanism of toxicity of coumatetralyl (and other anticoagulant rodenticides), i.e. vitamin K1 antagonism, is independent of the route of exposure, classification for specific target organ toxicity repeated exposure (STOT RE) will be relevant for the dermal and inhalation routes as well.

Specific concentration limits

The critical effect of coumatetralyl (impaired blood clotting and haemorrhages) occurs at a very low level 0.021 mg coumatetralyl/kg bw/day (male rats, 16 week oral study). The ratio between this effect level and the guidance value (GV) for category 1 STOT RE 10 mg/kg bw/day is 476. Therefore, specific concentration limits are proposed for coumatetralyl. Based on the ECHA Guidance on the Application of the CLP Criteria (2009), these should be calculated as

$$SCL_{\text{-STOT cat1}} = \frac{ED}{GV_{\text{cat1}}} = \frac{0.021 \text{ mg/kg bw/day} \times 100\%}{10 \text{ mg/kg bw/day}} = 0.2\%$$

$$SCL_{\text{-STOT cat2}} = \frac{ED}{GV_{\text{cat2}}} = \frac{0.021 \text{ mg/kg bw/day} \times 100\%}{100 \text{ mg/kg bw/day}} = 0.02\%$$

No adjustment for preferred values is needed.

4.8.3 Conclusions on classification and labelling for repeated dose toxicity (STOT RE)

Classification of coumatetralyl as STOT RE Cat 1; H372: “Causes damage organs (blood coagulation) though prolonged or repeated exposure” is proposed. No specification of route of exposure is warranted.

Proposed specific concentration limits:

$C \geq 0.2\%$: STOT RE cat 1: H372

$0.02\% \leq C < 0.2\%$: STOT cat 2 H373

4.9 Germ cell mutagenicity (Mutagenicity)

Coumatetralyl has been tested for genotoxic potential *in-vitro* and *in-vivo* with various end points.

4.9.1 In-vitro genotoxicity

The *in-vitro* screening program included an Ames test, an *in vitro* recombination assay in yeast and an *in vitro* test for gene mutations in mammalian cells.

Coumatetralyl was not found to be a point mutagen in studies on bacteria (Herbold,1986a). The bacterial reverse mutation assay from 1986 was conducted in accordance with generally accepted scientific principles and is found acceptable with respect to the four strains used. However, the test does not follow the updated OECD guideline from 1997 in which the inclusion of a fifth strain is recommended (Salmonella typhimurium strain TA 102 or E. coli WP2) in order to detect certain oxidising mutagens, cross-linking agents and hydrazines that may not be detected by the other Salmonella typhimurium strains. However, as there is no indication from kinetic studies that these effect types could occur, the negative result of the study is considered valid.

In an *in vitro* test for gene mutations in eukaryotic cells (Chinese hamster V79 cells), coumatetralyl was non-mutagenic in the HPRT forward mutation assay, both with and without metabolic activation (Herbold, 2004).

In addition, no mitotic recombinant effects occurred in the yeast strain *Saccharomyces cerevisiae* D7 (Herbold,1986b)..

No *in vitro* test on chromosome aberrations was performed. However the relevant endpoint (damage to the chromosomes) is covered by the *in vivo* micronucleus assay, which would have been the recommended choice for a follow-up procedure, if the *in vitro* cytogenicity study in mammalian cells had been performed and showed to be positive.

Table 4.8: *In-vitro* genotoxicity of coumatetralyl

Test system, Method, Guideline	Organism/ strain(s)	Concentrations tested	Result		Remark	Reference
			+ S9	- S9		
<i>In-vitro</i> gene mutation study in bacteria, Methods comparable to OECD 471, No GLP	Salmonella typhimurium, TA 1535, 1537, 98, 100	<u>First test:</u> + S9/-S9: 0 – 12500 µg/plate <u>Repeat test:</u> + S9/-S9: 0 – 2000 µg/plate (TA 1535) 0 – 8000 µg/plate (TA 100, 1537, 98)	Neg.	Neg.	Doses from 250 µg/plate onward cause bacteriotoxic effects	Herbold (1986a)
<i>In-vitro</i> mitotic recombination assay in yeast, Methods comparable to OECD 481, No GLP	<i>Saccharomyces cerevisiae</i> D7	<u>First and repeat test:</u> + S9/-S9: 0 – 10000 µg/ml	Neg.	Neg.	Cytotoxicity was observed over the entire range of concentrations used. Substance precipitation at 5000 µg/ml and above.	Herbold (1986b)

Test system, Method, Guideline	Organism/ strain(s)	Concentrations tested	Result		Remark	Reference
			+ S9	- S9		
<i>In-vitro</i> gene mutation assay in mammalian cells (HPRT assay) OECD 476	V79 cells	<u>First and repeat test:</u> + S9/-S9: 75-900 µg/ml	Neg.	Neg.	No precipitation occurred in the medium with or without S9 mix. Significant concentration-related cytotoxicity.	Herbold (2004)

4.9.2 In vivo genotoxicity

In the *in vivo* micronucleus test (Herbold 1987), which is compliant with the OECD guideline at the time but not performed according to GLP, the administration of single oral doses of coumatetralyl at doses up to 1000 mg/kg induced the same clinical signs as observed in the acute toxicity studies (apathy, reduced motility, digging and grooming movements, bristling coats, staggering gaits, prostration on stomach, salivation, jumping spasms and dyspnoea) and a reduced erythrocyte formation. In the second trial of the test, at the 48-hour sample time, there was a statistically significant increase ($p \leq 0.05$) in micronucleated polychromatic erythrocytes (MPE) per 1000 polychromatic erythrocytes (PCE) at the highest dose level (1000 mg/kg). However, the effect is not considered biologically meaningful because:

- 1) there was no evidence of a dose-related increase in MPE,
- 2) the incidence of MPE in the negative control group was relatively low (1.0 ± 0.8) compared to the negative control group in test 1 (1.2 ± 1.1) and in test 2, sample time 72 h (1.7 ± 1.4), and
- 3) there was no increase in MPE per 1000 PCE in the first test (750 mg/kg).

Current guidelines recommend the scoring of more than 2000 PCE. The potential effect on the chromosomes is not adequately clarified, because the slide assessment was not extended such that more than 2000 PCE were scored for MPE incidence per animal. However, despite the lower number of PCE, and the study is considered acceptable, because a clear positive response of the positive control in the first test demonstrated sufficient sensitivity of the test system. Thus, it is considered unlikely that the performance of a repeat test would detect a statistically significant, dose-related response at a 1.5-fold increase level over control using 7-10 animals/group with a background incidence of 1-1.5 MPE/1000, when the first test did not show any increase.

A negative *in vivo* dominant lethal test was reported in IUCLID. However, the study and report qualities are deficient. The result may have been biased by too low doses (no toxicity seen), and the low number of animals used (max. 15 instead of 30-50 females per group).

Table 4.8: *In vivo* genotoxicity of coumatetralyl

Type of test, Method/ Guideline	Species, Strain, Sex, no/group	Frequency of application	Sampling times	Dose levels	Results	Remarks	Reference
<i>In-vivo</i> micronucleus assay, Comparable to OECD	Mouse, NMRI, 5/sex/group	One oral application	Bone marrow, <u>First test:</u> 24, 48, 72h post-	<u>First test:</u> 0 or 750 mg/kg bw <u>Second test:</u> 0, 500, 750 or 1000 mg/kg	No clastogenic effects. Same clinical signs	Maximum tolerable dose: 500 mg/kg bw	Herbold (1987)

Type of test, Method/ Guideline	Species, Strain, Sex, no/group	Frequency of application	Sampling times	Dose levels	Results	Remarks	Reference
474, No GLP			application <u>Second test:</u> 48 and 72h post-application	bw	as seen in acute toxicity studies. Reduced erythrocyte formation.		
<i>In-vivo</i> Dominant lethal test OECD 478	Mouse, Swiss, 5 m/ group	5 daily oral applications	Treated males treated over 8 weeks with 3 females/week. Females sacrificed day 14 of gestation	0.015; 0.03 x 0.06 mg/kg bw/day	Negative. No substance-related induction of lethal mutations.		Balakrishna Murthy (1989)

From Doc. III –A6.6

4.9.3 Human information

No information from humans is available on the mutagenicity of coumatetralyl.

4.9.4 Other relevant information

QSAR analysis of the results of a structural alert test performed using a computer program – DEREK showed no indication of a potential genotoxicity.

4.9.5 Summary and discussion of mutagenicity

The available data indicate that coumatetralyl does not cause permanent transmissible changes in the amount or structure of a single gene or gene segments, a block of genes or chromosomes. Overall coumatetralyl is unlikely to pose a genotoxic hazard to man.

4.9.6 Conclusion on classification and labelling

No Classification/labelling for genotoxicity according to Directive 67/548/EEC is warranted. No Classification/labelling for germ cell mutagenicity according to Regulation 1272/2008 is warranted. The TC C&L group concluded in November 2006 that classification of coumatetralyl for mutagenicity was not required.

