EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate D - Food Safety: production and distribution chain
D3 - Chemicals, Contaminants and Pesticides

Warfarin
SANCO/10434/2004 final
23.9.2005

Review report for the active substance **warfarin**

finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 23 September 2005
in view of the inclusion of warfarin in Annex I of Directive 91/414/EEC

1. Procedure followed for the re-evaluation process

This review report has been established as a result of the re-evaluation of warfarin, made in the context of the work programme for review of existing active substances provided for in Article 8(2) of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

Commission Regulation (EEC) No 3600/92([1]) laying down the detailed rules for the implementation of the first stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC, as last amended by Regulation (EC) No 2266/2000([2]), has laid down the detailed rules on the procedure according to which the re-evaluation has to be carried out. Warfarin is one of the 90 existing active substances covered by this Regulation.

In accordance with the provisions of Article 4 of Regulation (EEC) No 3600/92 C.F. Spiess & Sohn on 2 July 1993, Gaeleo Ltd. on 16 July 1993 (replaced by Chemoswed AB on 10 April 1995 and by DuPont Chemoswed AB on 1 January 1996), Vetyl Chemie on 16. July 1993, Hentschke und Sawatzki on 17 July 1993, B. V. Luxan on 21 July 1993, Sorex Limited on 23 July 1993, Killgerm Chemicals on 26 July 1993 and B. H. Schilling on 26 July 1993 notified to the Commission of their wish to secure the inclusion of the active substance warfarin in Annex I to the Directive.

In accordance with the provisions of Article 5 of Regulation (EEC) No 3600/92, the Commission, by its Regulation (EEC) No 933/94([3]), as last amended by Regulation (EC) No 2230/95([4]), designated Ireland as rapporteur Member State to carry out the assessment of warfarin on the basis of the dossiers submitted by the notifiers. In the same Regulation, the Commission specified furthermore the deadline for the notifiers with regard to the submission to the rapporteur Member States of the dossiers required under Article 6(2) of Regulation (EEC) No 3600/92, as well as for other parties with regard to further technical and scientific information; for warfarin this deadline was 30 April 1995.

[1] OJ No L 366, 15.12.1992, p.10.

[2] OJ No L 259, 13.10.2000, p.27.

[3] OJ No L 107, 28.04.1994, p.8.

[4] OJ No L 225, 22.09.1995, p.1.

Chemoswed AB as the representative of the warfarin task force comprising Chemoswed AB, C.F. Spiess & Sohn, Vetyl Chemie, Hentschke und Sawatzki, Sorex Ltd., and Killgerm Chemicals submitted a dossier to the rapporteur Member State. That dossier contained substantial data gaps, taking into account the supported uses. B.H. Schilling officially withdrew from the registration process on 26 September 1994. The other notifier B. V. Luxan did not submit a complete dossier. Information has furthermore been submitted by a third party, European Federation of Agricultural Workers.

In accordance with the provisions of Article 7(1) of Regulation (EEC) No 3600/92, Ireland submitted on 8 May 1996 to the Commission the report of its examination of the dossier. Moreover, in accordance with the same provisions, the Commission and the Member States received also the summary dossier on warfarin from DuPont Chemoswed as representative of the warfarin task force on 20 September 1996.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the Commission forwarded for consultation the report of the examination by the Rapporteur Member State to all the Member States as well as to DuPont Chemoswed being the designated representative of the warfarin task force on 24 June 1996.

The Commission organised an intensive consultation of technical experts from a certain number of Member States, to review the report of the examination by the Rapporteur Member State and the comments received thereon (peer review), in particular on each of the following disciplines:

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions

The meetings for this consultation were organised on behalf of the Commission by Pesticides Safety Directorate in York, United Kingdom, from September to December 1996.

In accordance with the provisions of Article 6(4) of Directive 91/414/EEC concerning consultation in the light of a possible unfavourable decision for the active substance the Commission organised a tripartite meeting with the representatives of the task force and the rapporteur Member State for this active substance on 24 March 1997.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the dossier, the report of the examination by the Rapporteur Member State, the peer review report (i.e. full report) and the comments and clarifications on the remaining issues, received after the peer review were referred to the Standing Committee on Plant Health, and specialised working groups of this Committee, with participation of experts from the 15 Member States. This final examination took place from 1997 to 12 February 1999.

As a result the Scientific Committee on Plants was consulted. The report of this Committee was formally adopted on 6 June 2000[5]. The Committee was requested to comment on the acceptability

[5] Opinion of the Scientific Committee on Plants regarding the inclusion of warfarin in Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market. **SCP/WARFAR/002-Final**

of using clinical data generated following repeated warfarin use as an anti-coagulant in human medicine for establishing an Acceptable Daily Intake (ADI) and an Acceptable Operator Exposure Level (AOEL). The Committee was of the opinion that it is not necessary to allocate an ADI for warfarin. However, data available from the extensive clinical use of warfarin as an anticoagulant may confidently be expected to support the establishment of an ADI, should this be considered necessary. An AOEL can likewise be established based on human data, taking into account that in rats about 15% of the applied dose is absorbed through the skin.