4.10 Carcinogenicity

4.10.1 Non-human information

No long-term study was conducted for the evaluation of the carcinogenicity of coumatetralyl. A waiver (Lautraite, 2003b) was submitted for the non-conduction of such a study. The scientific justification for the non-conduction of a carcinogenicity study with coumatetralyl is based on:

- the lack of mutagenic/genotoxic effects of coumatetralyl,
- the absence of any other effects in the subchronic study in rats that may lead to non-genotoxic carcinogenesis,
- the absence of any carcinogenic effects following long-term administration of warfarin, a coumarin compound, in humans. The argument of structural relationship with warfarin, is acceptable with respect to the mechanism of action of the two compounds. However, coumatetralyl is not metabolised to any compound related to warfarin in chemical structure. Carcinogenic effects of metabolites can thus not be completely excluded based on the SAR argument. However, due to the restrictions on human exposure required in the proposal for Annex I inclusion, non-genotoxic carcinogenicity is of low concern. Potential for genotoxic carcinogenicity of metabolites is expected to be low because of the non-mutagenic effect of coumatetralyl itself.
- the low risk of long-term exposure during manufacturing and use and of long-term exposure of the public population as well as indirect exposure via the environment, due to the physico-chemical properties of the substance and the formulation and their use pattern.

It is foreseen that the practical difficulties in finding suitable, non-lethal doses for long-term administration of coumatetralyl would be almost impossible to overcome and the conduct of such a study would possibly be unethical and contrary to Directive 86/609/EEC on animal welfare.

4.10.2 Human information

No data are available.

4.10.3 Other relevant information

In addition to the elements brought forward in the waiver, the applicant has submitted the results of a structural alert test performed using a computer program – DEREK. In that QSAR analysis coumatetralyl has no indication of a potential genotoxicity or carcinogenicity.

4.10.4 CONCLUSION ON CLASSIFICATION AND LABELLING

According to the criteria of directive 67/548/EEC and those of Regulation 1272/2008, no classification and labelling for carcinogenicity is warranted for coumatetralyl.

4.11 Reproductive toxicity

Key studies shaded in grey in the table. Summaries of these studies can be found in the appended CAReport, section 6. Reliability indicators are included in column 2.

Table 4.10: Summary table of reproductive studies with coumatetralyl

Route of exposure	Test type, Method, Guideline	Species, Strain, no/group	Exposure Period	Doses	Critical effects 1) dams 2) foetuses	Maternal toxicity NOAEL / LOAEL	Teratogenicity Embryo-toxicity NOAEL / LOAEL	Reference
	Study of fertility	Not performed. Justification for non-submission available						Lautraite (2004)
Oral / gavage Reliability 2	Developmental toxicity test, OECD 414, US-EPA, Subdivision F, § 83-3 and 712-C-94-207 Valid	Rat, HanIbm: WIST, 25 f/dose group and 29 f/control	Day 6-20 post mating	0, 0.035, 0.07 or 0.14 mg/kg bw	1) profuse bleedings, symptoms of anaemia and mortalities at 0.07 mg/kg and above. 2) no evidence for teratogenic potential	NOAEL = 0.035 mg/kg bw; LOAEL = 0.070 mg/kg bw	Teratogenicity NOAEL: 0.14 / LOAEL >0.14 mg/kg bw; Embryotoxicity NOAEL: 0.14 / LOAEL: >0.14 mg/kg bw	Becker & Biedermann (1996a)
Oral / gavage Reliability 2	Developmental toxicity test, OECD 414, US-EPA, Subdivision F, § 83-3 and 712-C-94-207 Valid	Rabbit, Chbb:CH 24 f/group	Day 6-27 post mating	0, 0.0125, 0.025 or 0.05 mg/kg bw/day	1) internal and external bleedings and mortalities at 0.025 mg/kg and above 2) at 0.05 mg/kg bw total post implantation loss in one dam.	NOAEL 0.0125 mg/kg bw /; LOAEL 0.025 mg/kg bw	<u>Teratogenicity:</u> NOAEL: 0.05 / LOAEL > 0.05 mg/kg bw; <u>Embryotoxicity:</u> NOAEL: 0.025 mg/kg bw / ; LOAEL: 0.05 mg/kg bw	Becker & Biedermann (1996b)

From Doc. III A-6.8.1 and A-6.8.2

4.11.1 Effects on fertility

4.11.1.1 Non-human information

No single or multiple generation studies are available for coumatetralyl.

A scientifically justified waiver for the required multigeneration study with coumatetralyl based on the following argument was accepted by the RMS:

- the long half-life of the active compound would result in high body levels following the pre-mating period thus rendering the animals susceptible to death by haemorrhage from the natural events of reproduction and parturition,
- technical difficulties in achieving of a sub-MTD level at which a potential reproductive effect could be seen. The practical difficulties of long-term administration of coumatetralyl are such that an attempt at a study would be certain to fail and would be unethical and contrary to Directive 86/609/EEC.
- the absence of effect on reproduction in the developmental toxicity studies in rats and rabbits.
- residue levels in plant foodstuffs and water are expected to be negligible due to the physical-chemical properties and the use pattern of the product.
- the absence of residues in plant foodstuffs and water.

4.11.1.2 Human information

No human data are available on effects on fertility of coumatetralyl.

Warfarin, which is structurally and functionally comparable to coumatetralyl, was not classified for fertility.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

No teratogenic effects on the developing foetus were seen in the animal species (rat and rabbit) tested.

In the **rat**, the NOAEL for teratogenicity and embryotoxicity is 0.14 mg/kg bw, the highest dose tested. Administration of coumatetralyl caused dose-related maternal mortalities at 0.07 mg/kg bw and above. Thus NOAEL of 0.035 mg/kg bw and effect level (LOAEL) of 0.07 mg/kg bw was established for maternal toxicity (Becker and Biedermann, 1996a).

In the **rabbit** the NOAEL for teratogenic effects is 0.05 mg/kg bw, the highest dose tested. For embryotoxicity, the NOAEL was 0.025 mg/kg bw based on the effect on one dam at the dose level of 0.05 mg/kg bw, near total post-implantation loss (probably secondary due to intrauterine bleeding) The NOAEL for maternal toxicity is 0.0125 mg/kg bw, and the LOAEL 0.0250 mg/kg bw/day. Administration from 0.025 mg/kg bw and above caused serious substance-related deaths and external and internal bleedings in the dams. (Becker and Biedermann, 1996b).

The NOAELs for developmental toxicity in the two developmental studies in rats and rabbits may suggest a species difference with NOAEL for rabbits of 0.025 mg/kg bw/day whereas the NOAEL for rats is 0.14 mg/kg bw/day. However, the NOAELs for teratogenicity for both species are the highest doses tested in the respective studies, and the suggested difference related to choice of dosage. Maternal toxicity occurs at dose levels in both rats and rabbits lower than development NOAELs, and the possible embryotoxicity effect in rabbits is suggested to be secondary to the maternal toxicity.

4.11.2.2 Human data

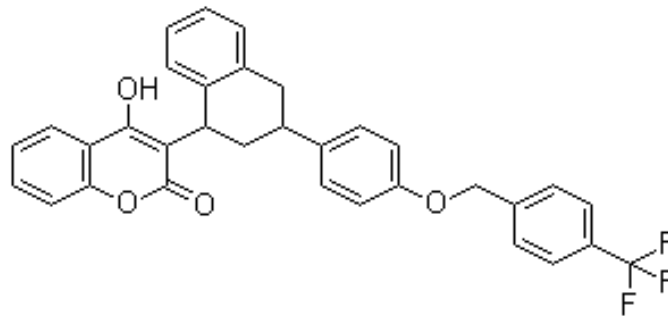
No data are available from human on coumatetralyl for this endpoint. However, information on the structurally and functionally related substance warfarin is available (see point 4.11.2.3 below).

4.11.2.3 Other relevant information

Read across analysis

Coumatetralyl is a hydroxycoumarin derivative. The hydroxycoumarin derived anticoagulants are often referred to as “first” and “second generation”, where first generation hydroxycoumarin derivatives anticoagulants were developed in the 40’s, while the more potent second generation anticoagulant were developed later, when resistance was noted to first