An updated dossier was submitted to the rapporteur Member State on behalf of the warfarin Task Force (comprising C.S. Spiess & Sohn GmbH & Co, Killgerm Chemicals Ltd, W. Neudorff GmbH KG and Hentschke & Sawatzki OHG), on 28th June 1999. C.S. Spiess & Sohn GmbH & Co was the lead company.

The dossier did not contain substantial data gaps, taking into account the supported uses. Therefore, the Warfarin Task Force (represented by EBRC Consulting GmbH), was considered to be the main data submitter.

In accordance with the provisions of Article 7(1) of Regulation (EEC) No 3600/92, Ireland submitted on 24 June 2002 to the Commission the report of its examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of warfarin in Annex I to the Directive. Moreover, in accordance with the same provisions, the Commission and the Member States received also the summary dossier on warfarin from EBRC Consulting GmbH on 7th March 2003.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the Commission forwarded for consultation the draft assessment report to all the Member States as well as to EBRC Consulting GmbH being the designated representative of the warfarin task force, on 26 June 2002 .

The Commission organised an intensive consultation of technical experts from a certain number of Member States, to review the draft assessment report and the comments received thereon (peer review), in particular on each of the following disciplines:

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The meetings for this consultation were organised on behalf of the Commission by the Pesticide Safety Directorate (PSD) in York, United Kingdom, from March to September 2003.

No full report was circulated after the second Peer Review.

The present review report contains the conclusions of the final examination; given the importance of the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications submitted after the peer review as basic information for the final examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

2. Purposes of this review report

This review report, including the background documents and appendices thereto, has been developed and finalised in support of the Directive 2006/5/EC concerning the inclusion of warfarin in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing warfarin they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In accordance with the provisions of Article 7(6) of Regulation (EEC) No 3600/92, Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to all operators having notified for this active substance under Article 4(1) of this Regulation.

The information in this review report is, at least partly, based on information, which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated to have regulatory access to the information on which this review report is based.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing warfarin will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each warfarin containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the use, which was proposed and supported by the main data submitter and mentioned in the list of uses supported by available data (attached as Appendix IV to this Review Report).

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

Since the plant protection products containing warfarin are not used on plants or plant products, use, consequent on application consistent with good plant protection practice, has no harmful effects on

human or animal health. Additional intake from water and products of animal origin are not expected to give rise to intake problems.

The review has identified several acceptable exposure scenarios for operators, workers and bystanders, which require however to be confirmed for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 6 of this report.

4. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of warfarin are given in Appendix I.

The review has established that for the active substance notified by the main data submitter, the warfarin task force, (represented by EBRC Consulting GmbH) none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.

5. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints were identified during the re-evaluation process. These endpoints are listed in Appendix II.

6. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing warfarin

On the basis of the proposed and supported uses (as listed in Appendix IV), the following particular issues have been identified as requiring particular and short term attention from all Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

-Member States must pay particular attention to the operator safety and must ensure that the conditions of authorisation include appropriate protective measures;

- Member States should pay particular attention to the protection of birds and non-target mammals. Conditions of authorisation should include risk mitigation measures, where appropriate.

7. List of studies to be generated

No further studies were identified which were at this stage considered necessary in relation to the inclusion of warfarin in Annex I under the current inclusion conditions.

Some endpoints however may require the generation or submission of additional studies to be submitted to the Member States in order to ensure authorisations for use under certain conditions. This may particularly be the case for

- a bird reproduction study for use conditions where breeding birds might be exposed.

All other active substances used as rodenticide are covered by stage 4 of the review programme; their evaluation may identify particular aspects or concerns which may not have been identified during the review of warfarin. Therefore it would be appropriate, as soon as decisions are taken for the other rodenticides, to reconsider, in line with scientific progress, the properties and potentially related risks to humans and the environment of warfarin. If necessary further data to conclude such evaluation may be requested.

8. Information on studies with claimed data protection

For information of any interested parties, Appendix III gives information about the studies for which the main data submitter has claimed data protection and which during the re-evaluation process were considered as essential with a view to annex I inclusion. This information is only given to facilitate the operation of the provisions of Article 13 of Directive 91/414/EEC in the Member States. It is based on the best information available to the Commission services at the time this review report was prepared; but it does not prejudice any rights or obligations of Member States or operators with regard to its uses in the implementation of the provisions of Article 13 of the Directive 91/414/EEC neither does it commit the Commission.

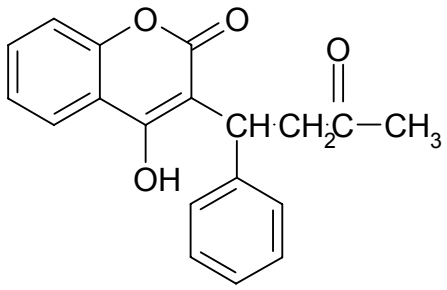
9. Updating of this review report

The technical information in this report may require to be updated from time to time in order to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the **Standing Committee on the Food Chain and Animal Health**, in connection with any amendment of the inclusion conditions for warfarin in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

WARFARIN

Common name (ISO)	WARFARIN
Chemical name (IUPAC)	(RS)-4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin 3-(α-acetonyl-benzyl)-4-hydroxycoumarin
Chemical name (CA)	4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one
CIPAC No	70
CAS No	81-81-2 [unspecified stereochemistry]
EEC No	201-337-6 [EINECS]
FAO SPECIFICATION	---
Minimum purity	≥ 990 g/kg
Molecular formula	$C_{19}H_{16}O_4$
Molecular mass	308.3
Structural formula	

Melting point	165 ºC (purity 100%)	
Boiling point	N.A.	
Appearance	White powder (purity 100%)	
Relative density	1.35 (purity 100%)	
Vapour pressure	≤ 3 x 10^{-5} hPa (≤ 3 x 10^{-3} Pa) at 20ºC	
Henry's law constant	≤ 3.5 x 10^{-3} Pa m^3 /mol at 20ºC	
Solubility in water	4.9mg/l, pH4 ; (Citrate buffer 50mM) 267mg/l, pH7 ; (Carbonate buffer 0.5mM) 66.1g/l, pH9 ; (Carbonate buffer 245mM)	
Solubility in organic solvents	Solvent	Concentration
	Heptane	6.4 mg/l
	Xylene	780 mg/l
	1,2-Dichloroethane	21.2g/l
	Methanol	22.2g/l
	Acetone	54.6g/l
	Ethyl acetate	16.9g/l
Partition co-efficient (log P_{ow})	Log P_{ow} = 0.7 at pH7 and 30 - 36°C)	
Hydrolytic stability (DT_{50})	Stable at pH 4, 7 and 9 at 50°C	
Dissociation constant	PK_a = 5.19 ± 0.03 in aqueous solution at 20ºC	
Quantum yield of direct photo-transformation in water at λ >290 nm	Φ (warfarin in water) = ≤ 0.0004	
Flammability	Not flammable	
Explosive properties	Not explosive	
UV/VIS absorption (max.)	Absorption at 272, 282.5 and 306nm at neutral pH. Absorption at 212.5, 293.5 and 311nm at alkaline pH.	
Photostability in water (DT_{50})	$T_{1/2}$ = ≥ 54 days	

APPENDIX II

END POINTS AND RELATED INFORMATION

WARFARIN

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Effectively 100% with maximum plasma concentration in 2 – 12 hours (human)
Distribution:	57% widely distributed after epicutaneous administration mostly to the skin, carcass, liver, GI tract and blood. >99% of plasma Warfarin is protein-bound (rat)
Potential for accumulation:	Evidence for accumulation after repeated dose-application (plasma half-lives ca. 40 - 163 hours after administration of 2, 5 and 10 mg (study in humans)
Rate and extent of excretion:	Biphasic; the t½ after oral / intravenous administration is 37 – 42 hours; a prolonged terminal elimination phase (human)
Toxicologically significant compounds:	Parent compound warfarin alcohols (anticoagulant activity in human)
Metabolism in animals:	Hydroxyl-metabolites (rat, human) and alcohol derivatives (human)

Acute toxicity

Rat LD_{50} oral:	112 ± 15.9 mg/kg bw (males) 10.4 ± 1.1 mg/kg bw (females)
Rat LD_{50} dermal:	40 mg/kg bw
Rat LC_{50} inhalation:	< 0.005 mg/l air 4 h (below the lowest aerosol concentration)
Skin irritation:	Non-irritant
Eye irritation:	Non-irritant
Skin sensitization (test method used and result):	Not a skin sensitiser (M & K test)

Short term toxicity

Target / critical effect:	Haemorrhage
Lowest relevant oral NOAEL / NOEL:	None established Lowest relevant lethal oral dose: 90 d oral rat: 0.077 mg/kg bw/ day
Lowest relevant dermal NOAEL / NOEL:	None established
Lowest relevant inhalation NOAEL / NOEL:	None established

Genotoxicity	Whereas in-vitro testing results appeared to be somewhat ambiguous the results of the subsequent in-vivo studies demonstrate the absence of a genotoxic potential of warfarin

Long term toxicity and carcinogenicity

Target / critical effect:	None established (no study submitted - not required)
Lowest relevant NOAEL:	None established
Carcinogenicity:	No evidence of carcinogenicity (based on human data)