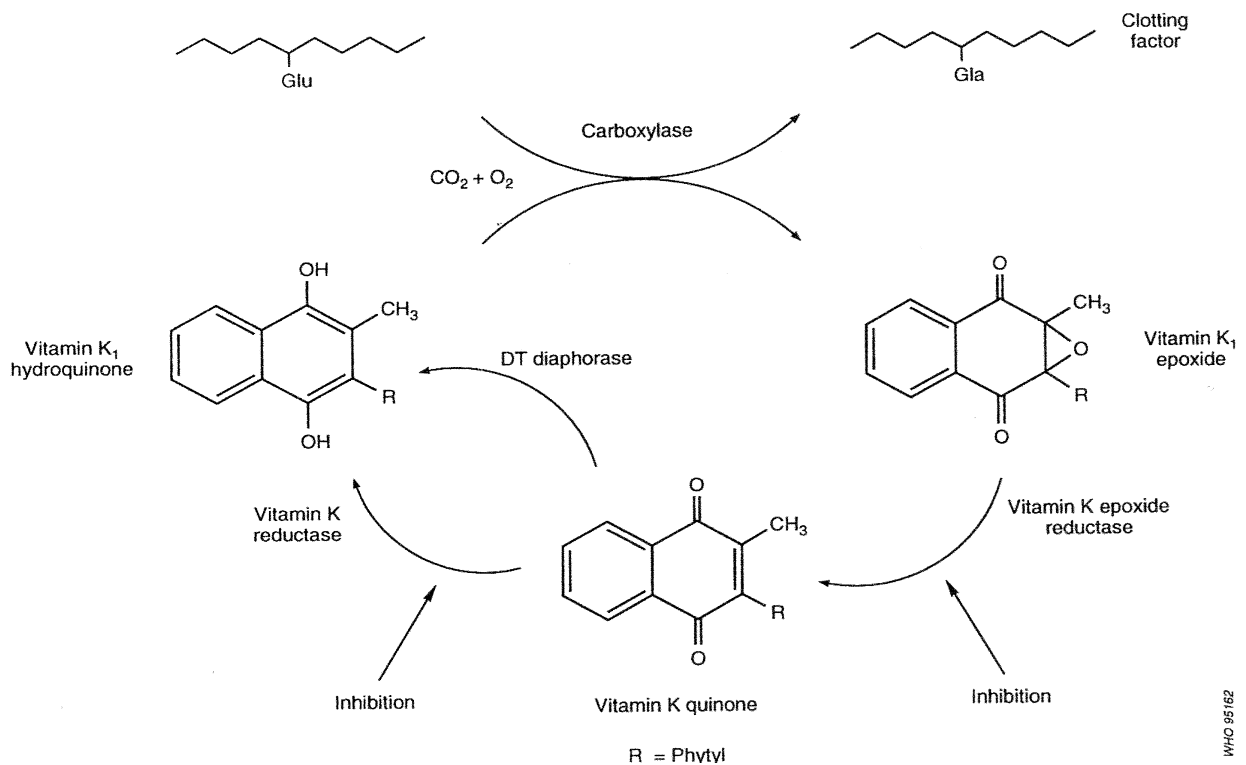
Flocoumafen



Mechanism of action

Hydroxycoumarin derivatives, including coumatetralyl and also warfarin, are vitamin K antagonists. Their use as rodenticides is based on the inhibition of the vitamin K-dependent step in the synthesis of a number of blood coagulation factors. Vitamin K is a co-enzyme, in its active form Vitamin K hydroquinone, which oxidation to vitamin K 2,3-epoxide provides energy for the carboxylation reaction. Coumarin derivatives block the microsomal vitamin K epoxide reductase enzyme, thereby leading to an accumulation of non carboxylated coagulation factor precursors in the liver (WHO, 1995). Figure 2 show the epoxy-cycle, indicating the points of action of hydroxyl-coumarins derivatives

Fig 2: Epoxy cycle: the mechanism of clotting inhibition caused by hydroxycoumarin-related anticoagulation (reproduced from EHC 175: Anticoagulant Rodenticides, IPCS, WHO, 1995).



WHO 95162

It has been demonstrated in the rat that daily administration of vitamin K can counteract the effect of warfarin on the carboxylation of coagulation proteins in the liver. However, the effect of hydroxycoumarins on bone Gla protein synthesis by osteoblasts are not affected by additional vitamin K (Howe & Webster, 1994). This is due to the fact that extrahepatic coagulation proteins do not carboxylate. Thus, extrahepatic vitamin K deficiency cannot be compensated.

Animal study on related substance

A recently performed developmental study on warfarin according to OECD 414 was filed to the Irish CA and a study summary of it would be included in its dossier for warfarin. The study reports subcutaneous haemorrhage at all dose levels (0.125; 0.150; 0.200 and an added group of 0.250 mg/kg bw/day) in the offspring, as well as visceral haemorrhage, central ocular cataract and skull malformations from 0.150 mg/kg bw/day. Maternal toxicity (deaths, vaginal bleeding and blood in the uterus at necropsy) was reported from 0.150 mg/kg bw/day. Thus, the NOAEL for maternal toxicity is set at 0.125 mg/kg bw/day (LOAEL_{maternal}: 0.150 mg/kg bw/day). Due to the bleeding in the offspring, seen at all doses, no NOEL could be set for developmental toxicity in this study.

Human data on related substance

Human exposure to warfarin to therapeutic use during the first trimester of pregnancy caused “warfarin embryopathy” or “foetal warfarin syndrome”, including foetal anomalies such as nasal hypoplasia and growth retardation due to bone anomalies. Exposure during second and third trimester of pregnancy may also lead to foetal loss, stillbirth and abortion due to foetal haemorrhage, microcephaly and/or hydrocephaly.

4.11.3 Summary and discussion of reproductive toxicity

4.11.3.1 Fertility

One and two generation studies are not available for coumatetralyl. No effects on the reproductive organs were reported in repeated dose toxicity studies. Warfarin, another well known coumarin derivate with the same chemically active group as coumatetralyl is not classified as toxic to fertility. Based on the available data, no classification for effects on fertility for is proposed.

4.11.3.2 Developmental toxicity

Coumatetralyl was tested for its developmental toxicity in rats and rabbits in studies conducted in accordance with accepted guidelines (unpublished studies). These studies did not reveal any teratogenic or other developmental effect (doses up to 0.14 mg/kg bw/day in the rat and 0.035 mg/kg bw/day in the rabbits). Maternal toxicity included deaths and internal bleeding and occurred at low doses (0.07 mg/kg bw/day in the rat, and 0.025 mg/kg bw/day in the rabbits).

However, due to the high toxicity of coumatetralyl due to its effect on vitamin K depletion, standard guideline studies are regarded as insufficient to establish whether coumatetralyl has a developmental effect as developmental toxicity may be masked by the high maternal toxicity.

In order to reach potential developmental toxic dose levels of coumatetralyl without high mortality and toxicity to the dams, studies with the addition of vitamin K to maintain blood coagulation in the dams would be needed.

Also, differences in the time line in development of the rat and human fetuses should be taken into consideration in the dosing period chosen in developmental studies with coumatetralyl. For example, mineralisation of the bones is mainly postnatal in the rat, while it occurs already during weeks 5-7 of pregnancy in humans (Howe & Webster, 1994). Such specifically designed studies are not available.

No data are available from humans on developmental effects of coumatetralyl.

The chemical structure of coumatetralyl and its mechanism of toxicity – as it is the case for other hydroxycoumarin substances - is the same as for warfarin. It has been demonstrated that this group of chemically related substances affect the coagulation cascade (through vitamin K hydroquinone deficiency) in humans and in laboratory animals.

Warfarin is classified as repr 1, R61 based on the occurrence of warfarin embryopathy following exposure of humans to therapeutic anticoagulating doses.

It appears from the data on warfarin that humans are less sensitive to the bleeding effect than rodents, but more sensitive to the teratogenic effect. However, the data do not permit to perform a quantitative calculation of the potency of the different anticoagulants.

The data indicate that human foetus is more sensitive to vitamin K deficiency than the mother. Measurements in humans show that vitamin K-levels in the foetus are very low (21-30 pg/ml) compared to those in the mother (395 – 565 pg/ml) (Howe & Webster, 1994).

No study is available on the possible placental passage of coumatetralyl. However, taking the molecular weight and the partition coefficient of coumatetralyl into consideration, placental passage of the substance is found likely to occur. In that situation, the induced vitamin K deficiency in the foetus may be enhanced by a direct action of coumatetralyl on the foetus.

A developmental study on warfarin (for details, please refer to the dossier by Ireland on warfarin) shows severe maternal toxicity from 0.150 mg/kg bw/day, and visceral and skeletal effects at the same levels. In addition, the offspring show subcutaneous haemorrhage at all dose levels, including 0.125 mg/kg bw/day. Thus the effect level (LOAEL) in dams is 0.150 mg/kg bw/day, the NOAEL being 0.125 mg/kg bw/day. For the developmental effect, the LOAEL is 0.125 mg/kg bw/day, and no NOAEL could be set.

The study on warfarin shows that the primary mechanism of action of warfarin is the impairment of the blood coagulation in the dams as well as in the offspring. Indication of a teratogenic potential of the compound is present at maternally toxic doses. However, it is not possible to extrapolate the information to the ability of coumatetralyl to induce teratogenic effects in humans.

4.11.3.3 Effects on or via lactation

The amount of coumatetralyl transferred to milk is unknown and there are no studies of effects via lactation during postnatal development. Consequently, no conclusion can be drawn from the available information and no classification is proposed.

4.11.4 4.11.5 Comparison with criteria

4.11.4.2 Fertility

Based on the available data, no classification for effects on fertility for coumatetralyl is proposed.

4.11.4.3 Development

Coumatetralyl did not cause any observed teratogenic effects in the experimental animal studies. However, due to the difficulties in the design of an optimal study protocol for the detection of potentially teratogenic effects following exposure to coumatetralyl, no clear conclusion can be drawn from the standard guideline studies.

Coumatetralyl is part of the same group of chemicals, the hydroxycoumarin derivatives, as warfarin (WHO, 1995). Coumatetralyl has also the same mode of action as warfarin, which is a well documented human teratogen classified as a reproductive toxicant (Repr. Cat 1; R61 - Repr. 1A H360D). Warfarin has been shown to cause teratogenicity in humans and in experimental animals. Based on analogy consideration to warfarin classification of coumatetralyl for developmental toxicity by, is relevant.

Warfarin and other rodenticides have been discussed at Technical meetings on Biocides. During these discussions it was realised that conventional developmental toxicity tests on rodenticide anticoagulants were difficult to perform and interpret, and it was suggested by the Rapporteurs to perform a read-across of developmental toxicity data from warfarin, already classified as a human developmental toxicant in Repr. Cat 1; R61. In 2006 the Specialised Experts group for classification for reproductive toxicity under directive 67/548/EC discussed the issue of read-across from warfarin for developmental toxicity and came to the following conclusion (ECBI/51/07):

“Warfarin is an established human teratogen classified as Repr. Cat. 1; R61. It is uncertain whether teratogenicity of warfarin can be detected in pre-natal developmental toxicity studies (including OECD guideline 414). The teratogenic mechanism of warfarin is likely to involve maternal Vitamin K depletion and/or direct effects on embryo/foetus via transplacental exposure. Given the vitamin K inhibition, there is concern that other anti-vitamin K (AVK) compounds could cause similar teratogenic effects as warfarin in humans.