Reproductive toxicity

Target / critical effect - Reproduction:	No data submitted; not required
Lowest relevant reproductive NOAEL / NOEL:	None established
Target / critical effect - Developmental toxicity:	Haemorrhagic syndrome in foetuses, structural malformations of the hind limbs, internal hydrocephalus, metabolic damage of foetus livers (rat, repeated dose of 0.04 - 8 mg/kg bw/day); maxillonasal hypoplasia, calcium deposits in cartilage of the nasal septum and epiphyseal cartilage of vertebrae and long bones (rat, 100 mg/kg bw subcutaneous injection); foetal death, haemorrhaged placentaes, malformations, prolonged prothrombin time (mouse single dose of 1 - 4 mg/kg bw i.p. at various stages of pregnancy). These effects in laboratory animal species have also been observed in humans.
Lowest relevant developmental	None established

NOAEL / NOEL:	Lowest relevant developmental adverse dose: Rat: 0.04 mg/kg bw/day Human: 0.036 mg/kg bw/day
Delayed neurotoxicity	Not an organophosphorus compound, therefore acute delayed neurotoxicity studies were not conducted. No evidence of neurotoxicity from other studies and human experience
Other toxicological studies	Anticoagulant potency of (S)-Warfarin 6.6 times greater than that of (R)-Warfarin (rat) Longer plasma half-life of (S)-Warfarin (rat)
Medical data	Long-term toxicity: Human long-term therapeutic maintenance dose 1.0-13 mg/day (corresponding to 0.015-0.2 mg/kg bw/day: prolongation of prothrombin time); isolated cases of bleeding episodes, skin necrosis and hepatotoxicity mostly in connection with miscalculation or misdosing during medical therapy; No indication of any higher cancer incidence (retrospective studies in human); LOAEL: 0.03 mg/kg bw/day (lowest human long-term maintenance dose) Reproductive toxicity: Stillbirth or abortion, microcephaly, hydrocephaly, nasal hypoplasia, bone anomalies, growth retardation (human, dose level 2.5 - 12.5 mg/day ≅ 0.03 – 0.2 mg/kg bw/day) LOAEL: 0.015 mg/kg bw/day

Summary

	Value	Study	Safety factor
ADI:	Not applicable, residues not in food chain, none set		100
AOEL systemic:	0.0002 mg/kg bw/d	lowest human therapeutic dose (0.015 mg/kg bw/day)	100
AOEL inhalation:			
AOEL dermal:			
ARfD (acute reference dose):	Not relevant for this compound		

Dermal absorption	15 % (based on *in-vivo* rat dermal absorption study 24

hour exposure; SCP)

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:	10% - 20% (n = 2)
Non-extractable residues after 100 days:	10% - 42% (n = 2)
Major metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)	No relevant metabolites ≥ 10% AR detected. {Two metabolites Hydroxycoumarin and Hexahydrocoumarin each represented <5% AR}

Supplemental studies

Anaerobic:	No data reported / not considered necessary
Soil photolysis:	No significant degradation under 29 days continuous irradiation – soil photolysis not considered a relevant degradation route
Remarks:	

Rate of degradation

Laboratory studies

DT_{50}lab (20 °C, aerobic):	
DT_{90}lab (20 °C, aerobic):	
DT_{50}lab (10 °C, aerobic):	
DT_{50}lab (20 °C, anaerobic):	

Field studies (country or region)

DT_{50f} from soil dissipation studies:	
DT_{90f} from soil dissipation studies:	
Soil accumulation studies:	No data reported, not considered necessary, since significant soil contamination will not arise
Soil residue studies:	

Remarks: e.g. effect of soil pH on degradation rate	

Adsorption/desorption

K_f / K_{oc}:	K_F 14.15, range 0.66 – 46.77, n=4 K_{OC} 174, range 18 – 390, n=4
K_d:	
pH dependence:	Yes. Warfarin adsorption strongly depends on pH and organic matter content. Adsorption increases with decreasing soil pH

Mobility

Laboratory studies:

Column leaching:	Moderate leaching potential <1% in acidic soils of high organic matter content
Aged residue leaching:	No data reported – not relevant

Field studies:

Lysimeter/Field leaching studies:	No data reported – not relevant

Remarks:	

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:	PH 5.0 stable (50°C) PH 7.0 stable (50°C) PH 9.0 stable (50°C) No significant hydrolysis expected at temperatures of environmental relevance
Major metabolites:	
Photolytic degradation:	No significant degradation under 14 days continuous irradiation (20-25°C)
Major metabolites:	

Biological degradation

Readily biodegradable:	No
Water/sediment study: DT_{50} water: DT_{90} water: DT_{50} whole system: DT_{90} whole system: Distribution in water / sediment systems (active substance) Distribution in water / sediment systems (metabolites)	No data reported – not considered necessary
Accumulation in water and/or sediment:	

Degradation in the saturated zone	
Remarks:	

2.3 Fate and behaviour in air

Volatility

Vapour pressure:	≤ 3 x 10^{-5} hPa (≤ 3 x 10^{-3} Pa) at 20ºC
Henry's law constant:	≤ 3.5 x 10^{-3} Pa m^3/mol at 20ºC