The other AVK rodenticides have not shown teratogenic effects in conventional rat and rabbit developmental studies and there is no data in humans. Given the uncertainties surrounding the ability of standard pre-natal developmental toxicity studies to detect warfarin teratogenicity the predictive values to humans of these studies is uncertain.

On the basis of currently available data, there are no convincing arguments that other AVKs including the second generation compounds could not pass the placenta. Both the mechanism of action and the possible placental passage give reason for concern of possible teratogenicity in humans.

Considering the available information the Specialised Experts unanimously agreed that the AVK rodenticides should collectively be regarded as human teratogens. Therefore the other AVK rodenticides should be classified as Repr. Cat. 1; R61.”

New animals studies have been performed on warfarin and on flocoumafen. Draft summaries of the new data will be included in the CLH-reports for the respective substances

However, The Danish EPA does not believe that the new data can be used to change the conclusion on the classification on coumatetralyl. The new data cannot be used to negate the evidence that the structurally and functionally analogue compound warfarin is a human teratogen, which is classified in Repr. Cat 1A; R360D in Annex VI to CLP.

Specific concentration limits

Potential developmental effects of coumatetralyl would be expected at very low doses, and the possibility of setting specific concentration limits for developmental toxicity should therefore be considered - using the newly developed guidance document for setting specific concentration limits (SCL) for reproductive toxicants within the CLP regulation. However, it is recognized that a potency evaluation is very difficult where the classification is based on read across from other substances, and no direct estimate of the developmental toxicity potency is possible.

4.11.4.4 Effects on or via lactation

No conclusion can be drawn from the available information and no classification is proposed.

4.11.5 Conclusions on classification and labelling

The available guideline animal studies on did not show any developmental toxicity effects. However, due to the difficulties in the design of an optimal study protocol for the detection of potential teratogenic effects following exposure to coumatetralyl without mortality, these studies are regarded not to be suitable to evaluate the developmental toxicity potential of anticoagulants.

Since coumatetralyl belongs to the same chemical group and has the same well-known mode of action by which warfarin causes teratogenicity in humans and in experimental animals (through vitamin K inhibition), classification of coumatetralyl for developmental toxicity as Repr. Cat. 1; R61 (Directive 67/548/EEC), respectively Repr. 1A H360D (Regulation EC 1272/2008), by analogy consideration with warfarin, is proposed.

Developmental effects of coumatetralyl would be expected at very low doses, and the possibility of setting specific concentration limits for developmental toxicity should therefore be explored.

No classification for effects on fertility or effects on or via lactation is proposed.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Acute, sub-chronic and developmental toxicity studies conducted with coumatetralyl active ingredient (a.i.) or formulations in rats and rabbits show typical clinical signs of anticoagulant effect mainly including bleeding, pallor and signs of haemorrhages.

Considering all these studies, no particular finding can be attributed to a neurotoxic origin. Moreover, a review of the data available for anticoagulant rodenticides shows that no neurotoxicity has been evidenced for this class of compounds.

Thus, there is no need to further investigate coumatetralyl effects by conducting neurotoxicity studies as these would be unethical for animal welfare reasons.

4.12.1.2 Immunotoxicity

No indication of immunotoxicity of coumatetralyl was seen in the available studies. No studies were performed on this end-point.

4.12.1.3 Specific investigations: other studies

No further animal studies on human health end-points were available with coumatetralyl.

4.12.2 Conclusions on classification and labelling

No further human health end-points lead to classification proposals.

5 ENVIRONMENTAL HAZARD ASSESSMENT

In this section summaries and evaluation of data for which robust study summaries are presented in the annex: “CLH report coumatetralyl RSS CAR environment” which is reproduced from the final CAR report under the review programme under the biocides directive (98/8/EC are reported, as far as possible in summary tables. Due to an interim period agreement, the robust study summaries are not available in IUCLID.

5.1 Degradation

Table 5.1 Hydrolysis of coumatetralyl

Guideline / Test method	pH	Temperature [°C]	Initial TS concentration, C ₀ [µg/ml]	Reaction rate constant, K _h [1/s x 10 ⁵]	Half-life, DT ₅₀ [h]	Coefficient of correlation, r ²	Reference
OECD guideline “Hydrolysis as a function of pH”	4, 7, 9	5 and 55	2 - 2.5	n.a.	Long	n.a.	Wilmes, 1983;

From Doc III A7.1.1.1.1

Table 4.1.2 Photodecomposition of coumatetralyl

Guideline / Test method	Initial molar TS concentration	Total recovery of test substance [% of appl. a.s.]	Photolysis rate constant (k _p ^c)	Half-life (t _{1/2E})	Extrapolated Half-life (t _{1/2}) in sunlight	Reference
Exposition to artificial light and pilot study in sunlight	1.4 mg/l	-	-			Wilmes, 1982;

5.1.1 Stability

Hydrolysis

The hydrolysis of coumatetralyl was studied in accordance with the OECD guideline 111 “Hydrolysis as a function of pH” at pH 4, 7 and 9 in citrate, phosphate and borate buffer solutions.

The active ingredient content of the samples incubated at 55 °C was not observed to have changed, as compared with the refrigerated samples (degradation after 5 days at 50 °C < 10 %).

Conclusion:

Coumatetralyl is stable to hydrolysis.

Photolysis in water

From Doc III A7.1.1.1.2

The photolysis in water was studied in a saturated solution of coumatetralyl in distilled water containing 1.4 mg a.i./l. The samples were exposed to one each of two types of artificial light. In addition a range-finding experiment in sunlight was performed. Photolysis transformation products were isolated and identified in a test in which solutions of 100 mg coumatetralyl/l in distilled water/acetonitrile (2:1) were irradiated for 3 hours.

Conclusion:

Coumatetralyl was degraded rapidly by light under artificial not environmentally relevant conditions to a number of degradation products, of which salicylic acid was identified as a major product. Due to lack of information, no exact conclusion regarding possible degradation rate (half life) can be drawn. However, the results indicate that coumatetralyl is unstable to photolysis in water with an indicative DT < 1 day.

This result is in agreement with expected photolysis profile of coumatetralyl. Due to the UV absorption of the hydroxycoumarin chromophore in the range of 300 to 350 nm, photolytic degradation can be expected. For the structurally similar rodenticide difenacoum which also has the hydroxycoumarin chromophor photolytic half lives were 3.26, 8.05 and 7.32 h at pH 5, 7 and 9. (WHO environmental Health Criteria 175, Anticoagulant Rodenticides, WHO Geneva, 1995, Internet: <http://www.inchem.org/documents/ehc/ehc/ehc175.htm>)

Phototransformation in air

Calculation using AOPWIN (Atmospheric Oxidation Program) Version 1.91. The program is an adoption of the estimation methodology from Atkinson developed by Syracus Research Corporation. A chemical lifetime of coumatetralyl in air of utmost 3 hours (corresponding to a half-life of utmost 2 hrs) is to be expected. The atmospheric photochemical half-life was 2 hours based on ozone reaction and 2.4 hours (using 12-hour day) based on hydroxyl radicals.

5.1.2 Biodegradation

Biotic degradation

Biodegradation

Table 4.1.3 Biodegradation of coumatetralyl

Guideline	Test	Test	Inoculum	Addition	Test	Degradation	Reference
/	type ¹	para-		al	substanc		

			Type	Concentration	Adaptation			Incubation period	Degree [%]	
OECD 301 D (Closed Bottle Test)	Ready	O ₂	Secondary effluent	4 ml/l of final volume	yes ²	no	2 mg/l; 5 mg/l	28 d	1 % (2 mg/l); 0 % (5 mg/l)	Desmares-Koopmans, 2001a;
OECD 302 B (Zahn-Wellens/EMPA Test)	Inherent	DOC	Activated sludge	0.25 g/l dry matter in final mixture	yes ³	no	100.5 mg/l	28 d	8 %	Desmares-Koopmans, 2001b;

¹ Test on *inherent* or *ready* biodegradability according to OECD criteria

² secondary effluent was filtrated and aerated until inoculation

³ activated sludge was coarsely sieved, washed and aerated until required

From Doc III A7.1.1.2.1 and Doc III A7.1.1.2.2

Coumatetralyl was tested for its ready biodegradability by using the Closed Bottle Test according to OECD guideline No. 301 D. A second study was performed to investigate the inherent biodegradability of coumatetralyl (OECD guideline No. 302 B, Zahn-Wellens/EMPA Test). See table 4.1.3 for test parameters and results. For both tests, the reference substance was readily degraded, whereas coumatetralyl was found to be stable.

Aerobic degradation in soil (Doc III A7.2.1 (1) and A7.2.1 (2))

The soil metabolism of radioactive labelled Coumatetralyl under aerobic conditions was investigated in two studies. The half-life in soil is less than 30 days based on primary degradation and after 6 month more than 50% of the originally applied radioactivity was degraded to CO₂. The proportion of bound residues was about 30% under aerobic conditions. The detected metabolites indicate various degradation pathways via oxidation of the active ingredient, which lead to salicylic acid. Salicylic acid is rapidly mineralized to CO₂ by soil-micro organisms. None of the metabolites occurred at a level above 10%.

Anaerobic degradation in soil (Doc III A 7.2.2.4)

Under anaerobic conditions, no degradation (< 1 %) of coumatetralyl took place during 60 days. No metabolites and no [¹⁴C]CO₂ were formed in a purely anaerobic system.

5.1.3 Summary and discussion of degradation

Coumatetralyl was not readily biodegradable under the conditions of the Closed Bottle Test and not inherently biodegradable under the conditions of the Zahn-Wellens/EMPA Test.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Table 4.1.8 Adsorption/desorption of coumatetralyl on soil

Guideline / Test method / Soil type	Adsorbed a.s. [mean %]	K_d ¹ [cm ³ /g]	K_{oc} ² [cm ³ /g]	K_{des} ³ [cm ³ /g]	K_{om} ⁴ [cm ³ /g]	K_d / K_{des} ⁵	Degradation products		Reference
							Name	[%] of a.s.	
OECD 106									
Sand	53.1	2.27	403	6.67	234	0.34	n.a.	n.a.	Slangen, 2002; (Doc III A7.1.3)
Clay loam	59.5	3.10	185	241	107	0.013			
Silt loam	50.1	2.14	71	7.02	41	0.30			
Sandy loam	80.0	8.10	735	27	426	0.30			
Clay	55.4	2.67	115	41	67	0.065			

¹ K_d = adsorption coefficient

² K_{oc} = organic carbon normalised adsorption coefficient

³ K_{des} = desorption coefficient

⁴ K_{om} = organic matter normalised adsorption coefficient

⁵ K_d / K_{des} = adsorption / desorption distribution coefficient

From Doc III A7.1.3

The adsorption/desorption behaviour of coumatetralyl on soil was studied in five soils which represent major agricultural areas in Europe and North America, using the batch equilibrium method according to the OECD guideline No. 106.

The amount of test substance adsorbed to soil after 48 hours ranged from approximately 50 % (silt loam) to 80 % (sandy loam). The amount of material desorbed from the soil after 30.5 hours ranged from approximately 1 % (clay loam) to approximately 23 % (silt loam and sand).

The kinetics of adsorption and desorption showed that adsorption equilibrium and desorption equilibrium were reached within 24 hours in the soil types sand, silt loam and sandy loam, but not in clay loam and clay. Results of adsorption and desorption parameters are described in detail in table 4.1.8.

Conclusion:

Based on the K_{om} values and the mobility classification scheme according to Mensink, coumatetralyl can be considered to be immobile in sand, clay loam and sandy loam. It is considered to be slightly mobile in silt loam and clay. (Mensink B., M. Monforts, L. Wijkhuizen-Maslankiewicz, H. Tibosch and J. Linders, Manual for-summarising and evaluating the

environmental aspects of pesticides, National Institute of Public Health and Environmental Protection, the Netherlands, Report No. 679101022 (1995)).

5.2.2 Volatilisation

5.2.3 Distribution modelling

5.3 Aquatic Bioaccumulation

Table 4.1.10 Measurements of aquatic bioconcentration

Guideline / Test method	Exposure	Log Pow of a.s.	Initial concentration of a.s.	Steady-state BCF	Uptake rate constant [h ⁻¹]	Depuration rate constant [h ⁻¹]	Depuration time (DT ₅₀) [h]	Metabolites	Reference
OECD 305E	120 h	3.5 ¹	52 µg/l	11.4 (± 2.8) (whole fish)	0.56 (± 0.08)	0.05 (± 0.01)	14.1 (± 2.7)	-	Grau, 1992a;
				3.32 (± 1.2) (edible)	0.26 (± 0.06)	0.08 (± 0.02)	8.81 (± 2.49)		
				20.8 (± 6.0) (viscera)	1.02 (± 0.19)	0.05 (± 0.01)	14.1 (± 3.2)		

¹ value mentioned in the study

From Doc III A7.4.2

5.3.1 Aquatic bioaccumulation

A dynamic 456-hour study was conducted according to OECD guideline No. 305 E (1984) to evaluate the bioconcentration of [14C]-coumatetralyl in bluegill sunfish (*Lepomis macrochirus*).

The calculated bioconcentration factors for edible parts and whole fish are 3.32 (± 1.20) and 11.4 (± 2.8), respectively. They corresponded well with the respective observed bioconcentration factors of 3.0 X and 10.4 X for [14C]-coumatetralyl at 120 hours. These values corresponded to calculated steady-state total residue levels of 0.17 and 0.59 mg [14C]-coumatetralyl equivalents/kg for edible parts and whole fish, respectively.

24 hours after cessation of exposure 63, 69 and 67 % of the maximum measured plateau residues were depurated from edible portions, non-edible portions and whole fish, respectively. After 14

days in uncontaminated water more than 99 % of the maximum plateau radio-activity was depurated from edible portions, non-edible portions and whole fish, respectively.

The uptake rate and depuration rate constants as well as the depuration time (DT50) for whole fish, edible parts and viscera/non-edible parts are given in table 4.1.10.

Table 4.1.11 Estimations on aquatic bioconcentration

Basis for estimation	log P _{ow} (measured)	Estimated BCF for fish (freshwater)	Reference
	1.50	2.851 (log BCF = 0.455)	EPI-Win, v3.11, 2003

The bioconcentration factor for the test substance may be overestimated in the study because all calculations refer to radioactivity (sum of parent compound, metabolites and mineralization products).

5.3.2 Summary and discussion of aquatic bioaccumulation

Coumatetralyl is accumulated very rapidly by bluegill sunfish with a total residue bioconcentration factor of 11 X for whole fish. When exposure ceases, the residues are depurated quickly with a half-life of approximately 14.5 hours. Accumulation in edible parts is less (3 X) than in whole fish (11 X).

The Log P_{ow} is pH dependant as shown in Table 1.3; however, the result of the bioaccumulation study in fish demonstrates that accumulation of coumatetralyl is not to be expected.

5.4 Aquatic toxicity

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Table 4.2.1 Acute toxicity to fish

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [mg a.s./l]			Remarks	Reference
			Design	Duration	LC ₀	LC ₅₀	LC ₁₀₀		
Draft DIN 38 412	<i>Salmo gairdneri</i>	mortality	Static	96 h	32	48 (42-55)	76	nominal conc.	Hermann, 1983;
OECD 203	<i>Salmo gairdneri</i>	mortality	Static	96 h	32	53	100	nominal conc.	Sewell & McKenzie, 2003
Draft DIN 38 412	<i>Leuciscus idus melanotus</i>	mortality	Static	96 h	51	67 (61-73)	90	nominal conc.	Hermann, 1982;

From doc III A7.4.1.1. There are 3 studies described in the IUCLID data set (2 non key studies and therefore there is no study summary of these).

The acute toxicity on fish was investigated on rainbow trout (*Salmo gairdneri*) by Sewell & McKenzie, 2003 according to the OECD guideline 203 (2003). While all tests gave comparable results, the test performed according to OECD Guideline 203 was selected as the key study due to its higher reliability factor.

Following a preliminary range-finding test, juvenile fish were exposed in groups of ten, to an aqueous solution of coumatetralyl over a range of concentrations of 10, 18, 32, 56 and 100 mg/l for a period of 96 hours at a temperature of 12,5°C to 14,0°C under static conditions.

The number of mortalities and sub-lethal effects of exposure in test and control vessel were determined 3 and 6 hours after the start of exposure and then daily throughout the test until 96 hours.

Conclusion:

The 96-hour LC₅₀ value based on nominal test concentration was 53 mg/l.

5.4.1.2 Long-term toxicity to fish

Table 4.2.5 Prolonged acute toxicity to fish

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [µg/l]		Remarks	Reference
			Design	Duration	NOEC	LOEC		
OECD 204	<i>Oncorhynchus mykiss</i>	mortality	semi-static	21 d	5.0	15.8	nominal conc.	Grau, R., 1992;

From Doc III A7.4.3.1

The prolonged toxicity of coumatetralyl to rainbow trout (*Oncorhynchus mykiss*) was determined in a 21-day semi-static test according to OECD guideline No. 204 (1984). In the first part of the study four groups of ten fish were exposed to nominal concentrations of 15.8, 50.0, 158.0 and 500.0 µg/l and in the second part four groups of ten fish were exposed to nominal concentrations of 0.158, 0.50, 1.58 and 5.00 µg/l. Fish were examined each working day for the mortalities and symptoms of intoxication in the control, solvent control and test concentrations. Coumatetralyl concentrations were analysed during the study by means of HPLC.

The NOEC was determined to be 5.0 µg/l, the LOEC and the lowest lethal concentration (LLC) were 15.8 µg/l. A 21-day LC₅₀ value was not calculated. Observable symptoms were noted among the fish in the 15.8 (*Exophthalmus*, day 20) and 500.0 µg/l (fish mainly at the bottom and swimming behaviour slightly irregular (slight symptom), day 21) test levels. Neither mortalities nor symptoms of intoxication occurred in the control and the solvent control groups. There were no statistically significant difference in body weight, length and condition factor between the control and the treated groups. The analytical results were between 81 and 120 % and showed that the concentrations were in accordance with the nominal values and that the test substance was stable for the duration of the test. The prolonged acute study on fish is considered valid and acceptable.