Photolytic degradation

Direct photolysis in air:	According to spectral data no quantitatively relevant degree of photolysis is to be expected
Photochemical oxidative degradation in air DT_{50}:	An atmospheric half life of 2.4 hours for a 24 hour day was calculated according to AOP model
Volatilisation:	Not required

Remarks:	

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	Acute toxicity to rat	LD_{50}	1.6--323.0 mg/kg bw	(techn. A.i.)
	Acute toxicity to rat)	LD_{50}	1120-4000 mg/kg b.wt	(formulation)
Acute toxicity to birds:	Acute toxicity to Bobwhite quail	LD_{50}	>2000 mg/kg b.wt	(techn. a.i.)
Dietary toxicity to birds:	Dietary toxicity to Bobwhite quail	LC_{50}	4448 ppm	(techn. a.i.)
	Dietary toxicity to Mallard duck	LC_{50}	>5000 ppm	(techn. a.i.)
Reproductive toxicity to birds:				
Short term oral toxicity to mammals:				

Aquatic Organisms

Acute toxicity fish:	Rainbow trout: LC_{50} (65 mg/l) Bluegill Sunfish: LC_{50} (88 mg/l)
Long term toxicity fish:	Rainbow trout: NOEC (2.0 mg/l) Bluegill Sunfish: NOEC (-)
Bioaccumulation fish:	
Acute toxicity invertebrate:	Daphnia magna: EC_{50} (>105---130 mg/l) Daphnia magna (acute – 24 h): EC_{50} (180 mg/l)
Chronic toxicity invertebrate:	
Acute toxicity algae:	Selenastrum capricornutum: E_rC_{50} (>8.5-->83.2 mg/l)
Chronic toxicity sediment dwelling organism:	

Honeybees

Acute oral toxicity:	No data reported – not required due to lack of exposure
Acute contact toxicity:	No data reported – not required due to lack of exposure

Other arthropod species

Test species	% Effect
	No data reported – not required due to lack of exposure

Earthworms

Acute toxicity:	No data reported – not required due to lack of exposure
Reproductive toxicity:	No data reported – not required due to lack of exposure

Soil micro-organisms

Nitrogen mineralization:	Clear inhibition of microbial dehydrogenase activity (test with techn.a.i.)
Carbon mineralization:	At 550 mg/kg soil (test with techn.a.i.)

APPENDIX IIIA

WARFARIN

List of studies for which the main submitter has claimed data protection and which during the re-evaluation process were considered as essential for the evaluation with a view to Annex I inclusion.

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[6] on previous use in granting national authorizations
IIA 2.1	Krips, H.J.	1998	Determination of the melting temperature of warfarin technical NOTOX; Project 240672 GLP, unpublished	
IIA 2.2	Krips, H.J.	1998	Determination of the density of warfarin technical NOTOX; Project 240683 GLP, unpublished	
IIA 2.3.1	Schleich, W.	2001	Warfarin. Determination of the vapour pressure Infracor, Marl, Germany, AN-ASB 0172 GLP, unpublished	
IIA 2.3.1a	Battersby, R.V.	1999	Model calculation of the vapour pressure of warfarin EBRC Consulting GmbH, Hannover, 20.04.1999, 3 p. Not GLP, unpublished	
IIA 2.3.2	EBRC	2002	Henry's Constant Warfarin EBRC Consulting GmbH, Hannover, 05.02.2002, 3 p. Not GLP, unpublished	

[6] Entries are based on information received from the Notifier(s) and in certain cases Member States. Neither the Commission nor the Member States are responsible for the completeness or validity of this information received.