Conclusion:

For *Oncorhynchus mykiss* a 21-d NOEC of 5.0 µg/l was determined, the LOEC and the lowest lethal concentration (LLC) were 15.8 µg/l. The prolonged acute NOEC of 5.0 µg/l is used in the risk assessment for the aquatic compartment.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

5.4.2.2 Acute toxicity to invertebrates

Table 4.2.2 Acute toxicity to *Daphnia magna*

Guideline / Test method	Endpoint / Type of test	Exposure		Results [mg a.s./l]			Remarks	Reference
		Design	Duration	EC ₀	EC ₅₀	EC ₁₀₀		
OECD 202	Immobility	static	48 h	≥ 14	> 14	> 14	measured conc.	Heimbach, F., 1991a;

From Doc III A7.4.1.2

Coumatetralyl was investigated in a 48-hour static test for acute toxicity to water fleas (*Daphnia magna*) according to OECD guideline No. 202 (1984). The test animals were exposed to the nominal test substance concentrations 1.0, 1.8, 3.2, 5.6, 10.0 and 18 mg/l. Immobility of animals and symptoms were determined after 24 and 48 hours in the control, solvent control and the test concentrations. Concentrations tested were analysed at the beginning of the test and after the exposure period of 48 hours in the test vessels containing 1.0, 5.6 and 18 mg test substance/l.

After 48 hours the EC₅₀ value and the LOEC were > 14 mg/l. The NOEC was determined to be 14 mg/l. The results are based on measured test concentrations. No immobility of animals or symptoms of toxicity were observed in any of the groups. The measured concentrations were 75 to 83 % of the nominal concentrations (for an average 79.5 %). A determination of the active ingredient content at the end of the exposure period showed stability of the test concentrations under the conditions of the test.

Conclusion:

The acute toxicity test for *Daphnia magna* resulted in a 48 h-EC₅₀ of > 14 mg/l (maximum measured tested concentration). The NOEC was determined to be 14 mg/l.

5.4.2.3 Long-term toxicity to aquatic invertebrates

Table 4.2.6 Chronic toxicity to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [mg/l]		Remarks	Reference
			Design	Duration	NOEC	LOEC		
OECD 202, Part II	<i>Daphnia magna</i>	Reproduction	semi-static	21 d	0.10	0.32	nominal conc.	Heimbach, F., 1992;

From Doc III A7.4.3.4

Coumatetralyl was tested for inhibition of reproduction of water fleas according to the OECD guideline No. 202, Part II (1984). Water fleas (*Daphnia magna*) were exposed in a 21-day semi-static test to aqueous test medium containing the test substance at the nominal concentrations 0.10, 0.32, 1.0, 3.2, 10 and 18 mg/l. Stock solutions were prepared with dimethylformamid. On day 2, 5, 7, 9, 12, 14, 16 and 19 after the start of the study and additionally on day 21, the number of offspring which had been born during the previous two or three days in each test container were counted. At the same time the surviving parents were recorded. The coumatetralyl concentrations in the test water were determined during the course of the study by means of HPLC.

The NOEC was determined to be 0.10 mg/l, the LOEC was 0.32 mg/l. There was no mortality in the control or the solvent control higher than 20 %, the level which is regarded as the natural rate of mortality. Three broods were clearly recognisable. A delay in brood times could not be observed. The mean number of newborn water fleas per adult was 141 in the control and 142 in the solvent control. Compared to control organisms, there was a biological and statistical significant reduction of reproduction at all test concentrations higher than 0.10 mg/l. At the end of the study, the body lengths of the parent control animals and those of the solvent control animals indicated well developed females. Compared to control organisms, at all concentrations higher than 0.10 mg/l a significant decrease in body length was found.

Conclusion:

The chronic NOEC for *Daphnia magna* was determined to be 0.10 mg/l, the LOEC was 0.32 mg/l.

5.4.3 Algae and aquatic plants

5.4.3.1 Growth inhibition on algae

Table 4.2.3 Acute toxicity on algae

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [mg a.s./l]			Remarks	Reference
			Design	Duration	NOEC	E _b C ₅₀ ¹	E _r C ₅₀ ²		
OECD 201, ISO 8692	<i>Scenedesmus subspicatus</i>	growth inhibition	static	72 h	5.6	15.2	> 18	Nominal conc.	Heimbach, F., 1991b;
				96 h	5.6	14.8	> 18		

¹ calculated from the area under the growth curve; ² calculated from growth rate

From Doc III A7.4.1.3

The effect on growth inhibition of algae was studied on the green alga *Scenedesmus subspicatus* in a 96-hour static test with the nominal concentrations 1.0, 1.8, 3.2, 5.6, 10 and 18 mg/l. The test was performed according to the OECD guideline No. 201 (1984) and ISO guideline ISO 8692 (1989). After 24, 48, 72 and 96 hours, the cell counts were determined photometrically in the control, solvent control and the test concentrations. At the beginning of the test, concentrations tested were analysed after preparing the test solutions by means of HPLC. The analyses indicated that starting measured concentrations were similar to nominal values and, therefore, the results of the test were based on nominal concentrations. As the test substance was deemed to be stable in water, the exposure concentrations were not determined at the end of the study.

The effect of coumatetralyl on the growth of biomass was characterised with an E_bC_{50} value of 15.2 mg/l after 72 h and 14.8 mg/l after 96 h. The influence of coumatetralyl on the algae growth rate resulted in an E_rC_{50} of > 18 mg/l after 72 h and 96 h, respectively. The LOEC was determined to be 10 mg/l, the NOEC 5.6 mg/l. The results are based on nominal concentrations. No abnormalities, e.g. morphological changes were observed. The mean measured concentration levels ranged from 78 to 94 % of nominal concentrations (for an average: 90.8 %).

The growth in the control containers after 72 hours showed a rate of multiplication that is greater than a factor of 16 and thus the quality criterion of the OECD and/or ISO guideline is fulfilled. The test concentrations prepared in this test corresponded well to the nominal concentrations. However, according to the rapid degradation by light of the test substance, a degradation of the substance during the test is possible. This study is not decisive for the RA.

Conclusion:

The effect of coumatetralyl on the growth of biomass was characterised with an E_bC_{50} value of 15.2/14.8 mg/l after 72/96 h, respectively. The influence of coumatetralyl on the algae growth rate resulted in an E_rC_{50} of > 18 mg/l after both 72 h and 96 h.

5.4.4 Other aquatic organisms (including sediment)

5.4.4.1 Inhibition of microbial activity (aquatic)

Table 4.2.4 Inhibition of microbial activity (aquatic)

Guideline / Test method	Species / Inoculum	Endpoint / Type of test	Exposure		Results [mg a.s./l]			Remarks	Reference
			Design	Duration	EC ₂₅	EC ₅₀	EC ₇₅		
ISO 8192	activated sludge	inhibition of respiratory rate	analytical parameter : oxygen consumption	duration of the study: 24 h	538	4210	32,900		Müller, G., 1991;

From Doc III A7.4.1.4

To assess the toxicity of coumatetralyl to bacteria a test was investigated according to the ISO 8192, "Test for inhibition of oxygen consumption by activated sludge" (1986). A defined quantity of activated sludge from laboratory sewage treatment plant was exposed to coumatetralyl at the nominal concentrations 560, 1000, 1800, 3200 and 5600 mg/l. The respiratory rate of each mixture was determined and compared to that measured in a mixture without test substance. At nominal test substance concentrations of 560 – 5600 mg/l, inhibition of respiratory rate was observed between 23.8 % and 55.6 %. The EC_{50} value of coumatetralyl was determined to be 4210 mg/l. The reference substance 3, 5-Dichlorophenol was used to control the sensitivity of the activated sludge. It should be noted that the test concentration is above the water solubility.

Conclusion:

The EC_{50} value of coumatetralyl was determined to be 4210 mg/l.

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

Comparison with classification criteria included in the paragraph below.

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

The harmonized classification on Annex I to Directive 67/548/EC included in Annex VI of Regulation 1272/2008 is R52-53 (Harmful to aquatic organisms may cause long-term adverse effects in the aquatic environment) respectively Aquatic Chronic, category 3, H412 (Harmful to aquatic life with long lasting effects) according to DSD respectively CLP criteria.

In Directive 67/548/EC the classification is based on the acute toxicity combined with fate properties.

The EC₅₀ and LC₅₀ values available for coumatetralyl are in the range of 10 mg/l to 100 mg/l (Sewell & McKenzie, 2003; Heimbach, F., 1991a and b), and the substance is not rapidly degradable (*Desmares-Koopmans, 2001a and b*). Thus, according to Directive 67/548/EC, the substance is classified R52-53.

With respect to classification according to the CLP criteria, implementing elements GHS, the criteria are divided into acute (short term) and chronic (long-term hazard) effects, the latter being based on long-term (chronic) data. With the second ATP, the criteria include attribution of M-factors.

In the data set for coumatetralyl the lowest NOEC_(fish) was 5 µg/l (0.005 mg/l) (Grau, R., 1992). For non rapidly degrading substances the following table for classification and attribution of M-factor in relation to chronic effect ranges applies:

EC ₁₀ or NOEC (mg/l)	Chronic category
0.1-1	2
0.01-0.1	1
0.001-0.01	1, M-factor = 10
0.0001-0.001	1, M-factor = 100
Etc.	Etc.

With the lowest NOEC being in the toxicity band 0.001 mg/l – 0.01 mg/l the resulting classification under CLP is Chronic category 1 with M-factor = 10, H410 (Warning. Very toxic to aquatic life with long lasting effects). No classification for acute aquatic toxicity is applied.

6 OTHER INFORMATION

7 REFERENCES

Ahmed, A.A., H. Arif, A.H. Nounou & R.I. Hamed (1983): Haematological effect of the rodenticide “Racumin“ in dogs. *Vet. Med. J.* 31, pp. 115-120.

Anderson, C. & W. Bornatsch (1998): Benzopyranone-[phenyl-UL-14C]coumatetralyl: *In-vitro* Metabolism in Subcellular Fractions of Rat Liver. Bayer AG, Institute for Metabolism Research and Residue Analysis, Leverkusen, Report No. MR 523/98, 1998-10-26 (unpublished).

Anderson, C. (1999): Benzopyranone-[phenyl-UL-14C]coumatetralyl: Investigation of the Biokinetic behaviour and the Metabolism in the Rat. Bayer AG, Institute for Metabolism Research and Residue Analysis, Leverkusen, Report No. MR 524/98, 1999-01-15 (unpublished).

Andrews (1996) pilot study 3-week feeding rat cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Andrews, P. & A. Romeike (1997): Racumin[®] 0.75% Tracking Powder (c. n.: coumatetralyl) – Study for subchronic oral toxicity in rats (feeding study for 16 weeks). BAYER AG, Institute of Toxicology, Report No. 26470, 1997-07-21 (unpublished).

Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29.

Balakrishna Murthy (1989) subacute mouse, dominant lethal test cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Bayer AG (1999): Safety Data Sheet: Racumin techn. S. Bayer AG, Animal Health, SDS No. 065599/10, 1999-10-28.

Bayer AG, Zeneca Public Health, Sorex Ltd., Rhone Poulenc, Liphia SA, American Cyanamid Company (Eds., 2003): *The Treatment of Anticoagulant Rodenticide Poisoning – Advice to Veterinarians.*

Bayer Crop Science, 2004, Safety Data sheet Racumin techn. S, Bayer Crop Science, SDS No. 102000006018, 2004-02-23, MO-04-002516

Becker, H. & K. Biedermann (1996a): Developmental toxicity study with Racumin in the rat, RCC, Research & Consulting Company Ltd and RCC Umweltchemie AG, Report No. R 6741, 1996-11-21 (unpublished).

Becker, H. & K. Biedermann (1996b): Developmental toxicity study with Racumin in the rabbit. RCC, Research & Consulting Company Ltd and RCC Umweltchemie AG, Report No. R 6742, 1996-11-27 (unpublished).

Berny, Ph (1999): Clinical trial: evaluation of secondary poisoning in dogs with coumatetralyl. Ecole Nationale Veterinaire, Marcy L'Etoile, France, Report No. 98-UEPC-02, 14-MAY-1999 (unpublished).

Bhide, M.B. (1984a): Report on primary skin irritation test on rabbits with Racumin tech. of Bayer (India) Ltd., Bombay, Indian Institute of Toxicology, Report, 1984-06-29 (unpublished).

Bhide, M.B. (1984b): Report on primary mucous membrane irritation test on rabbits with Racumin tech. of Bayer (India) Ltd., Bombay, Indian Institute of Toxicology, Report, 1984-06-29 (unpublished).

Bissinger, H. (2001): Oxarin Determination in Racumin by HPLC-Validation Report, Bayer AG, Central Research-Analytical Department, Uerdingen, Germany, 2001-03-15 (unpublished).

Böcker (2004): Statement on container stability of coumatetralyl. Bayer Environmental Science, Formulation Technology, 2004-01-15 (unpublished)

Bomann, W. (1992a): Racumin techn. (c.n.: coumatetralyl) – Investigations of acute oral toxicity in rats. BAYER AG, Department of Toxicology, Report No. 21726, 1992-10-05 (unpublished).

Bomann, W. (1992b): Racumin techn. (c.n.: coumatetralyl) – Investigations of acute oral toxicity in rabbits. BAYER AG, Department of Toxicology, Report No. 21727, 1992-10-05 (unpublished).

Bomann, W. (1992c): Racumin techn. (c.n.: coumatetralyl) – Investigations of acute dermal toxicity in rats, BAYER AG Department of Toxicology, Report No. 21729, 1992-10-05 (unpublished).

Brumhard, B. (2004a): Method 00824 for the Determination of Residues of coumatetralyl in Soil by HPLC-MS/MS. Bayer Crop Science AG, Development, ROCS, Monheim, Method No. 00824, DRAFT-Report No. MR-096/03, 2004-01-13 (unpublished).

Brumhard, B. (2004b): Enforcement Method for the Determination of coumatetralyl in Drinking and Surface Water by HPLC-MS/MS. Bayer Crop Science AG, Development, ROCS, Monheim, Method No. 00820, DRAFT-Report No. MR-076/03, 2004-01-08 (unpublished).

Desmares-Koopmans, M.J.E. (2001a): Ready Biodegradability: Closed Bottle Test with coumatetralyl. Report, NOTOX B.V., 's-Hertogenbosch, the Netherlands, Project No. 311873, 2001-05-15 (unpublished).

Desmares-Koopmans, M.J.E. (2001b): Inherent Biodegradability: 'Zahn-Wellens / EMPA Test' with coumatetralyl. Report, NOTOX B.V., 's-Hertogenbosch, the Netherlands, Project No. 311884, 2001-06-19 (unpublished).

Eason, C.T., P. Fisher, C. O'Connor, A. Airley & G. Wright (2003): Bioaccumulation of coumatetralyl Versus Brodifacoum. Landcare Research, Lincoln, New Zealand, Report No. LC0203/050, March 2003 (unpublished).

EPI-Win v3.11 (2003): Calculation of the Bioconcentration factor with BCFWIN v. 2.15, November 2003.

Gerlach (1994): Racumin techn. and Racumin S techn.: Oxarin-High performance liquid chromatographic method, Bayer AG, ZF-DZA Analytik Uerdingen, Krefeld, Germany, Report No. 2301-0222901-92E, 1994-04-19 (unpublished).

Grau, R. (1992a): Coumatetralyl: Bioconcentration in fish. Bayer AG, Institute for Environmental Biology, Leverkusen, Germany, Report No. BF-008, 1992-05-07 (unpublished).

Grau, R. (1992b): Coumatetralyl (Technical Grade) Prolonged Toxicity (21 days) to Rainbow Trout in a Semi-static Test. Bayer AG, Institute for Environmental Biology, Leverkusen, Report No. FF-318, 1992-06-05 (unpublished).

Grau, R. (1992c): Coumatetralyl (Technical Grade) Acute oral Toxicity to Japanese Quail. Bayer AG, Institute for Environmental Biology, Leverkusen, Germany, Report No. VW-158, 1992-07-08 (unpublished).

Grau, R. (1992d): Coumatetralyl (Technical Grade) 5-Day-Dietary LC50 to Japanese Quail. Bayer AG, Institute for Environmental Biology, Monheim, Report No. VW-159, 1992-06-30 (unpublished).

Heimbach, F. (1991a): Acute toxicity of coumatetralyl (tech.) to waterfleas (*Daphnia magna*). Bayer AG, Institute for Environmental Biology, Leverkusen, Germany, Report No. HBF/Dm 107, 1991-12-12 (unpublished).

Heimbach, F. (1991b): Growth Inhibition of Green Algae (*Scenedesmus subspicatus*) by coumatetralyl (tech.). Bayer AG, Institute for Environmental Biology, Leverkusen, Germany, Report No. HBF/A1 96, 1991-12-09 (unpublished).

Heimbach, F. (1992): Influence of coumatetralyl (tech.) on the Reproduction Rate of Water Fleas. Bayer AG, Institute for Environmental Biology, Leverkusen, Report No. HBF/rDm 40, 1992-01-13 (unpublished).

Heitkamp, D. (2001): Determination of Safety-relevant Data of Racumin S Technical, coumatetralyl. Bayer AG, WD-SI, Process and Plant Safety, Leverkusen, Study No. 00/00625, 2001-01-22 (unpublished).

Hellpointner, E. (2003): Coumatetralyl: Enforcement Method No. 00810 for the Determination of coumatetralyl in Air by HPLC-UV and Confirmation via DAD-Spectra Matching, Bayer Crop Science AG, Development Metabolism and Environmental Fate, Monheim, Germany, Report MEF-102/03, Method No. 00810, 2003-07-25 (unpublished).

Hellpointner, E. (2004): Calculation of the chemical lifetime of Coumatetralyl in the troposphere. Bayer CropScience AG, Development Metabolism / Environmental Fate, Monheim, Germany, BCS Report MEF-04/233, 2004-05-26 (unpublished).

Herbold, B. (1986a): ENE 11183B (c. n.: coumatetralyl) - Salmonella/microsome test to evaluate for point mutagenic effect. BAYER AG, Institute of Toxicology, Report No. 15070, 1986-09-15 (unpublished).

Herbold, B. (1986b): ENE 11183B (c. n.: coumatetralyl) – Test on *S. cerevisiae* D7 for the induction of mitotic recombination. BAYER AG Institute of Toxicology, Report No. 15071, 1986-09-15, (unpublished).

Herbold, B. (1987): ENE 11183B (c.n.: coumatetralyl) – Micronucleus test on the mouse to evaluate for clastogenic effect. BAYER AG, Institute of Toxicology, Report No. 15407, 1987-01-12, (unpublished).

Hermann & Unterstenhöfer (1962): subacute oral rat cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Hermann (1982) Orfe ecotox cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Hermann (1983) Rainbow trout ecotox cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Hermann 1960 acute tox oral rabbit cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Hermann 1973 acute tox oral mouse cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Howe AM & Webster WS (1992): The warfarin embryopathy: a rat model showing maxillofacial hypoplasia and other skeletal disturbances, *Teratology*, **46**(4) 379-90

Howe AM et al. (1992): Binder's syndrome due to prenatal vitamin K deficiency: A theory of pathogenesis, *Australian Dental Journal*, **37**(6):453-60.