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[6] on previous use in granting national authorizations
IIA 2.5.1/03	Fristedt, T.	1995	NMR- and mass-spectrum on dicusat (warfarin), batch VF979 Pharmacia, Oncology Immunology, 11p. Not GLP, unpublished	
IIA 2.6/01	Walter, D.	1998	Water solubility of warfarin GAB/IFU, Study code: 98304/01-PCSB GLP, unpublished	
IIA 2.7/01	Walter, D.	1998	Solubility of warfarin in organic solvents GAB/IFU, Study code: 98304/01-PSBO GLP, unpublished	
IIA 2.8	Meinerling, M.; Herrmann, S.	2001	Determination of the partition coefficient (n-octanol/water) of warfarin techn. by high performance liquid chromatography (HPLC) IBACON, Rossdorf, Germany, Project No.: 12003186 GLP, unpublished	
IIA 2.9/01	Raghavan, K.S.	1994	Hydrolysis of warfarin sodium warfarin Pharmacy R&D; Doc. No.: 94-0584 Not GLP, unpublished	
IIA 2.2/02; 7.2.1.2/01	Kloepfer, W.	1992	Determination of the phototransformation of Warfarin in water in accordance with the UBA Test Guideline "Phototransformation of chemicals in water, part A, Direct Phototransformation" Battelle Europe; Doc. No.: BE-P-78-91-PHO-01 GLP, unpublished	
IIA 2.11.1	Krips, H.J.	1998	Determination of the flammability of warfarin technical NOTOX; Project 240694 GLP, unpublished	
IIA 2.11.2	Krips, H.J.	1998	Determination of the relative self-ignition temperature of warfarin technical NOTOX; Project 240705 GLP, unpublished	
IIA 2.13/01	EBRC	1999	Report: explosivity EBRC Consulting GmbH, Hannover, 3 p. Not GLP, unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[6] on previous use in granting national authorizations
IIA 2.14/01	Krips, H.J.	1998	Determination of the surface tension of an aqueous solution of warfarin technical NOTOX; Project 240716 GLP, unpublished	
IIA 5.2.2/01	Daamen, P.A.M.	1994	Assessment of acute dermal toxicity with warfarin technical in the rat NOTOX; Doc. No.: 110464 GLP, unpublished	
IIA 5.2.3/01	Busch, B.	1985	Acute inhalation LC50 of warfarin technical in Sprague-Dawley rats Food & Drug Research Laboratories, Inc.; FDRL Study No.: 8359 GLP, unpublished	
IIA 4.1.1/01	Persson, D.; Borgkvist, M.	1995	Specification and routine tests for active substances Pharmacia; Doc. No.: S 385; 46 98 50 Not GLP, unpublished	
IIA 4.1.1/02	de Ryckel, B.	1999	Analysis of 5 batches of Warfarin technical products, and of 2 batches of Warfarin Sodiumsalt technical products (copy of full report, but without chapters 5 and 6 containing analytical results, and thus only for description of method and validation parameters; for a full copy, see reference 1.11/01) Departement de Phytopharmacie, Belgium, Project no. EBRC/PJ/BA 9318/Ch.1703 to Ch.1709/1998/212, 14.06.1999 GLP, unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[6] on previous use in granting national authorizations
IIA 4.2.2/01	Mende, P.	2001	Residue analysis of warfarin in soil. Method validation GAB/IFU, Study code: 20011279/01-RVS GLP, unpublished	
IIA 4.2.2/02	Kurth, H.-H	1999	Adsorption/desorption of warfarin on soil Fraunhofer-Institut für Umweltchemie und Ökotoxikologie, Germany, GLP-Code:SPI-001/7-13 GLP, unpublished	
IIA 4.2.3/01	Mende, P.	2001	Residue analysis of warfarin in drinking water and surface water. Method validation GAB/IFU, Study code: 20011279/01-RVW GLP, unpublished	
IIA 8.2.6/02	Hertl, J.	2001	Toxicity of warfarin techn. to Scenedesmus subspicatus in an algal growth inhibition test IBACON, Rossdorf, Germany, Project No.: 12002210 GLP, unpublished	

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 5.1.1/01	Leuschner, J.	1999	Absorption study of 14C-labelled warfarin by topical administration for 6 or 24 hours in Sprague-Dawley rats LPT Report No. 11687/98 GLP, unpublished	
IIA 5.2.2/01	Daamen, P.A.M.	1994	Assessment of acute dermal toxicity with warfarin technical in the rat NOTOX; Doc. No.: 110464 GLP, unpublished	
IIA 5.2.3/01	Busch, B.	1985	Acute inhalation LC50 of warfarin technical in Sprague-Dawley rats Food & Drug Research Laboratories, Inc.; FDRL Study No.: 8359 GLP, unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 5.2.4/01	Pels Rijcken, W.R.	1994	Primary skin irritation/corrosion study with warfarin technical in the rabbit (4-hour semi-occlusive application) NOTOX; Doc. No.: 110475 GLP, unpublished	
IIA 5.2.5/01	Pels Rijcken, W.R.	1994	Acute eye irritation/corrosion study with warfarin technical in the rabbit NOTOX; Doc. No.: 110486 GLP, unpublished	
IIA 5.2.6/01	Daamen, P.A.M.	1994	Assessment of contact hypersensitivity to warfarin technical in the Albino Guinea pig (Maximization-Test) NOTOX; Doc. No.: 110497 GLP, unpublished	
IIA 5.4.1/01	van de Waart, E.J.	1994	Evaluation of the mutagenic activity of warfarin technical in the ames salmonella/microsome test (with independent repeat) NOTOX; Doc. No.: 110508 GLP, unpublished	
IIA 5.4.1/02	van de Waart, E.J.	1994	Evaluation of the mutagenic activity of warfarin technical in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat) NOTOX; Doc. No.: 110519 GLP, unpublished	
IIA 5.4.1/03	van de Waart, E.J.	1994	Evaluation of the ability of warfarin technical to induce chromosome aberrations in cultured peripheral human lymphocytes NOTOX; Doc. No.: 110521 GLP, unpublished	
IIA 5.4.2/01	Grötsch, W.	1999	Final report in vivo micronucleus test of warfarin in mice L+S AG, Germany, Study No.: 06287188/1 Not GLP, unpublished	
IIA 5.4.2/02	Grötsch, W.	1999	Final report in vivo micronucleus test of warfarin in mice L+S AG, Germany, Study No.: 06287188/2 Not GLP, unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 5.4.2/03	Leuschner, J.	1999	Unscheduled DANN synthesis (UDS) test of warfarin, sodium salt after oral administration to Sprague-Dawley rats LPT Laboratory of Pharmacology and Toxicology, Hamburg, Germany, Report No.11731/98 Not GLP, unpublished	

~~B.7 Residue data~~

~~Annex point/ reference number~~	~~Author(s)~~	~~Year~~	~~Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not~~	~~Reports on previous use in granting national authorizations~~

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 7.1.1.1.1/01	Bieber, W.-D.; Kroehn, R.	1991	Degradation (metabolism) of warfarin in soil NATEC; Doc. No.: NA 89 9252 Not GLP, unpublished	
IIA 7.1.1.1.1/02	Kurth, H.-H.	1999	Aerobic soil degradation of warfarin Fraunhofer Institut Umweltchemie und Ökotoxikologie, GLP-Code: SPI-001/7-15 GLP, unpublished	
IIA 7.1.1.1.2/02	Kurth, H.-H.	1999	Soil photolysis of warfarin Fraunhofer Institut Umweltchemie und Ökotoxikologie, GLP-Code: SPI-001/7-06 GLP, unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 7.1.1.2.1/01	Kellner, G.	1991	Abbau von Warfarin im Boden NATEC; Doc. No.: NA 91 9072 GLP, unpublished	
IIA 7.1.1.2.1/02	Todt, K.; Niemann, I.; Thiele, E.	1989	Degradation of warfarin in soil NATEC; Doc. No.: NA 89 9719 Not GLP, unpublished	
IIA 7.1.1.2.1/03	Kellner, G.	1991	Degradation of warfarin in soil NATEC; Doc. No.: NA 91 9072 GLP, unpublished	
IIA 7.1.2/01	Kurth, H.-H.	1999	Adsorption/desorption of warfarin on soil Fraunhofer-Institut für Umweltchemie und Ökotoxikologie, Germany, GLP-Code: SPI-001/7-13 GLP,unpublished.	
IIA 7.2.1.2/01	Kloepfer, W.	1992	Determination of the phototransformation of Warfarin in water in accordance with the UBA Test Guideline "Phototransformation of chemicals in water, part A, Direct Phototransformation" Battelle Europe; Doc. No.: BE-P-78-91-PHO-01 GLP, unpublished	
IIA 7.2.1.3.1/01	Alexanderson, T.	1992	Evaluation of the aerobic biodegradability of organic compounds CENOX AB, Report 222 Not GLP, unpublished	
IIA 7.2.2/01	Battersby, R.V.	1999	Predictive model calculation of the atmospheric oxidation behaviour (AOP) Warfarin EBRC Consulting GmbH, Hannover, Germany, 11.06.1999, 6 p. Not GLP, unpublished	

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 8.1.1/01	Beavers, J.B.	1985	An acute oral toxicity study in the bobwhite with warfarin Wildlife International Ltd.; Doc. No.: 205-103 GLP, unpublished	
IIA 8.1.2/01	Beavers, J.B.	1985	A dietary LC50 study in the bobwhite with warfarin Wildlife International Ltd.; Doc. No.: 205-101 GLP, unpublished	
IIA 8.1.2/02	Beavers, J.B.	1985	A dietary LC50 study in the mallard with warfarin Wildlife International Ltd.; Doc. No.: 205-102 GLP, unpublished	
IIA 8.2.1/01	McAllister, W.A.; Cohle, P.	1984	Acute toxicity of warfarin technical to Bluegill sunfish Analytical Bio-Chemistry Laboratories Inc.; Doc. No.: 32460 GLP, unpublished	
IIA 8.2.1/01	Günther	1984	Fish toxicity, Orfe Ökolimna, 8p. Not GLP, unpublished	
IIA 8.2.1/02	Günther	1984	Fish toxicity, rainbow trouts Ökolimna; 8p. Not GLP, unpublished	
IIA 8.2.2.1/01	Dommröse, A.-M.	1989	Investigation of the test substance warfarin in a prolonged toxicity test on fish (rainbow trout) NATEC; Doc. No.: NA 88 9867/3.3 GLP, unpublished	
IIA 8.2.3/01	Dommröse, A.-M.	1990	Bioaccumulation (flow-through test) with the test substance warfarin in fish (rainbow trout) NATEC; Doc. No.: NA 88 9867/3.4 GLP, unpublished	
IIA 8.2.6/01	Hertl, J.	2001	Toxicity of warfarin techn. to Scenedesmus subspicatus in an algal growth inhibition test IBACON, Rossdorf, Germany, Project No.: 12002210 GLP, unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 8.2.4/01	Forbis, A.D.; Georgie, L.; Burgess, D.	1984	Acute toxicity of warfarin technical to Daphnia magna Analytical Bio-Chemistry Laboratories Inc.; Doc. No.: 32462 GLP, unpublished	
IIA 8.2.4/02	Günther	1984	Daphnia toxicity Ökolimna; 6p. Not GLP, unpublished	
IIA 8.2.4/04	Hertl, J.	2001	Acute toxicity of warfarin techn. to Daphnia magna in a 48-hour immobilization test IBACON, Rossdorf, Germany, Project No.: 12001220 GLP, unpublished	
IIA 8.2.5/01	Dommröse, A.-M.	1990	Investigation of the test substance warfarin in a prolonged immobilisation and reproduction test on daphnia magna NATEC; Doc. No.: NA 88 9867/3.2 GLP, unpublished	
IIA 8.2.6/01	Dommröse, A.-M.	1989	Wachstumshemmtest an Algen NATEC; Doc. No.: NA 88 9867/3.1 GLP, unpublished	
IIA 8.2.6/02	Zschaler, R.	1989	Growth inhibition test on algae NATEC; Doc. No.: NA 88 9867/3.1 GLP, unpublished	
IIA 8.6.3/25	Kenward, R. Woodburn, M Robertson, P. Wall, S.	1989	Grey squirrels at phesant sites. Game Conservancy Review , pp 4 Not GLP unpublished.	