Howe AM & Webster WS (1994): Vitamin K – its essential role in craniofacial development, *Australian Dental Journal*, **39**(2) 88-92.

Irish draft CA-report on warfarin, unpublished, sept. 2005.

Jungheim (2000): Physicochemical Properties - Racumin S Technical, coumatetralyl. Bayer AG, ZF-Zentrale Analytik, Leverkusen, Report No. N 00/0106/01 LEV, 2000-11-08 (unpublished).

Jungheim (2001): Dissociation constant / Solubility in Organic Solvents - Racumin S Technical (coumatetralyl). Bayer AG, ZF-Zentrale Analytik, Leverkusen, Report No. N 00/0106/04 LEV, 2001-02-05 (unpublished).

Erstling and Jungheim (2002a): Water Solubility - Racumin S Technical (coumatetralyl). Bayer AG, ZF-Zentrale Analytik, Leverkusen, Report No. N 00/0106/06 LEV, 2002-11-28 (unpublished).

Erstling and Jungheim (2002b): Partition coefficient (n-Octanol/Water) - Racumin S Technical (coumatetralyl). Bayer AG, ZF-Zentrale Analytik, Leverkusen, Report No. N 00/0106/07 LEV, 2002-12-06 (unpublished).

Kaussmann, M. (2000): Spectral Data of coumatetralyl. Bayer AG, Agrochemical Division, Monheim, Study No. 15-600-2136, 2000-12-13 (unpublished).

Kimmerle (1958) acute tox guinea pig oral cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Kimmerle (1970a) dermal tox rat acute cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Kimmerle (1970b) dermal tox rat acute cited in Andrews, P. (1999): Coumatetralyl – Pharmacological and Toxicological Expert Opinion. Bayer AG, Toxicology, Wuppertal, Report, 1999-04-29

Lautraite, S. (2003a): Coumatetralyl - Waiver for acute and sub-chronic toxicity studies in rat by inhalation. Bayer CropScience, Document No. MO-03- 015576, 2003-08-12

Lautraite, S. (2003b): Coumatetralyl - Waiver for chronic toxicity study in dogs, chronic/carcinogenicity study in rodents, and multigeneration study in rodents. Bayer CropScience, Document No. MO-03- 006927, 2003-05-06

Moellhoff (1981): Leaching Characteristics of the Plant Treatment Agent, coumatetralyl. Bayer AG, Reports to the Federal Biological Institute (BBA), Report No. 7800/81 (BBA Standard soil 2.1), Report No. 7801/81 (BBA Standard soil 2.2), Report No. 7802/81 (BBA Standard soil 2.3), 1981-02-06 (unpublished).

Müller, G. (1991): Investigation of the ecological behaviour of Racumin S. Bayer AG, Institute for Environmental Analysis and Evaluation, Leverkusen, Germany, Study number 283 A/91, 1991-07-12 (unpublished).

Mundy, D. E. and A. F. Machin (1982): The multi-residue determination of coumarin-based anticoagulant rodenticides in animal materials by high-performance liquid chromatography, Ministry of Agriculture, Fisheries and Food, Central Veterinary Laboratory, New Haw, Weybridge, Surrey, Great Britain, *Journal of Chromatography*, 234 (1982), pp 427 – 435.

O'Connor, C.E., G. Wright & C. Eason (2001): Liver Persistence and Half-life of coumatetralyl in the Rat. Landcare Research, Lincoln, New Zealand, Research Contract Report No. LC0001/084, September 2001.

Odenthal, A. (2002): Validation of HPLC-method 2001-0004804-02-Determination of coumatetralyl in formulations, Bayer AG, BCS-Development/Formulation Technology, Monheim, Germany, Report No. VB1-2001-0004804, 2002-09-10 (unpublished).

Olf (2000): Vapour Pressure, Physical-chemical Properties - Racumin S Technical, coumatetralyl. Bayer AG, ZT-TE, Leverkusen, Report No. 00/028/01, 2000-10-20 (unpublished).

Olf (2001): Surface Tension, Physical-chemical Properties - Racumin S Technical, coumatetralyl. Bayer AG, ZT-TE, Leverkusen, Report No. 00/028/03, 2001-01-17 (unpublished).

Pauluhn, J. (1982): ENE 11 183 b (Endrocid; active substance of Racumin) – Investigations of acute inhalation toxicity. BAYER AG, Institute of Toxicology, Report No. 11344, 1982-12-17 (unpublished).

Renhof, M. (2003a): Acute skin irritation/corrosion on rabbits – coumatetralyl, Bayer AG, Bayer HealthCare Toxicology - Experimental Toxicology, Report in preparation, 2003-xx-xx (unpublished).

Renhof, M. (2003b): Acute eye irritation/corrosion on rabbits – coumatetralyl, Bayer AG, Bayer HealthCare Toxicology - Experimental Toxicology, Report No. AT00880, 2003-12-17 (unpublished).

Sakr, E.E., M.M. Lotfy & R.I. Hamed (1986): Pathological effect of Racumin in dogs. J. Egypt. Vet. Med. Ass. 46, pp. 179-188.

Scholz, K. (1987a): Degradation of [14C] coumatetralyl (Racumin®) in soils under aerobic conditions. Bayer AG, Institute for Metabolism Research, Monheim, Germany, Report No. PF 2741, 1987-02-04 (unpublished).

Scholz, K. (1987b): Metabolism of [14C] coumatetralyl (Racumin®) in soil under aerobic and anaerobic conditions, Bayer AG, Institute for Metabolism Research, Monheim, Germany, Report No. PF 2832, 1987-06-05 (unpublished).

Seidel, E. (2002): Determination of coumatetralyl in formulations-Assay-HPLC-external standard, Bayer AG, BCS-D Formulation Technology, Monheim, Germany, Report No. 2001-0004804-02E, 2002-09-23 (unpublished).

Slangen, P.J. (2002): Development and Validation of an Analytical Method for coumatetralyl and Soil Adsorption/Desorption of coumatetralyl on five Soils (Screening Test). Report, NOTOX B.V., s'Hertogenbosch, the Netherlands, Project No. 333473, 2002-03-29 (unpublished).

Smeykal, H. (2006): Coumatetralyl (AE C518298) Oxidising properties A17. Bayer AG, report no. 20060941.01 Siemens AG, Frankfurt am Main, Germany. (unpublished).

Steffens, W. (2003): Report: Clinical Toxicology experience with coumatetralyl, Bayer AG, 2003-7-25 (unpublished).

Steinmann-Steiner, W.& Steffens, W. (2003): Occupational medical experiences with 4-hydroxy-3-(1,2,3,4-tetrahydro-L-naphthalenyl)-2H-1-benzopyran-2-one (Racumin), Bayer AG, 2003-8-13 (unpublished).

Stepec (1998): Specification (Racumin S techn.). Bayer AG, Animal Health Development, 1998-11-02.

Stöcker, R.H. (2001): Appearance of the Substance Racumin S Technical. Bayer AG, BG Animal Health, Analytical Department, Leverkusen, Report No. SKD APP01/2001, 2001-08-14 (unpublished).

Stöcker, R.H. (2004): Henry's law constant of Racumin S technical (coumatetralyl). Bayer Environmental Science, Analytical Services, Report No. SKD Hen 01/04, 2004-01-27.

Stropp, G. (1998): Racumin Techn. S – Study for the skin sensitisation effect in guinea pigs. BAYER AG, Department of Toxicology, Report No. 27301, 1998-03-17 (unpublished).

TGD for Risk Assessment (2003): Technical Guidance Document in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances and Commission Directive 98/8/EEC concerning the Placing of Biocidal Products on the market. ECB, JRC, Ispra, Italy.

Van Erp, Y.H.M. (2001): Acute Toxicity Study in the Earthworm *Eisenia fetida fetida* with coumatetralyl. Report, NOTOX B.V., s'Hertogenbosch, Netherland, Project No. 311862, 2001-06-07 (unpublished).

Veith (2000): Material accountability study, Racumin S techn. (coumatetralyl). Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany, Study No. D 00/0002/00 DOR, 2000-12-01.

WHO (1995): Anticoagulant Rodenticides, Environmental Health Criteria 175, IPCS.

Wilmes, R. (1982): Racumin (coumatetralyl): Orientating Light Stability. Bayer AG, Institute for Metabolism and Residue Research, Monheim, Report, 1982-05-21 (unpublished).

Wilmes, R. (1983): Fate/Behaviour of Crop Protection Products in Water, Bayer AG, Report No. WLF HA 027, 1983-03-23 (unpublished).

G. Wright, C. Radford and P. Fisher (2003): Method: Determination of coumatetralyl in Liver by HPLC: Methodology and Validation of Analyses. Landcare Research, Toxicology laboratory, Lincoln, New Zealand, Landcare Research Contract Report: LC0304/040, December 2003

8 ANNEXES

Study summaries document IIIA from the final CA-report for coumatetralyl, for end-points relevant for this report, are attached to this report in IUCLID-database.

The Annexes include

Annex 1: Confidential information on identity of the substance,

Annex 2: Identity and Physico-Chemical properties of the substance.

Annex 3: Study summaries related to Human Health effects of the substance.

Annex 4: Study summaries related to Environmental effects and fate of the substance