APPENDIX IIIB

WARFARIN

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

~~**XXX RMS please list the studies which have been submitted during the process of evaluation.**~~

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 2.5.2	Heintze, A.	2002	UV/VIS adsorption spectrum, infrared adsorption-spectrum, H-NMR spectrum and mass spectrum of warfarin. GAB/IFU Niefern-Oschelbronn, Germany Study Code: 20021048/01-PCSD GLP, Un-puplished
IIA, 1.9	Heintze, A.	2002	Sodium warfarin techn. Determination of purity of five techn. Batches; GAB/IFU Niefern-Oschelbronn, Germany. Study Code 20021028/01-R5B GLP, Un-published
IIA, 2.9.1	Heintze, A.	2002	Abiotic degradation of warfarin; Hydrolysis as a function of pH. Arbeitgemeinschaft GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, Germany. Study Code: 20021048/01- PCHY GLP, Un-published
IIA, 2.9.4	Heintze, A.	2002	Ionisation constant of warfarin in water. Arbeitgemeinschaft GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, Germany. Study Code: 20021048/01- PCDC GLP, Un-published
IIIA, 2.6.2	Wilfinger, W.	2003	Pour (Bulk) and tap density of Curattin Haftstreupuder Arbeitgemeinschaft GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, Germany. Study Code: 20021455/01- PCF1 GLP, Un-published
IIIA, 2.8.6.1	Franke, J.	2003	Particle size distribution Sicherheitstechnik, Siemens Axiva GmbH & Co. KG, Germany Report No. 20021480.01

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 4.1.	Mende, P.	2003	Validation of a Confirmatory Method for Analysis of Warfarin in Warfarin Technical Grade Material. Study code: 20021065/01-RVF} Arbeitgemeinschaft GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, Germany. Study Code: 20021065/01- RVF Un-published
IIA, 4.2.4	Heintze, A.	2002	Validation of an analytical method for the determination of warfarin from air or airborne warfarin containing dust (Curattin Haftstreupuder) from air. GAB/IFU Niefern-Oschelbronn, Germany, Study Code: 20021045/01-CMLU

~~B.6 Toxicology and metabolism~~

~~Annex point/ reference number~~	~~Author(s)~~	~~Year~~	~~Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not~~

~~B.7 Residue data~~

~~Annex point/ reference number~~	~~Author(s)~~	~~Year~~	~~Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not~~

~~B.8 Environmental fate and behaviour~~

~~Annex point/ reference number~~	~~Author(s)~~	~~Year~~	~~Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not~~

~~B.9 Ecotoxicology~~

~~Annex point/ reference number~~	~~Author(s)~~	~~Year~~	~~Title~~ ~~Source (where different from company)~~ ~~Company, Report No.~~ ~~GLP or GEP status (where relevant)~~ ~~Published or not~~

APPENDIX IV

List of uses supported by available data

WARFARIN

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Storage protection	EU	Cumarax Rattenring	F ~~and I~~	Rattus norvegicus	BB	0.04%	Cumarax Rattenring is a ready-to-use solid, ring-formed bait for protection of harvested crops from rats, elimination of rats ~~in sewers,~~ along ditches and brooks ~~and in houses.~~ The rings must be laid out by hand near hiding places or tracks of rats. New rings must be laid out 1-2 days approx. until elimination of the rats is achieved.				Each ring (250g) contains 100mg warfarin. Ditches and brooks: 1 ring for 50m (approx.) bank. ~~Sewage: 1-3 rings per shaft.~~ ~~Domestic use: 1 ring per 10 animals (100 mg a.s.).~~			N.A.	

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions