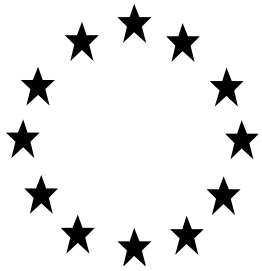
Directive 98/8/EC concerning the placing of biocidal products on the market

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

Assessment Report



Warfarin

Product-type 14 (Rodenticides)

September 2009

Annex I - Ireland

Warfarin (PT 14)

Assessment Report

Finalised in the Standing Committee on Biocidal Products at its meeting on [date] in view of its inclusion in Annex I to Directive 98/8/EC

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. PROCEDURE FOLLOWED

This assessment report has been established as a result of the evaluation of Warfarin as product-type 14 (Rodenticides), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I or IA to the Directive.

Warfarin (CAS no. 81-81-2, racemic mixture) was notified as an existing active substance, by the "Warfarin Task Force" that comprises of the following three applicant companies: Killgerm Chemicals, Hentschke & Sawatzki KG and Vetyl Chemie GmbH, hereafter referred to as the applicant, in product-type 14.

Commission Regulation (EC) No. 2032/2003 of 4 November 2003[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 5(2) of that Regulation, Ireland was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for Warfarin as an active substance in product-type 14 was 28th March 2004, in accordance with Annex V of Regulation (EC) No. 2032/2003.

On 23rd March 2004, the Irish competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 27th September 2004.

On 7th October 2005, the Rapporteur Member State submitted, in accordance with the provisions of Article 10(5) and (7) of Regulation (EC) No. 2032/2003, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 10th October 2005. The competent authority report included a recommendation for the inclusion of Warfarin in Annex I to the Directive for PT 14.

In accordance with Article 12 of Regulation (EC) No 2032/2003, the Commission made the competent authority report publicly available by electronic means on 11th October 2005. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

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

[1] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. OJ L 123, 24.4.98, p.1.

[2] Commission Regulation (EC) No 2032/2003 of 4 November 2003 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market and amending Regulation (EC) No 1896/200. OJ L 307, 24.11.2003, p.1.

On the basis of the final competent authority report, the Commission proposed the inclusion of warfarin in Annex I to Directive 98/8/EC and consulted the Standing Committee on Biocidal Product on 17 September 2009.

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

1.2. PURPOSE OF THE ASSESSMENT REPORT

This assessment report has been developed and finalised in support of the decision to include Warfarin in Annex I to Directive 98/8/EC for product-type 14. The aim of the assessment report is to facilitate the authorisation in Member States of individual biocidal products in product-type 14 that contain Warfarin. In their evaluation, Member States shall apply the provisions of Directive 98/8/EC, in particular the provisions of Article 5 as well as the common principles laid down in Annex IV.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available at the Commission website[3], shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of 98/8/EC, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

1.3. OVERALL CONCLUSION IN THE CONTEXT OF DIRECTIVE 98/8/EC

The overall conclusion from the evaluation is that it may be expected that there are products containing Warfarin for the product-type 14, which will fulfil the requirements laid down in Article 10(1) and (2) of Directive 98/8/EC. This conclusion is subject to:

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

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

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

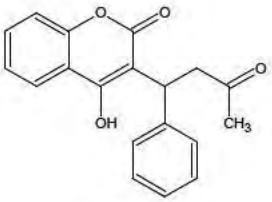
Furthermore, these conclusions were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions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

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

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. PRESENTATION OF THE ACTIVE SUBSTANCE

2.1.1. Identity, Physico-Chemical Properties and Methods of Analysis

CAS No.:	81-81-2 racemic mixture
EINECS No.:	201-377-6
IUPAC name:	(RS)-4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin
CA name:	4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one
Common name:	Warfarin
Synonyms:	Athrombine-K, Brumalin, Coumadin, Coumafene (France), Dethmor, Kumatox, Rodafarin, Solfarin, Zoocoumarin (Russia), W.A.R.F. 42
Molecular formula:	C19H16O4
Purity:	Minimum purity ≥990 g/kg
Structural Formula:	
Molecular mass:	308.25 g/mol

Warfarin is a solid, white powder with a melting point of 165°C. It has a vapour pressure of 3.47 x 10^{-3} Pa and a Henry's law constant of ≤3.5 x 10-3 Pa m^3/mol at 20°C. Therefore, warfarin is not considered to be volatile. The molecule is slightly soluble in apolar organic solvents and readily soluble in polar organics. The partition coefficient indicates that the molecule is not fat soluble (log kow = 0.7 at pH 7). No reactivity towards container material is known. It is not volatile, does not exhibit surface activity, is not flammable, explosive and is not susceptible to oxidation. Warfarin does not classify from a physical-chemical point of view.

A validated method using HPLC/MS was provided for the active substance in the technical material as manufactured. HPLC involved the uses of a reversed-phase column and acetonitrile/water/formic acid (50: 50: 0.2 v/v) mobile phase. The detection system employed LCQ Duo Ion Trap System, electro spray interface (esi) and the monitored ions were m/z = 308 - >161.

2.1.2. Intended Uses and Efficacy

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

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

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

Warfarin is used to control:

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

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.2.2. Effects on target organism(s)

Warfarin is a first-generation multi-dose anticoagulant rodenticide. It disrupts the normal blood clotting mechanisms resulting in increased bleeding tendency and, eventually, profuse hemorrhage and death. Effectiveness of the active substance depends on exposure (i.e. consumption of the bait by the target organism). For effective and comprehensive control of rats and mice a bait concentration in wax blocks up to 0.079 % (m/m) ≡ 790 mg/kg in granular bait up to 0.079 % (m/m) ≡ 790 mg/kg is proposed.

2.1.2.3. Humaneness

The use of warfarin as a rodenticide could potentially cause suffering of vertebrate target organisms. The use of anti-coagulant rodenticides is necessary as there are at present no other valuable measures available to control the rodent population in the European Union. Rodent control is necessary to prevent disease transmission, contamination of food and feeding stuffs and structural damage. It is recognised that such substances do cause pain in rodents but it is considered that this is not in conflict with the requirements of Article 5.1 of Directive 98/8/EC 'to avoid unnecessary pain and suffering of vertebrates', as long as effective, but comparable less painful alternative biocidal substances or biocidal products or even non-biocidal alternatives are not available. Such a comparative assessment is not under the scope of this report, but should be preformed when possible alternatives have been evaluated and all data are available.

2.1.2.4. Resistance

The phenomenon of resistance or to presumed changes in the susceptibility of rat populations to rodenticides is almost all referred to populations of rats and mice to the anticoagulants of first generation, such as Warfarin, and second generation, such as Bromadiolone and Difenacoum. Repeated use of coumarin-like anticoagulants as a rodenticide may lead to the development of resistance in rat and mice populations.

The resistance of Warfarin in rats has been observed to be inheritable, with the phenotypic expression appearing to be conducted to a single autosomal gene. Resistance to Warfarin in rats is characterised by changes to enzymes involved in the metabolism of vitamin K, which reduce the effect of Warfarin to inhibit the metabolism of vitamin K. In mice, the resistance in some strains depends on a reduction in sensitivity of hepatic vitamin KO reductase that is similar to the mechanism evaluated for Warfarin resistant rats. However, there is evidence that other resistance mechanisms may exist in some mice populations.

Resistance to Warfarin in rodent populations was identified approximately 20 years after the first use of Warfarin to control rodents in wild rats of the strain R*attus norvegicus* (Norway rat, Brown rat). Resistance to Warfarin has also been observed in *Mus musculus* (House mice). Resistance to Warfarin

(and other anticoagulant rodenticides) have been reported across Europe and in N. America. Evidence of Warfarin-resistant rat and mouse strains in various geographical locations has also indicated that these resistant rodent strains are restricted to distinct areas, so that rodent populations in most areas are still well controlled by Warfarin. Additionally, where there is no evidence of resistance to Warfarin in rodent populations there is no reason to suspect a lack of efficacy of Warfarin-based products and it is possible to state that Warfarin is fully active against rodent populations in such areas.

Where the potential for the development of resistance in rodent populations to anticoagulants is considered an issue, suitable management strategies are considered necessary for the use of such rodenticides in controlling populations of rats and mice. Suitable management strategies may include safety zones where resistance has been detected, the mixed-use of anticoagulants, the use of alternative rodenticides, or prompt and effective use of anticoagulants when a rodent problem is identified. Additionally, where resistance to anticoagulants is considered problematic it may be justified to carry out monitoring programmes on rodent populations in order to assess the further spread of resistant rats to new areas.

2.1.3. Classification and Labelling

Proposal for the classification and labelling of the active substance

Hazard symbol: (for labelling)	T^+ -	Very Toxic
Indication of danger:	Skull and Crossbones -	
Risk Phrases: (for labelling)	R26/27/28 R61 R48/23/24/25 R52	Very toxic by inhalation, in contact with skin and if swallowed May cause harm to the unborn child Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed Harmful to aquatic organisms
Safety Phrases: (for labelling)	S27/28 S36/37 S45 S61 S53	After contact with skin, take off immediately all contaminated clothing and wash immediately with plenty of water Wear suitable protective clothing and gloves In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible) Avoid release to the environment. Refer to special instructions/Safety data sheets. Avoid exposure - obtain special instructions before

Specific concentration limits	C ≥ 7.0% 1.0% ≤ C < 7.0% 0.1% ≤ C < 1.0% 0.01% ≤ C < 0.1%	T+; R61-26/27/28-48/23/24/25 T; R61-23/24/25-48/20/24/25 T; R61-20/21/22-48/24/25 Xn; R48/21/22

Justification for the proposal

Classification of warfarin was based on the result of studies presented and is in accordance with the principles of Annex VI of Council Directive 67/548/EEC (with amendments and adaptations).

Proposal for the classification and labelling of the products Tox-Vetyl neu Fertigköder and Tox-Vetyl Festköder.

Hazard symbol	Symbol letter: Xn Indication of danger: Harmful	
Risk phrases	R48/21/22	Harmful: danger of serious damage to health by prolonged exposure through in contact with skin or if swallowed
Safety phrases	S2: S13: S20/21: S37 S46: FS13	Keep out of reach of children. Keep away from food, drink and animal feeding stuffs. When using do not eat, drink or smoke. Wear suitable gloves If swallowed, seek medical advice immediately and show this container or label. Avoid contact during pregnancy

Justification for the proposals

Studies regarding the toxicity of the biocidal products were not included in the application. It was agreed, however, that the classification of the products should be based on that of the active substance. The concentration of warfarin is below that requiring classification under the general guidance. However, due to the high toxicity of warfarin specific concentration limits for human effects have been proposed and the classification proposal is based on these specific concentration limits.

It should be noted that the specific concentration limits for warfarin are still under discussion. If these limits are accepted the biocidal products will be classified for repeated dose toxicity (Xn R48/21/22).

Although the products do not require classification for developmental toxicity based on the proposed specific concentration limits the active substance is a category 1 developmental toxicant and a precautionary phrase regarding this fact is required on the label. The additional safety phrase FS13 “Avoid contact during pregnancy” has been applied.

2.2. SUMMARY OF THE RISK ASSESSMENT

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard Identification

Human health effects of the active substance

Warfarin is a so-called first-generation anticoagulant. Ingestion of a lethal dose leads to death due to internal haemorrhaging with a time delay of several days after intake. Warfarin, just like other coumarin derivatives, acts as a vitamin K antagonist. Vitamin K in its reduced form (KH2) is essential in the synthesis of blood coagulation factors, taking place in the vertebrate liver. KH2 is recycled in a two-step process by reductases. Warfarin blocks these reductases, resulting in the depletion of Vitamin K stores. Consequently, the synthesis of blood coagulation factors is disrupted, which leads to loss of blood clotting ability.

Anticoagulant therapy with Warfarin predominantly during the early stages of pregnancy has been reported to cause birth defects known as “Warfarin embryopathy”. Case reports and clinical reviews are presented in the dossier. Consequently, Warfarin has long since been classified as reprotoxic (Repr. cat. 1, R 61). A variety of animal studies have been reported which primarily were aimed at investigating the mechanisms of toxicity. The results obtained in different investigations with Warfarin on pre- and postnatal development with and without the addition of Vitamin K in laboratory animals showed effects caused by the direct anticoagulant activity of the compound, e.g. haemorrhagic syndrome, and effect on the skeletal system induced by suppression of vitamin-K-dependant proteins of bones comparable to the anomalies described as Warfarin embryopathy in humans.

2.2.1.2. Effects Assessment

Absorption, distribution, metabolism and excretion

Absorption of Warfarin and Sodium Warfarin after oral intake may be seen as complete. Upon sustained skin contact, Warfarin may be absorbed at a rate of approx. 15 % (13.3% and 14.4% were absorbed by rat skin after 6 h and 24 h exposure, respectively). The toxic effect (identical with the mode of action in target organisms) is disturbance of the synthesis of blood clotting factors via inhibition of vitamin K reductases. Warfarin is distributed quickly throughout the plasma, and the liver, being the target organ, has the greatest affinity of any tissue examined. In the liver, Warfarin is inactivated by metabolism to compounds of either non- or clearly decreased anticoagulant activity. Warfarin is metabolised predominantly by hydroxylation.

Acute toxicity

The acute oral toxicity of Warfarin in the rat has been reported and it appears to be strongly dependent on strain and sex. In those cases where male and female animals were tested, LD_{50} values for female animals (range: 5–58 mg/kg b.w.) were 5–10 fold lower than for males (range: 1.6–323 mg/kg b.w.). The ranges for the LD_{50} values in other animal species tested are far above this level, for example in mice 374–675 mg/kg, in rabbits ca. 800 mg/kg, in dogs ca. 200–300 mg/kg, thus demonstrating the particular sensitivity of the rat species.
Other routes: The acute dermal toxicity judged by the percutaneous LD_{50} was 40 mg/kg for females alone, was estimated between 20 and 80 mg/kg for males. The inhalation LD_{50} in rats (male and female) was assessed to be below the lowest aerosol concentration i.e. <0.005 mg/l in the test.

Irritation, corrosivity and sensitisation

Warfarin has been shown experimentally to be free of any skin or eye irritating properties, and is not a skin-sensitising agent.

Repeated dose toxicity

Rodents, and rats in particular, are the target species for rodenticides such as Warfarin due to their particular susceptibility. Thus, experiments with repeated administration even at low levels are hampered due to the high sensitivity of this species to Warfarin: for example, the oral uptake of a dose of 0.077 mg/kg b.w./day led to a mortality of 50% of the test animals (notwithstanding massive haemorrhaging), whereas this dose (for an average individual of 70 kg b.w.) calculates to a dose of 5 mg/day, which for human standards is a common and average therapeutic dose level, expected to lead to a desired prothrombin time prolongation of a factor between 1.5 and 2.5.

Acceptable Exposure Levels (AELs) were derived from human data because No Observable Adverse Effect Levels (NOAELs) for Warfarin could not be derived from rodent repeated dose studies because of the particular susceptibility of rodents to anticoagulant effects.

Genotoxicity

The genotoxicity of warfarin was investigated via a standard set of *in-vitro* genotoxicity tests. A bacterial reverse mutation test, a mammalian chromosome aberration and a mammalian cell gene mutation were reported. The reverse mutation test was negative but somewhat ambiguous results were generated in the other *in-vitro* tests.

However, the results of two independent mouse micronucleus tests and a rat UDS assay were all negative. In consequence, it was concluded that Warfarin lacks genotoxic potential *in vivo*.

Chronic toxicity/Carcinogenicity

Carcinogenicity studies have not been performed for the same reasons as discussed under “repeated-dose toxicity”. In addition, epidemiological studies conducted in patients chronically treated with warfarin (or other anticoagulant) have reported no evidence of increased incidence of malignancies.

In view of the lack of *in vivo* genotoxicity and the long-term human clinical use, there is no reason to suspect any carcinogenic activity.

Reproductive toxicity

Anticoagulant therapy with Warfarin predominantly during the early stages of pregnancy has been reported to cause birth defects known as “Warfarin embryopathy”. Case reports and clinical reviews are presented in the dossier. Consequently, Warfarin has long since been classified as reprotoxic (Repr. cat. 1, R 61). A variety of animal studies have been reported which primarily were aimed at investigating the mechanisms of toxicity. The results obtained in different investigations with Warfarin on pre- and postnatal development with and without the addition of Vitamin K in laboratory animals showed effects caused by the direct anticoagulant activity of the compound, e.g. haemorrhagic syndrome, and effect on the skeletal system induced by suppression of vitamin-K-dependant proteins of bones comparable to the anomalies described as Warfarin embryopathy in humans.

In rats the NOAEL for teratogenicity and embryotoxicity found to be 0.04 mg/kg bw/d (Mirkova, E.and Antov, G. 1983).

Neurotoxicity

No neurotoxic effects have been reported over many decades of Warfarin long-term use as an anticoagulant drug. This data negates the need for any neurotoxicity animal testing.

Other toxicological studies

None submitted.

Medical data

In over 40 years of use of Warfarin in rodenticide practice, there appears to be only one reported case of occupational exposure resulting in Warfarin poisoning due to the lack of use of appropriate PPE (gloves). Dermal absorption of Warfarin is also seen as the cause of a tragic epidemic in Vietnamese infants. All other case reports where the exposure exerted effects ranging from severe haemorrhage to a fatal outcome can be attributed to misuse of Warfarin-containing products.

AOEL (Acceptable Operator Exposure Level)

Based on long lasting experience with Warfarin as a drug in human anticoagulation therapy, a long-term LOAEL of 0.02 mg/kg bw/d has been identified. This value is derived from the lowest therapeutic dose of 1 mg/day. This dose is considered a (No Effect Level) NEL for reproductive effects, and a LOAEL for anticoagulant effects has been taken forward for risk characterisation. For an average adult (60 kg bw) and by applying an assessment factor of 100 (10 for intra-species and 10 for severity of effect), this NEL/LOAEL can be recalculated to a systemic AOEL value of 0.0002 mg/kg bw/d.

AOEL 0.0002 mg/kg bw/d.

2.2.1.3. Exposure Assessment

Professional exposure

Potential risks to workers from the two example formulations evaluated are associated with the dermal route of exposure. Inhalation exposure of pest control operators (PCO) is generally considered to be insignificant in view of the nature of the products. Acute effects were considered to be not relevant for professional and amateur users in view of the generally low but chronic exposure levels. Assuming daily contact of PCOs with Warfarin containing products, the risk characterisation indicates that workers are adequately protected by use of personal protective equipment (PPE) if the baits are individually wrapped limiting exposure to the cleanup phase of the operation.

Professional exposure to Warfarin wax block rodenticide (based on default values in Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2 (June 2002)).

Operator	**Glove use**	**Total Systemic Exposure (µg/kg bw/day)**	**MOE**	**% of AOEL**
Professional operators	Yes	0.09875	203	49
	No	0.9875	20	494

Non trained professionals	Yes	0.02468	810	12
	No	0.2468	81	123

Professional exposure to Warfarin wax block rodenticide (based on values taken from CEFIC studies).

Operator	**Glove use**	**Total Systemic Exposure (µg/kg bw/day)**	**MOE**	**% of AOEL**
Professional operators	Yes	0.038	526	19
	No	0.38	53	190
Non trained professionals	Yes	0.0047	4255	2.4
	No	0.047	426	24

Summary of professional exposure to Warfarin grain rodenticide (based on default values in Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2 (June 2002)).

Operator	**Glove use**	**Total Systemic Exposure (µg/kg bw/day)**	**MOE**	**% of AOEL**
Professional operators	Yes	0.0049	4082	2.5
	No	0.049	408	25
Non trained professionals	Yes	0.001235	16194	0.62
	No	0.01235	1619	6.2

Summary of primary exposure to Warfarin grain rodenticide (based on values taken from CEFIC studies).

Operator	**Glove use**	**Total Systemic Exposure (µg/kg bw/day)**	**MOE**	**% of AOEL**
Professional operators	Yes	0.0205	976	10
	No	0.205	98	103
Non trained professionals	Yes	0.0025	8000	1.3
	No	0.025	800	13

Non-professional exposure

Non-trained professionals (NTPs) (e. g. farmers) and amateurs (consumers) are assumed to use rodenticides much less frequently. The corresponding risk characterisation shows that Warfarin containing products can be safely used by NTPs and amateurs without PPE if the baits are individually wrapped limiting exposure to the cleanup phase of the operation Therefore, there is a safe used identified for PCOs, NTPs and amateurs.

Non-professional exposure to Warfarin wax block rodenticide (based on default values in Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2 (June 2002)).

Operator	Glove use	Total Systemic Exposure (μg/kg bw/day)	MOE	% of AOEL
Amateurs	No	0.2468	81	123

Non-professional exposure to Warfarin wax block rodenticide (based on values taken from CEFIC studies).

Operator	Glove use	Total Systemic Exposure (μg/kg bw/day)	MOE	% of AOEL
Amateurs	No	0.047	426	24

Non-professional exposure to Warfarin grain rodenticide (based on default values in Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2 (June 2002)).

Operator	Glove use	Total Systemic Exposure (μg/kg bw/day)	MOE	% of AOEL
Amateurs	No	0.01235	1619	6.2

Non-professional exposure to Warfarin grain rodenticide (based on values taken from CEFIC studies).

Operator	Glove use	Total Systemic Exposure (μg/kg bw/day)	MOE	% of AOEL
Amateurs	No	0.025	800	12.5

Secondary exposure

Secondary exposure of members of the general public has generally been identified as acute, since repeated unwitting contact to Warfarin is not expected. Potential secondary exposure to Warfarin has been identified in the case that members of the general public handle dead rodents or bait. The calculations show that there is a risk associated with the accidental ingestion of bait by and infant, however, addition of a bittering agent is expected to limit this possibility. Calculations suggest that there is no risk to the general public from secondary exposure to warfarin baits at 0.079% w/w.

Additionally, in annual reports of the American Association of Poison Control Centres for example, a percentage of up to ca. 15 % of reported accidental pesticide exposures (without fatal outcome) were attributed to anticoagulant rodenticides which primarily involved small children (< 6 years). However, neither the compounds in question were identified, nor the extent of exposure or illness caused were reported. However, fatal outcomes were never recorded in such cases. Overall, Warfarin poisoning incidents of the general public are considered as rare, which is in line with the characterisation of bait ingestion as “accidental”.

Summary of indirect exposure scenarios

	Contact with dead rodents and bait					
	Dermal contact (mg)	**% ai**	**Dermal absorption**	**Systemic exposure (mg)**	**Body weight (kg)**	**Systemic exposure (µg/kg/day)**
Adult	1000	0.079	15%	0.1185	60	1.975
Child	1000	0.079	15%	0.1185	15	7.9
	Ingestion of bait					
	Quantity ingested (mg)	**% ai**	**Systemic exposure (mg)**	**Body weight (kg)**	**Systemic exposure (µg/kg/day)**	
Infant	10	0.079	0.0079	10	0.79	
Infant	5000*	0.079	3.8	10	395	

* 5g consumed without bittering agent.

2.2.1.4. Risk Characterisation

Acceptable uses have been found for Pest Control Operators (PCOs), Non-Trained Professionals (NTPs) and amateurs if the baits are individually wrapped limiting exposure to the cleanup phase of the operation. In addition, possible concern regarding accidental infant ingestion can be mitigated by the addition of a bittering agent.

In view of the intended use as a rodenticide, contact of the products to food, feedingstuffs or basic commodities is not expected. Accordingly, residues of Warfarin with respect to consumer safety are generally considered to be irrelevant. An ADI is therefore not proposed.

When warfarin is used in accordance with the proposed instructions of use, it does not pose a risk to PCOs, NTPs or amateurs.

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and Distribution in the Environment

Biodegradation

Biodegradation of Warfarin in sewage treatment plants was investigated under aerobic and anaerobic conditions. Warfarin can be regarded as readily biodegradable under aerobic conditions as it fulfilled the criteria of the OECD ready biodegradability test. As a consequence of this and in line with the biodegradation testing strategy of the TNsG, no further biodegradation tests in aquatic media were performed. At test concentrations of 100 mg OC/L Warfarin is not degradable under anaerobic conditions.
In soil, at initial high concentrations (550 mg/kg), Warfarin was observed to slowly degrade [DT_{50} of ca. 150 days (Document III A 7.2.1)]. In subsequent studies, this was related to an inhibition effect on soil micro-organisms (assessed by dehydrogenase activity). However, at practically relevant concentrations (5 mg/kg), a more rapid degradation rate was observed [DT_{50} ~53 days (1^{st} order)]. Within a period of 100 days metabolism of Warfarin by soil bacteria leads to a large amount of non-extractable residues (10-42%) or rapid further mineralisation (10-20%). Warfarin was observed to degrade to two main metabolites (3-(α-hydroxybenzyl)-4-hydroxycoumarin and hexahydrocoumarin) each accounting for ~5 % of the detected radioactivity. No other metabolite, > 10%, was identified in these soil studies. However, three metabolites were observed to form in a rodent toxicokinetic study -

7-hydroxy, 4'-hydroxy and 6-hydroxy warfarin – forming in rat urine and faeces at maximum levels of 35%, 21% and 15.4%, respectively. These metabolites would potentially be released to the environment via rodent urine and faeces and, hence, exposure levels in the environment were modelled in Document II-B.

Abiotic degradation

Warfarin is not susceptible to hydrolysis in water. Furthermore, direct photolysis in water was experimentally investigated and confirmed not to contribute to degradation under environmentally relevant conditions. A soil photolysis study, (supportive study, Document III A 7.2.2.4) revealed no significant degree of degradation.
Warfarin is not expected to pose a threat to the atmosphere as it exhibits a medium to low volatility (3.0×10^{-5} hPa at 20°C) and is rapidly broken down in the atmosphere by ozone and photolytically generated hydroxyl radicals [DT_{50} = 7.2 hr, European scenario, 24 hr time frame]. It is also unlikely to form acidifying components and to contribute to stratospheric ozone depletion in the absence of Cl, Br or F substitutents.

Distribution/Mobility

No field dissipation studies/soil residue or accumulation studies were performed with Warfarin, since any soil contamination is likely to be low in product applications and DT_{50} values at environmentally relevant soil application rates are less than 60 days.
In soil adsorption/desorption studies, the adsorption coefficient was K_{FOC} ~390 for slightly acidic soils (pH ~5.3) with a high organic carbon content (12 %OC). Moderate to low levels of sorption was found for less acidic soils with a low organic carbon content. Leaching is not considered a relevant aspect of the environmental fate of Warfarin due to a lack of exposure, since in rodenticide baiting operations, target organisms should consume the product or unconsumed bait should be collected at the end of the pest control operation, thereby minimising the release of the substance to soil. In addition, final concentrations of Warfarin in the bait material are low (max. 0.079% w/w), and Warfarin may additionally be expected to be adsorbed onto the bait matrix. However, it is noted that soils containing a low amount of organic matter and high pH, exhibited a moderate leaching potential when treated with a granular formulation of Warfarin. While under certain soil conditions (mainly alkaline soil types of low organic matter content) Warfarin may be more prone to leaching from the soil profile, the manner of use of Warfarin and the low rate of application mitigate against leaching to lower subsoil depths and ultimately to groundwater sources.

Bioaccumulation

Significant bioaccumulation potential of warfarin is not evident based on the experimental data and model estimations.

2.2.2.2. Effects Assessment

Effects on aquatic organisms

The acute toxicity of Warfarin was investigated in fish, daphnia and algae, so that sufficient data are available to allow classification and labelling of the active ingredient according to the requirements of Annex VI of directive 67/548/EEC. The proposed classification and labelling (R52) is based upon the following acute toxicity endpoints: fish LC50 = 65 mg/L, Daphnia magna EC50 (48h) > 100 mg/L, algae ErC50 (0–72h) > 80 mg/L.
Experimental data were generated for bioconcentration in fish and for chronic exposure in fish and daphnia. The most sensitive species regarding long-term exposure was Daphnia magna, with a NOEC of 0.059 mg/L. In a bioaccumulation test in rainbow trout, the concentration of Warfarin increased

rapidly reaching steady state concentrations within the first days of exposure (BCFmax =21.6). After termination of exposure however, the warfarin concentration decreased rapidly and was no longer detectable in any of the treated fish within <11 days.
Concentrations of Warfarin in activated sludge treatment showed no inhibition of organic matter breakdown up to 100 mg/l and 15% inhibition at 400 mg/l.
In some of the aquatic toxicity tests, considerable difficulty was experienced in obtaining homogenized samples even with using high concentrations of the solvent acetone. However, more recent tests were performed using filtrate obtained from supersaturated solutions. Overall, the resulting toxicity profile for Warfarin was generally consistent, and is considered of sufficient quality to characterize the parent compound as regards its hazard classification.

Effects on terrestrial organisms

The recommended outdoor uses of Warfarin as a rodenticide will involve only use in the form of baits containing low (≤0.079% w/w) concentrations of Warfarin. Since the outdoor use does not involve direct application of products containing Warfarin to soil, large area soil contamination can be excluded. Finally, minor contamination that may be caused by contact of soil with Warfarin containing bait will, if any, be strictly isolated to the contact surface and to only a very small fraction of the Warfarin contained in the bait. Therefore, any quantitatively relevant exposure of soil macro-organisms is not conceivable. Accordingly testing for effects on earthworms was not considered necessary.
Apart from haemorrhaging as a typical symptom of anticoagulant poisoning, no other detectable adverse effects at all were reported in acute and short-term avian toxicity studies (A7.5.3.1.1 and A7.5.3.1.2). Warfarin therefore is considered to be of low acute and short-term toxicity to birds, producing acute LD50 values of > 2000 mg/kg and a dietary 5-d NOEL of 213 ppm. No long-term or reproduction study in birds were submitted by the Notifiers for Warfarin. However, sufficient argumentation was provided to justify a direct read-across from a reproductive study on Coumatetralyl in which the NOEC for the reproductive toxicity was determined to be 60 mg a.s./kg food (= 6 mg a.i./kg bw/day). The NOEC for parental toxicity, based on mortality was 20 mg a.s./kg food (= 2 mg a.i./kg bw/day). Further long term testing with warfarin was not considered necessary in view of animal welfare considerations.
Reference was also made to a long-term study in tawny owls (Strix aluco) (Townsend, M.G. et al., 1981), in which the owls were fed ad libitum on Warfarin poisoned mice. The administered doses affected plasma prothrombin levels, but did not induce any other physical or behavioural changes. Based on the residue data reported in this study, a long-term NOAEL of 17.1 mg Warfarin/kg diet was determined.
Various experimental and observational studies confirmed that Warfarin entails a potential secondary poisoning hazard for carnivorous animals. However, secondary toxicity will in reality be considerably lower than expected on the basis of simple exposure calculations, since Warfarin can be expected to be subject to rapid and extensive metabolism to less toxic compounds in primary consumers. However, the quality of the data did not allow the establishment of no-effect levels.

2.2.2.3. PBT Assessment

PBT assessment

Persistence

A substance is considered to fulfil the persistence criteria when a DT_{50} value is > 60 days in marine water (or > 40 days in freshwater) or > 180 days in marine sediment (or > 120 days in freshwater sediment). The criteria for a substance to be considered as very persistent are when a DT_{50} value is > 60 days in marine waters or freshwater or > 180 days in marine or freshwater sediment.
No half-life data are available for Warfarin in marine water or sediment [Document IV 7.1.2.2.2, 7.1.1.2.3.]. The decision whether a substance is potentially persistent needs to be based on other

experimental data. The TGD states 'readily biodegradable substances (fulfilling or not fulfilling the 10-day window criterion) are considered as not persistent in the PBT assessment. Consequently, Warfarin is not regarded as persistent in the environment.

Bioaccumulation

A substance is considered to fulfil the B (bioaccumulative) criterion when the bioconcentration factor (BCF) exceeds a value of 2,000 l/kg and the vB criterion (very bioaccumulative) when the BCF exceeds a value of 5,000 l/kg.
The maximum BCF value for warfarin, determined in fish was 21.6 (see Table A7.4.3.3.1-7 Doc. III-A7 P. 114 (173) which is two orders of magnitude less than the trigger value of the B criterion (>2000).

Toxicity

The toxicity criterion used in the TGD is a chronic NOEC for aquatic organisms of less than 0.01mg/l. Daphnia magna was the most sensitive of the aquatic organisms to the long-term effects of warfarin, but the observed NOEC of 0.059 mg/L still exceeds the T criterion.

POP assessment

Persistence

Warfarin does not fulfill the screening criteria (Annex D of the Stockholm Convention) for persistency (evidence that the half-life of the chemical in water/sediment might be greater than two/six months or that its half-life in soil is greater than six months).

Bioaccumulation

Warfarin does not fulfill the screening criteria for bioaccumulation (evidence that the bioconcentration factor in aquatic species for the chemical is greater than 5,000 or, in the absence of such data, that the log Kow is greater than 5).

Long-range environmental transport

It is not expected that Warfarin will be transported long distances in the environment, since it is readily biodegradable and does not fulfill the screening criterion for bioaccumulation. Additionally, Warfarin is not expected to distribute over long-ranges in the environment via atmospheric routes, since it is rapidly broken down in the atmosphere by ozone and photolytically generated hydroxyl radicals [DT_{50} = 7.2 hr, European scenario, 24 hr time frame].

Toxicity

Warfarin does not fulfill the screening criteria for "adverse effect" in terms of its ecotoxicity.

2.2.2.4. Exposure Assessment

Warfarin has been widely used as a rodenticide for many years both in indoor and outdoor applications. The active substance is offered to the target animals in form of baits. Direct environmental exposure of rodenticides may take place when applied outdoors on public and private areas in and around buildings or constructions (farm buildings, railway stations, harbour areas etc.), on water banks, in and around sewer systems, waste disposal sites and waste dumps. Indoor

application may result in environmental exposure via the sewage system (e.g. during cleaning processes after a rat control operation) and release of residues or carcasses to dumps.

The environmental exposure of Warfarin formulated as a rodenticide wax block and grain bait was assessed in accordance with the Technical Guidance (TGDs) and EUBEES rodenticide documents. PECs were generated for the primary receiving environmental compartments (e.g. air, soil, and water) and for secondary compartments such as sediment.

Four exposure scenarios (sewer system, in and around buildings, open fields and waste dumps) were considered appropriate for a rodenticide application method employing a wax block or a grain/pellet.

Aquatic compartment

The practical use of Warfarin in rodenticide baits is not expected to lead to any significant contamination of surface waters. The relevant aquatic exposure scenarios for Warfarin based on the ESD for PT14 were for sewer systems and in and around buildings.

PECsw and PECsed values for sewer system were calculated at 6.39×10^{-6} mg/L and 2.25×10^{-5} mg/kg, respectively. The PECstp value calculated for sewer system scenario was 6.39×10^{-5} mg/L.

Three metabolites were observed to form in a rodent toxicokinetic study - 7-hydroxy, 4'-hydroxy and 6-hydroxy warfarin – forming in rat urine and faeces at maximum levels of 35%, 21% and 15.4%, respectively. These metabolites would potentially be released to the environment via rodent urine and faeces and, hence, exposure levels in the environment were modelled for aquatic systems. For the sewer system scenario PECstp values were determined at 3.63×10^{-5}, 2.17×10^{-5}, and 1.61×10^{-5} mg/l for 7-hydroxy, 4'-hydroxy and 6-hydroxy Warfarin, respectively. A simultaneous concentration of all metabolites in the sewer system was determined at 7.41×10^{-5} mg/l. For the sewer system scenario PECsw values were determined at 3.63×10^{-6}, 2.17×10^{-6}, and 1.61×10^{-6} mg/l for 7-hydroxy, 4'-hydroxy and 6-hydroxy Warfarin, respectively. A simultaneous concentration of all metabolites in the sewer system was determined at 7.41×10^{-6} mg/l.

Atmospheric compartment

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

Terrestrial Compartment

The recommended use of Warfarin as a rodenticide is not expected to result in any relevant exposure of honeybees or other beneficial arthropod species. Use of rodenticide baits in the modes proposed will not predispose any quantitatively relevant exposure to the relevant ecosystems concerned; accordingly testing for effects on such species was not considered necessary.

Animals and birds other than target-rodents may be poisoned with Warfarin via consumption of baits (primary or accidental poisoning) or consumption of rodents which have incorporated Warfarin (secondary poisoning). However, the recommended application methods of Warfarin as a rodenticide, under practically relevant conditions is not considered to result in any danger of prolonged or repeated exposure to adult birds, or to breeding-places in the brooding period. This argumentation is based on the recommended use patterns, which involve either (i) indoor use as bait, or (ii) outdoor use usually involving laying out treated wheat grains as bait in bait stations, which are specifically designed to prevent accidental poisoning of birds. Although oral uptake of Warfarin-treated bait (such as wheat grains) by birds cannot be completely ruled out, this route of exposure should only be incidental, but not of any prolonged or repeated nature.

According to the ESD for PT14, exposure of soil (and thus soil organisms) to Warfarin may occur by application of wax blocks and grain bait following the use in and around buildings, in open areas and in waste dumps. Exposure to soil may also arise from the use of sewage sludge in agriculture. However, exposure arising from this application is considered to be covered by the other scenarios since their pattern of use could potentially lead to the highest concentration of active substance in soil. PECs values for in and around buildings was calculated at 0.683 mg/kg. For open fields PECs values for the wax block and grain bait were determined at 1.64 and 6.833 mg/kg, respectively. For waste dumps PECs values were determined for time points at Day 2.13, Day 24 and Day 28, which resulted in PECs values of 1.54×10^{-3}, 1.35×10^{-4} and 6.53×10^{-5} mg/kg, respectively. PECs for Warfarin in agricultural soil arising from sewage sludge application generated using EUSES 1.0 ranged from 1.59×10^{-5} mg/kg (30 days) to 2.00×10^{-6} mg/kg (180 days).

Three metabolites were observed to form in a rodent toxicokinetic study - 7-hydroxy, 4'-hydroxy and 6-hydroxy warfarin – forming in rat urine and faeces at maximum levels of 35%, 21% and 15.4%, respectively. These metabolites would potentially be released to the environment via rodent urine and faeces and, hence, exposure levels in the environment were modelled for terrestrial systems. For the in and around buildings scenario PECs values were determined at 0.02457, 0.01474, and 0.01077 mg/kg for 7-hydroxy, 4'-hydroxy and 6-hydroxy Warfarin, respectively. A simultaneous concentration of all metabolites in and around buildings was determined at 0.05008 mg/kg. For the waste dump scenario PECs values were determined at 0.02681, 0.01604, and 0.01184 mg/kg for 7-hydroxy, 4'-hydroxy and 6-hydroxy Warfarin, respectively. A simultaneous concentration of all metabolites for waste dumps was determined at 0.05469 mg/kg.

Primary exposure:

A hypothetical hazard of primary exposure to rodenticide bait material is given for any seed-eating bird. However, since Warfarin is applied either in the form of wax-bound bait blocks which are virtually impossible to be ingested by birds, or in the form of grain-based bait which has to be deployed in tamper-resistant bait boxes or under other suitable cover, direct exposure of birds is minimised. The only possible risk of exposure arises from bait carriage by rodents, which is, however, considered to be quantitatively insignificant. In view of these prerequisites, primary exposure of birds to Warfarin must be considered to be incidental, but not of any prolonged or repeated nature. Nonetheless, PEC's in selected non-target animals in primary poisoning scenarios were derived based on the formulae and default values proposed by the EUBEES-ESD for rodenticides as follows:

Expected concentrations of Warfarin in selected non-target animals in primary poisoning scenarios after one meal followed by a 24 hour elimination period (concentration of Warfarin in rodenticide bait 0.079%) (based on 90 % elimination)

Species		Body weight [g]	Daily mean food intake [g]	Bait consumption [g]	Estimated daily uptake of Warfarin [mg/kg]		
					Realistic worst case		Normal use
					Tier 1	Tier 2	
Dog	*Canis familiaris*	10000	– [$]	600.0	47.4	34.1	≅ 0
Pig	*Sus scrofa*	80000	– [$]	600.0	5.93	4.27	≅ 0
Pig, young	*Sus scrofa*	25000	– [$]	600.0	18.96	13.7	≅ 0
Tree sparrow *)	*Passer montanus*	22	7.6	7.6	273	197	≅ 0
Chaffinch *)	*Fringilla coelebs*	21.4	6.42	6.42	237	171	≅ 0
Wood pigeon *)	*Columba palumbus*	490	53.1	53.1	85.6	61.6	≅ 0
Pheasant *)	*Phasianus colchicus*	953	102.7	102.7	85.1	61.3	≅ 0

*) Body weight and food intake values as given in the EUBEES-ESD by default
$) Not stated in the EUBEES-ESD; simplistically, a maximum bait consumption of 600 g is assumed

Expected concentrations of Warfarin in selected non-target animals in primary poisoning scenarios after one meal followed by a 24 hour elimination period (concentration of Warfarin in rodenticide bait 0.079%) (based on 90 % elimination)

Species		Expected concentrations of Warfarin [mg/kg bw]		
		Normal use	Realistic worst case – Tier 1	Realistic worst case – Tier 2
Dog	*Canis familiaris*	≅ 0	4.74	3.41
Pig	*Sus scrofa*	≅ 0	0.59	0.427
Pig, young	*Sus scrofa*	≅ 0	1.90	1.37
Tree sparrow	*Passer montanus*	≅ 0	27.3	19.7
Chaffinch	*Fringilla coelebs*	≅ 0	23.7	17.1
Woodpigeon	*Columba palumbus*	≅ 0	8.56	6.16
Pheasant	*Phasianus colchicus*	≅ 0	8.51	6.13

Secondary exposure:

Predatory and scavenging birds and mammals may be exposed to warfarin via consumption of intoxicated rodents (dead or moribund). Accordingly, PEC's in selected non-target animals in secondary poisoning primary poisoning scenarios were assessed following the methods set out in the EUBEES-ESD for rodenticides, as summarised below:

$PEC_{oral, predator}$ estimations for qualitative risk assessment for acute situation:

$PEC_{oral, predator}$ (worst case, acute) = 166 mg/kg rodent

$PEC_{oral, predator}$ (intermediate, acute) = 83.4 mg/kg rodent

$PEC_{oral, predator}$ (normal case, acute) = 33.2 mg/kg rodent

$PEC_{oral, predator}$ estimations for quantitative risk assessment for long-term situation:

Tier 1 Scenario A – PECoral values for rodents feeding 5 days (EC5 rodent)

$PEC_{oral, predator}$ (worst case, chronic) = 83.39 mg/kg rodent

$PEC_{oral, predator}$ (intermediate, chronic) = 41.69 mg/kg rodent

$PEC_{oral, predator}$ (normal case, chronic) = 16.68 mg/kg rodent

Tier 1 Scenario B - PECoral values for rodents feeding 5 days, excreting for 2 days (EC7 rodent)

$PEC_{oral, predator}$ (worst case, chronic) = 3.99 mg/kg rodent

$PEC_{oral, predator}$ (intermediate, chronic) = 2 mg/kg rodent

$PEC_{oral, predator}$ (normal case, chronic) = 0.8 mg/kg rodent

Tier 2: Estimation of systemic concentrations in predators/carnivores

Expected concentrations of Warfarin in non-target animals (predatory birds/carnivores) due to secondary poisoning after a single day of exposure (concentration of Warfarin in rodenticide bait 0.079 %); concentrations in rodents are assumed to result from a proportion of 100 % Warfarin bait in their diet; predators/ carnivores are assumed to feed 50% on poisoned rodents.

Species		Body weight	Daily mean food intake	Amount a.i. consumed by the non-target animal [mg]		Concentration in non-target animal [mg/kg]	
		[g]	[g]	Day 5, before last meal	Day 5 or 14, after last meal	Day 5, before last meal	Day 5 or 14, after last meal
Barn owl	*Tyto alba*	294	72.9	0.32	3.20	1.09	10.88
Kestrel	*Falco tinnunculus*	209	78.7	0.35	3.45	1.65	16.5
Little owl	*Athene noctua*	164	46.4	0.20	2.04	1.24	12.4
Tawny owl	*Strix aluco*	426	97.1	0.43	4.26	1.00	10.0
Fox	*Vulpes vulpes*	5700	520.2	2.28	22.8	0.40	4.0
Polecat	*Mustela putorius*	689	130.9	0.57	5.74	0.83	8.3
Stoat	*Mustela erminea*	205	55.7	0.24	2.44	1.19	11.9
Weasel	*Mustela nivalis*	63	24.7	0.11	1.08	1.72	17.2

2.2.2.5. Risk Characterisation

Environmental risk in the aquatic compartment, including STP and sediment

PNEC derivation:

PNEC's relevant to risk characterisation in the aquatic compartment (hydrosphere) were derived from the most critical endpoints from toxicity studies relevant to the different aquatic compartments, as follows:

PNECSTP = 20 mg/L
(based on the EC10 of 200 mg/l from a respiration inhibition test , to which an assessment factor of 10 was applied)

PNECaquatic = 0.0012 mg/L
(Chronic toxicity data for two aquatic organisms were available so the PNEC was derived by dividing the lowest NOEC (0.059 mg/L from Daphnia study) by an assessment factor of 50)

PNECsediment = 0.00422mg/kg (wet weight)
(estimated following the equilibrium partitioning method and using the program EUSES 1.0)

Risk characterisation for the aquatic compartment:

The risk to the hydrosphere was characterised for both the parent material and the 3 toxicologically significant warfarin metabolites (7-hydroxy warfarin, 4'-hydroxy warfarin, 6-hydroxy warfarin) for two types of application methods, that is the wax block bait and grain bait. Since there is no ecotoxicological data presented on the metabolites, the PNEC values for the active substance was

used for risk characterisation, together with the PEC values as determined in Doc II B (Section 8.3) for the metabolites.

Wax block bait

PEC/PNEC ratios for Warfarin and metabolites for the different exposure situations concerning the hydrosphere, following wax block bait application:

WORST CASE Exposure scenario	Substance	PEC	PNEC	PEC/PNEC
STP, rodenticide treatment in the sewerage	Warfarin	6.39×10^{-5} mg/L	20 mg/L	3.20×10^{-6}
	Total metabolites	7.41×10^{-5} mg/L	20 mg/L	3.705×10^{-6}
Surface water, rodenticide treatment in the sewerage	Warfarin	6.39×10^{-6} mg/L	0.0012mg/L	0.0053
	Total metabolites	7.41×10^{-6} mg/L	0.0012 mg/L	6.175×10^{-3}
Sediment, rodenticide treatment in the sewerage	Warfarin	2.25×10^{-5} mg/kg	0.00422 mg/kg	0.0053

Grain bait

According to the EUBEES-ESD for rodenticides, the aquatic compartment may be exposed to Warfarin as a consequence of releases to the sewerage following cleaning operations after rodenticide campaigns in and around buildings. Since these releases are expected to be much lower than those from direct application in sewer systems, a separate risk characterisation for the grain bait was not considered to be required. Instead, the PEC/PNEC values for the wax block (see table above) may be adopted as dummy values and consequently represent a clear worst case.

Risk Characterisation for secondary poisoning via the aquatic food chain:

Not assessed as exposure via this food chain is considered to be negligible and warfarin is not bioaccumulative in fish (BCF = 21.6).

Summary aquatic risk assessment:

A risk for the aquatic environment resulting from rodenticide treatments (as wax block/grain bait) in sewer systems or in and around buildings is not indicated. According to Directive 98/83/EC, the limit value for pesticides [organic rodenticides] in water is 0.1 mg/L. The PEC of warfarin in surface water is less than this value [0.0639 mg/L]. This means that when warfarin is used in accordance with the assumptions of the ESD the drinking water criteria are complied with.

Environmental risk in the atmosphere

Estimated rate constants of photochemical reactions of Warfarin with hydroxyl and ozone radicals (based on a QSAR) indicated that any volatilised warfarin would be quickly degraded by photo-oxidation. Furthermore, the use pattern and means by which Warfarin is deployed together with its low volatility ($p \leq 3 \times 10^{-5}$ hPa, reference A3.2/01), ensure that exposure to the atmosphere is highly unlikely during its manufacturing, formulating, use or disposal phases (see Doc II-B). Based on this and the physical and chemical properties of the compound (it does not contain any Cl, Br or F substituents), warfarin is not expected to contribute to global warming, ozone depletions in the stratosphere, or acidification and thus no risk assessment for the atmosphere was carried out.

Environmental risk in the terrestrial compartment

PNEC derivation:

Specific data on the toxicity of warfarin and its metabolites to soil organisms (invertebrates) were not available so the PNEC for soil organisms was estimated using the equilibrium partitioning method and using the EUSES 1.0 program, as follows:

PNECsoil = 0.0028 mg/kg (wet weight)

Risk characterisation for the terrestrial(soil) compartment:

The risk to the terrestrial compartment was characterised in Doc IIC for both the parent material and the 3 toxicologically significant warfarin metabolites (7-hydroxy warfarin, 4'-hydroxy warfarin, 6-hydroxy warfarin) (individually and additive). Since there was no ecotoxicology data presented on the metabolites, the PNEC values for the active substance were used for risk characterisation. The risk characterisation therefore is worst-case, given that the metabolites are less than 10% as potent (in terms of their anticoagulant activity) as racemic Warfarin (see Doc II A, Section 3.1).

Exposure of soil to Warfarin may occur by application of wax blocks and grain bait following the use in and around buildings, in open areas and in waste dumps. Accordingly, six rodenticide scenarios were calculated for warfarin technical following the EUBEES-ESD for PT 14 and the TGD on risk assessment. Exposure to soil may also arise from the use of sewage sludge in agriculture. However, exposure arising from this application is considered to be covered by the other scenarios since their pattern of use could potentially lead to the highest concentration of active substance in soil. In addition, PECs for Warfarin in agricultural soil arising from sewage sludge application generated using EUSES 1.0 ranged from 1.59 x 10-5 mg/kg (30 days) to 2.00 x 10-6 mg/kg (180 days).

For the metabolite risk assessment, it was assumed that metabolite exposure concentrations determined for the waste dump scenario encompass the likely environmental concentrations envisioned from use of Warfarin in open areas following a rat control campaign. A summary of the worst case scenario PEC/PNEC ratios for warfarin and the additive metabolites are presented below:

Worst case PEC/PNEC ratios for technical warfarin under different exposure situations concerning the pedosphere.

Worst case exposure scenario	**PEC (mg/kg)**	**PNEC (mg/kg)**	**PEC/PNEC**
Buildings			
Wax block & grain bait (Tier 1 modelling)	0.683*	0.0028	**244**
Open area			
Grain bait (Tier 1 modelling)	6.833*	0.0028	**2440**
Waste dumps			
Wax block & grain bait. (Tier II modelling)	1.53×10^{-3}	0.0028	**0.55**

* localised spot contaminations immediately adjacent to bait (within 10 cm).

The PEC/PNEC ratios indicate a potential risk to terrestrial organisms from soil exposure, following application via wax block or grain bait, for all exposure scenarios. However, the fact that only spot contamination occurs in each case, i.e. only a small soil volume around a bait box or rat burrow are contaminated, overall exposure of soil may be considered to be insignificant. Furthermore, the PECs used in the calculation of the risk quotient for these scenarios (buildings/open areas/waste dumps) were generated using Tier 1 modelling which does not consider fate processes (i.e the fact that warfarin has been shown to be readily biodegradable). In addition, the PNECsoil was derived using

the equilibrium partitioning method based on the PNECaquatic, as no specific data on the toxicity of warfarin to soil organisms (invertebrates) were available).

Worst case PEC/PNEC ratios for relevant toxicological metabolites of warfarin (additive) under different exposure situations concerning the pedosphere.

Worst case exposure scenario	PEC (mg/kg)	PNEC (mg/kg)	PEC/PNEC
Buildings			
Wax block & grain bait (Tier 1 modelling)	0.05008*	0.0028	**17.89**
Open area			
Wax block & grain bait (Tier 1 modelling)	7.66*	0.0028	**2736**
Waste dumps			
Wax block & grain bait. (Tier I modelling)	0.05469	0.0028	**19.53**

* localised spot contaminations immediately adjacent to bait (within 10 cm).

The metabolite (additive) PEC/PNEC ratios presented above, indicate a localised risk to terrestrial organisms from exposure to the combined metabolites, in all scenarios, in particular following warfarin application in open areas. However, the PEC values are based on absolute worst case scenarios – e.g. the "open areas" and "around buildings" scenarios represent high spot contaminations immediately adjacent to bait, and in all cases, the PECs used in the calculation of the risk quotient were generated using Tier 1 modelling which does not consider fate processes (degradation/biotransformation). It is likely that a Tier 2 risk assessment, similar to that carried out for the active substance in waste dumps (incorporating the maximum amount of metabolite present on the soil area from releases via urine and faeces and considering biological degradation) would result in an acceptable risk. Also, the ratios presented are additive values for all three metabolites, which, again is extremely worst case e.g. when the metabolites were considered individually, a acceptable risk was identified for 6-hydroxy warfarin for the "buildings" and "waste dumps" scenarios (but not open areas). It should be borne in mind too that no actual ecotoxicological tests were performed with the metabolites in question so the PNEC used was derived for the parent active material (Warfarin) which, in turn was derived from the PNECaquatic using the equilibrium partitioning method (thus a conservative estimate). In any case, it is highly unlikely that any of these metabolites would pose a greater risk than the parent material, given that in reality, all three metabolites are less than 10% as potent as racemic warfarin.

Risk Characterisation for secondary poisoning via the terrestrial food chain:

The recommended use of Warfarin as a rodenticide is not expected to result in any relevant exposure of soil macro-organisms, so the testing for effects on earthworms was not considered necessary. Consequently, the risk characterisation for the food-chain soil → earthworm → worm-eating birds or mammals was not assessed.

The risk characterisation for the food-chain rodenticide/bait→ (rodent) → bait or rodent -eating mammal/bird has been assessed (see section below).

Summary terrestrial risk assessment:

In practice, the recommended use of Warfarin as a rodenticide is not expected to result in any relevant exposure of honeybees or other beneficial arthropod species, soil macroorganisms or soil microorganisms. Estimates of predicted soil concentrations likely to arise from spot or isolated contamination arising from spillage or placement of Warfarin baits were hypothetically calculated not to exceed 6.833 mg/kg soil (high spot contamination), even under worst case assumptions.

Risk quotients in excess of one were obtained for all emission scenarios for both the active substance and total metabolites, indicating a potential risk to organisms in the terrestrial environment (including

pedosphere) via use of Warfarin as wax block or grain bait in and around buildings, in open areas and in waste dumps. However, it should be borne in mind that only spot contamination occurs in each case, so that overall exposure of soil may be considered to be insignificant. In addition, the PECs used in the calculation of the risk quotients were generated using Tier 1 modelling which does not consider fate processes and the PNECsoil's were derived using the equilibrium partitioning (not based on actual toxicity endpoints).

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

Non-target vertebrates may be exposed to the active substance either directly by ingestion of exposed bait (primary poisoning) or indirectly by ingestion of the carcasses of target rodents that contain residues of the active substance (secondary poisoning).
The acute primary and secondary poisoning risk assessment was assessed in a qualitative, and not in a quantitative way, whereas a quantitative risk assessment was carried out to ascertain the primary and secondary risk from long-term exposure to warfarin.

PNEC derivation:

PNEC's relevant to risk characterisation for primary and secondary poisoning of non-target animals are as follows:

PNECbirds longterm = 0.66 mg/kg food

(Derived from a read-across study on coumetetralyl where the parental NOAEC was 20 mg a.i./kg food. An assessment factor of 30 was applied)

PNECpredatory birds = 0.57 mg/kg food

(Based on a dietary long-term NOEC of 17.1 mg/kg food from a secondary toxicity study in tawny owls to which an assessment factor of 30 was applied)

PNECmammal longterm = 0.013 mg/kg food

(Based on a long-term toxicity study in rats where the rats were dosed for more than 300 days at a rate of 0.02 mg/kg b.w./d without any mortality. The NOAEL of 0.02 mg/kg b.w./d was converted into a dietary NOEC by multiplication with a conversion factor of 20 (resulting in NOECmammal, food, chronic = 0.4 mg/kg food). The PNEC was then derived by dividing the chronic NOEC by an assessment factor of 30).

Primary poisoning:

Tier 1 - quantitative risk assessment (acute exposure)

The Tier 1 quantitative risk assessment assumed, as an absolute worst case, that non-target animals' diet consists of 100 % rodenticide bait and that the concentration of Warfarin in food is the relevant PECoral (in this case, 790 mg/kg food (ppm), as the content of active ingredient in the example formulation was 790 mg/kg Warfarin. This conservative approach resulted in PEC/PNEC ratios of 60770 for mammals and 1197 for birds, clearly highlighting a high risk to birds and non-target mammals if warfarin-containing products are freely consumed.

Tier 2 - qualitative risk assessment (acute exposure)

At Tier 2, a qualitative risk assessment for birds and mammals assuming 1d exposure with and without excretion was performed, whereby the expected concentrations (ETE) of warfarin in a

number of typical non-target birds and mammals were compared to relevant LD50 values for each of the animals in question. For the ETE calculations, worst case values assumed there is no bait avoidance by the non-target animal and that they obtain 100% of their diet in the treated area; second tier refinements assumed AV = 0.9, PT = 0.8 and PD = 1). The expected concentration of active substance after 1 meal followed by a 24 hr elimination period (assuming 90% elimination) was also determined.
This qualitative risk assessment indicated an acceptable primary poisoning risk to birds following acute warfarin exposure. However, the results suggested that non-target mammals could potentially die following a single uptake incident.

Tier 2 - qualitative risk assessment (long-term exposure)

Following UBEES ESD recommendations, a quantitative risk assessment was performed to characterise the primary poisoning risk to birds and mammals assuming 5d exposure with default (30%) and realistic (90%) excretion. EC5 values were thus estimated for the representative mammals and birds, using the EUBEES ESD spreadsheet calculator. Worst case step 1 values assumed there was no bait avoidance by the non-target animal and that they obtain 100% of their diet in the treated area; step 2 refinements assumed AV = 0.9, PT = 0.8 and PD = 1.

The resulting PEC/PNEC ratios were all > 1 indicating a clear primary poisoning hazard for non-target animals if the theoretical assumption is made that they feed for 5 days on a diet consisting exclusively or largely of rodenticide bait. This is the case regardless of whether moderate corrections for avoidance and food ratio are made (step 2) and even assuming an excretion rate of 90%.

It may be argued that this approach of comparing “internal concentrations” with a PNEC is intrinsically illogical. It is a fundamental principle of (eco-) toxicological risk assessment to compare doses with toxic endpoints. The “internal concentration”, however, is not a dose, thus not a PNEC, but instead a cumulative body burden of active substance present in the organism after receiving a series of daily doses.

A review of the various reported pesticide poisoning incidents indicate a low risk of primary exposure under practical conditions of use. Incidents of widespread accidental poisoning of wild birds were not recorded in the available literature. Thus, the primary poisoning hazards of birds may be considered to be generally low. Only a few incidental cases of poisoning with Warfarin on animal farms are reported for chicken, sheep, nursing pigs and their piglets. On these occasions, high rates of mortality were observed in sheep and chicken after the consumption of Warfarin contaminated diet (primary poisoning). However, All reported incidents on animal farms were caused by inappropriate use of Warfarin or lack of diligence with respect for hygiene of the stable and closing of rat holes.

The household animals mostly affected by Warfarin rodent control are dogs, followed by cats. However, incidents with cats are very rare, so that in consideration of their feeding behaviour, a risk for cats may be considered a minor problem. In comparison to the large amounts of Warfarin baits used for example in United Kingdom, relatively few deaths were suffered by dogs, and even less by cats. The majority of the fatal or near fatal dog exposure incidents are generally the result of one or, occasionally, two successive feedings.

The risk of Warfarin-poisoning of livestock and household animals can be reduced to a minimum when the rodenticide is handled with diligence and care. However, the use of Warfarin for rodent control in public areas (forests for example) may be a problem with respect to poisoning of non-target animals, because high amounts of bait are needed for successful rodent killing, and baits with Warfarin must be distributed over a wide area and Warfarin-contaminated rodents may be consumed by non-target animals. Mainly in Great Britain, where Warfarin is a widely used rodenticide for controlling the grey squirrel, intensive efforts have been made to investigate the risk from Warfarin to wildlife animals and to reduce non-target poisoning. Various animals (mammals and birds) were found to be potentially at risk for primary poisoning with Warfarin used for grey squirrel control.

Consequently, Warfarin baits are offered in specially constructed bait hoppers so that incidental poisoning of animals like birds or weasels through primary consumption of baits can largely be excluded. Only mice and (in same periods) voles were found to be poisoned in marked numbers as demonstrated in statistical evaluations between 1978 and 1989.

All of this information, together with the risk quotients derived above trigger the need for employment of risk mitigation measures such as the stringent use of careful baiting practises (see section on risk mitigation measures below). This is also acknowledged by the EUBEES-ESD, stating that normal use (adherence to good baiting practice) is expected to minimise primary poisoning hazards. Accordingly, exposure levels and PEC/PNEC ratios for normal use are estimated to be close to zero.

Secondary poisoning:

Acute exposure - qualitative risk assessment

The acute qualitative risk assessment involved a comparison of acute toxicity and expected concentration of warfarin in representative predatory bird and mammal species due to secondary poisoning after a single day of exposure. The systemic dose ("Cinternal, predator") was calculated from the EUBEES-formulae, assuming rodents fed 100% on warfarin and non-target animals fed 50% on poisoned rodents. The most relevant acute toxicity endpoints were the LD50's from a bobwhite quail (>2000 mg/kg) and a rat study (5.6 mg/kg).

The resulting assessment indicated that that predatory (or scavenging) birds are not at risk of secondary poisoning by acute exposure. Mammalian predators in contrast, may be at risk in the worst case that rodents have just ingested a full daily food requirement in the form of bait. However, this may be considered a rather unlikely situation in practice as moribund rodents (thus largely unable to feed) are much more likely to be captured by predators. In conclusion, acute secondary poisoning risk of predatory carnivores may be described as moderate to low, and thus acceptable.

Long-term exposure - quantitative risk assessment

The quantitative chronic risk assessment compared PECoral for predators with the PNECpredatory birds and the PNECmammal longterm using a tiered approach.

Tier 1

For the Tier 1 chronic risk assessment, two scenarios were considered: scenario A where the PEC values were determined using the EUBEES maximum day 5 (EC5) residue estimates and the (scenario B) where the PEC values were determined using the more realistic EUBEES EC7 residue estimates.

The Tier 1 PEC/PNEC values from the EUBEES-based risk characterisation were all > 1, indicating an unacceptable secondary poisoning risk for long-term exposure of all representative predatory birds and mammals.

Tier 2

The Tier 2 chronic risk assessment compares the calculated expected concentrations of Warfarin in some typical non-target avian and mammalian predatory species (due to secondary poisoning after a single day of exposure; concentration of Warfarin in rodenticide bait = 0.079 %) to the PNECpredatory birds and the PNECmammal longterm.

Even following certain refinements, the resulting Tier 2 PEC/PNEC values remained > 1 for all representative predatory birds and mammals indicating a secondary poisoning risk to birds and mammals following long-term exposure to warfarin.

Summary primary and secondary poisoning:

The intrinsic toxicity of warfarin to rats (the target species), renders the substance a potential poisoning risk to other non-target mammals (livestock, household animals, wild birds etc.) should they become exposed to it and consume it in appropriate quantities (primary poisoning). It is therefore crucial that exposure to Warfarin is reduced to a minimum through proper handling with diligence and care. Bait should be exclusively deployed in appropriately designed tamper-resistant bait boxes, under suitable cover or directly into rat burrow entrances. This should be clearly indicated on the label/directions for use. Primary poisoning risks may then be considered to be acceptable.

The hazard of secondary poisoning of predators is also a feature of an anticoagulant rodenticide simply due to its intended use and mode of action. Therefore, as expected, exposure estimations for warfarin based on general assumptions specific to general anticoagulants, indicate that the secondary poisoning hazard under practical conditions is not acceptable. However, monitoring data of wildlife mortalities indicate that wildlife animals are only rarely victims of secondary poisoning by warfarin. Furthermore, the recommended baiting practice (e.g. closure of baited rat holes in open areas and on waste dumps, bait deployment close to rat runs and burrows in buildings) should ensure negligible accessibility of poisoned rodents for predators in reality.

Risk mitigation measures:

To prevent non-target animals (especially dogs) from severe poisoning with Warfarin, operators should store the bait packages out of reach of the animals, and only small portions of bait should be placed at one site. Additionally, the baits should be manufactured in a form most unattractive to dogs and other non-target animals with respect to odour and flavour and deployed in tamper-resistant bait boxes, under suitable cover or directly into rat burrow entrances. The access to the bait compartment should be appropriately designed in terms of size to exclude mammals larger than the adults of the target species.

The usual baiting practices (e.g. closure of baited rat holes in open areas and on waste dumps, bait deployment close to rat runs and burrows in buildings) are aimed at reducing the accessibility of poisoned rodents for predators. Adherence to use instructions can therefore help to minimise secondary poisoning hazards. Dead rodents should be removed immediately to reduce risks to scavengers.

2.2.3. List of Endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the Provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

3. DECISION

3.1. BACKGROUND TO THE DECISION

Warfarin has been evaluated as a rodenticide against rats and mice for the use pattern "in and around buildings" and "sewers". It is a very potent rodenticide and its use poses a high risk of primary poisoning to non-target mammals and birds. Various experimental and observational studies confirmed that Warfarin also entails a potential secondary poisoning hazard for carnivorous animals. However, secondary toxicity will in reality be considerably lower than expected on the basis of simple exposure calculations, since Warfarin can be expected to be subject to rapid and extensive metabolism to less toxic compounds in primary consumers.
Emissions to the environment from the use of anticoagulant rodenticides in general cannot be prevented entirely. However, it is important to have a range of active ingredients for use in rodenticides in the EU in the interest of public health and hygiene, and the hazard of e.g. primary poisoning of non-target animals or exposure to soil can be reduced by the risk reduction measures/restrictions proposed.

There is a risk for development of resistant strains through the use of anticoagulant substances, unless measures are taken. Therefore, there is a need for having a variety of active substances available due to the problems of resistant populations of rodents. Warfarin is an effective rodenticide but care must be exercised with regard to the resistance potential of the molecule.

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

Formulated products containing bait concentration in wax blocks and granular bait up to 0.079 % shows sufficient effectiveness, and higher concentrations in ready to use baits should not be allowed in authorised products. The applicant has not indicated any marketing of premixes or of products with higher warfarin concentrations than 0.079% and therefore no such uses have been evaluated (see Appendix II).

The overall conclusion from the evaluation of warfarin, for use in product type 14 (rodenticides), is that it may be possible for Member States to issue authorisations of products containing warfarin in accordance with the conditions laid down in Article 5 of Dir. 98/8/EC.

Rodent control is needed to prevent disease transmission, contamination of food and feeding stuffs and structural damage. It is recognised that anticoagulants like warfarin do cause pain in rodents but it is considered that this is not in conflict with the requirements of Article 5.1 of Directive 98/8/EC 'to avoid unnecessary pain and suffering of vertebrates', as long as effective, but comparable less painful alternative biocidal substances or biocidal products or even non-biocidal alternatives are not available.

As several anticoagulants have been assessed for possible Annex I entry at the same time, being quite similar regarding the hazardous properties and associated risks, the Commission initiated a work on possible risk mitigation measures for all anticoagulant rodenticides. A document describing possible risk mitigation measures for all anticoagulant rodenticides has been agreed at the 24th CA-meeting (CA-March07-Doc.6.3– final). The document distinguishes between measures to be taken into account at European Union level through restrictions in the Annex I entry decision, and measures that can be taken into account at national level when products are to be authorised. The proposal for Annex I decision in chapter 3.2 and the elements to be taken into account by Member States when

authorising products, as described in Chapter 3.3, are based on this assessment report and on the Commission document on risk mitigation measures for anticoagulants used as rodenticides.

Assessed from the documentation for the active substance, warfarin, and the representative product, biocidal products intended to control rats may be sufficiently effective and without unacceptable effects to human health of the users. It is recognised that anticoagulant rodenticides may cause risk of both primary and secondary poisoning for non target animals and may pose a risk to young children if accidentally ingested and according to the criteria and guidance of the directive 98/8/EC, this substance should not normally be included in Annex I. However, the RMS believes that it is important to have a range of active ingredients for use in rodenticides in the EU in the interest of public health and hygiene. Therefore, the RMS recommends warfarin for inclusion into Annex I. However special precautions must be taken in order to avoid unacceptable resistance to the anticoagulant as well as it is of paramount importance that exposure to humans and non-target animals is minimised by relevant risk mitigation measures.
This conclusion relies on the fact that users of the biocidal product will be applying the basic principles of good practice and respect the conditions for the use recommended on the label of the product.

3.2. DECISION REGARDING INCLUSION IN ANNEX I OR IA

The substance Warfarin shall be included in Annex I to Directive 98/8/EC as an active substance for use in product-type 14 (Rodenticides), subject to the following specific provisions:

The maximum nominal concentration of the active substance in the products shall be:

1. 790 mg/kg and only ready-for-use products shall be authorised.

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

3. Primary as well as secondary exposure of humans, non-target animals and the environment are minimised, by considering and applying all appropriate and available risk mitigation measures. These include, amongst others, the possibility of restriction to professional use only, setting an upper limit to the package size and laying down obligations to use tamper resistant and secured bait boxes.

3.3. ELEMENTS TO BE TAKEN INTO ACCOUNT BY MEMBER STATES WHEN AUTHORISING PRODUCTS

- As professionals are likely to be exposed more often, products containing warfarin may be used by professional users if data are provided to show that occupational exposure is acceptable and/or the dermal absorption of warfarin from these products is below the percentage that would give an estimated exposure equal to the threshold level (AOEL) for repeated exposure (when calculations are based on the operator exposure study).

- Warfarin baits should not be placed so that food, feeding stuffs or drinking water could be contaminated.

- The size of the package placed on the market should be proportionate to the duration of the treatment and appropriate to the pattern of use of particular user groups.

- Product design and use restrictions should be optimised in order to ensure sufficient efficient rodent control while at the same time minimizing the risk for primary

poisoning. This could include the use of tamper resistant bait boxes and the need to secure the baits so that rodents cannot remove the bait from the bait box.

- When tamper-resistant bait stations are used, they should be clearly marked to show that they contain rodenticides and that they should not be disturbed.

- The restriction of products to specific areas and manners of use and also restrictions of products to professionals or trained professionals only should be considered.

- The use of Warfarin was not assessed as a tracking powder. Member States should be aware to fully evaluate this use pattern in relation to the risk posed to humans, animals and the environment if application is made at product authorisation.

- In addition to the elements already listed in Article 20(3) of Directive 98/8/EC, all packaging of anticoagulant rodenticides should be marked with the following standard phrases to protect humans, animals or the environment:

    1. Baits must be securely deposited in a way so as to minimise the risk of consumption by non-target animals or children. Where possible, secure baits so that they cannot be dragged away.
    2. Search for and remove dead rodents at frequent intervals during treatment (unless used in sewers), at least as often as when baits are checked and/or replenished. Dispose of dead rodents in accordance with local requirements.
    3. Unless under the supervision of a pest control operator or other competent persons, do not use anticoagulant rodenticides as permanent baits.
    4. Remove all baits after treatment and dispose them of in accordance with local requirements.
    5. Keep out of the reach of children. (This last safety precaution should always be carried on the label of the products, if not already legally required by 1999/45/EC. The others could be stated elsewhere on the packaging or on an accompanying leaflet together with the other directions for use and disposal of the product required by article 20(3) of Directive 98/8/EC.)

- Adequate safety instructions (including use of appropriate personal protective equipment) should be provided in the use instructions.

- Member States should be aware that the level of efficacy against mice of biocidal products containing Warfarin is proven to be acceptable prior to authorisation.

- Member states should encourage the application of Codes of Good Practices in rodent control. These measures could include (but should not be restricted to) the following factors:

    1. The population size of the target rodent should be evaluated before a control campaign. The number of baits and the timing of the control campaign should be in proportion to the size of the infestation.
    2. A complete elimination of rodents in the infested area should be achieved.
    3. The use instruction of products should contain guidance on resistance management for rodenticides.

4. Resistant management strategies should be developed, and warfarin should not be used in an area where resistance to this substance is suspected.
5. The authorisation holder shall report any observed resistance incidents to the Competent Authorities or other appointed bodies involved in resistance management.
6. When the product is being used in public areas, the areas treated must be marked during the treatment period and a notice explaining the risk of primary or secondary poisoning by the anticoagulant as well as indicating the first measures to be taken in case of poisoning must be made available alongside the baits.

3.4. REQUIREMENT FOR FURTHER INFORMATION

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

Identity of the active substance

Not applicable.

Physical and chemical properties of the active substance

Not applicable.

Physical and chemical properties of the biocidal product

Not applicable.

Methods of analysis

Not applicable.

Human health

Not applicable.

Environment

Not applicable.

3.5. UPDATING THIS ASSESSMENT REPORT

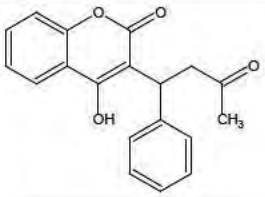
This assessment report may need to be periodically updated in order to take account of scientific developments and results from the examination of any of the information referred to in Articles 7, 10.4 and 14 of Directive 98/8/EC. Such adaptations will be examined and finalised in connection with any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

APPENDIX I: LIST OF ENDPOINTS

CHAPTER 1: IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, CLASSIFICATION AND LABELLING

Active substance (ISO Common Name)	Warfarin
Product-type	14

Identity

Chemical name (IUPAC)	(RS)-4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin
Chemical name (CA)	4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one
CAS No.	81-81-2 [racemic mixture]
EC No.	201-377-6 (EINECS)
Other substance No.	CIPAC: 70
Minimum purity of the active substance as manufactured (g/kg or g/l)	≥990 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Refer to Appendix I confidential data
Molecular formula	$C_{19}H_{16}O_4$
Molecular mass	308.25 g/mol
Structural formula	

Physical and Chemical Properties

Melting point (state purity)	165°C (Purity: 100.4%)
Boiling point (state purity)	Decomposes before boiling
Temperature of decomposition	≥ 290 C decomposition (Purity: 100.4%)
Appearance (state purity)	White, crystalline solid
Relative density (state purity)	1.35 (Purity: 100.4%)
Surface tension	72.8 mN/m (20 C)
Vapour pressure (in Pa, state temperature)	p (20°C) = 3.47 x 10^{-3} Pa
Henry's law constant (Pa m^3 mol^{-1})	≤ 3.5 x 10^{-3} Pa m^3/ mol at 20°C.
Solubility in water (g/l or mg/l, state temperature)	66.13 g/l[20°C, at pH = 9.14] 267 mg/l[20°C, at pH = 7.12] 4.9 mg/l [20°C, at pH = 4.07]
Solubility in organic solvents (in g/l or mg/l, state temperature)	n-heptane: 6.4 mg/l (20°C) xylol: 780 mg/l (20°C) 1,2-dichloromethane: 21.2 g/l (20°C) methanol: 22.2 g/l (20°C) acetone: 54.6 g/l (20°C) ethylacetate: 16.9 g/l (20°C
Stability in organic solvents used in biocidal products including relevant breakdown products	Not relevant
Partition coefficient (log P_{OW}) (state temperature)	log P_{ow}= 2.9 at pH4 at 30-35°C log P_{ow} = 0.7 at pH7 at 30-35°C log P_{ow} = 0.6 at pH9 at 30-35°C (all log P_{ow} results where calculated).
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 4: 96.2% remained after 5 days at 50°C pH 7: 98.9% remained after 5 days at 50°C pH 9: 98.9% remained after 5 days at 50°C
Dissociation constant	pK_a = 5.19 (20°C)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	ε282.5 = 11341 × mol^{-1} × cm^{-1} ε290 = 8134 × mol^{-1} × cm^{-1} ε306 = 10747 × mol^{-1} × cm^{-1} ε368 = 12 × mol^{-1} × cm^{-1}
Photostability (DT_{50}) (aqueous, sunlight, state pH)	No significant degradation (<10%) was observed following 14 days of continuous irradiation at 313nm (20-25°C) DT50 ≥ 54 days (estimated)
Quantum yield of direct phototransformation in water at Σ > 290 nm	≤ 0.0004
Flammability	Not flammable

Explosive properties	Not explosive

Classification and Proposed Labelling

With regard to physical/chemical data	Not required.
With regard to toxicological data	T+, Very Toxic R26/27/28, Very toxic by inhalation, in contact with skin and if swallowed R61, May cause harm to the unborn child R48/23/24/25, Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
With regard to fate and behaviour data	Not required
With regard to ecotoxicological data	R52, Harmful to aquatic organisms.

CHAPTER 2: METHODS OF ANALYSIS

Analytical Methods for the Active Substance

Technical active substance (principle of method)	LC/MS-MS (reversed-phase column, mobile phase: acetonitrile/water/formic acid, 50: 50: 0.2) with LCQ Duo Ion Trap System, electrospray interface (esi), monitored ions m/z = 308 - >161.
Impurities in technical active substance (principle of method)	Reversed-phase HPLC with DAD detection

Analytical Methods for Residues

Soil (principle of method and LOQ)	LC-MS/MS; LOQ = 0.02 mg/kg soil Samples, fortified with warfarin in the range 0.02 - 0.2mg/kg were extracted with acetonitrile /water /acetic acid (90, 10 and 0.1ml) while shaking. Sodium chloride (5g) was added to the samples and they were shaken for a further 5 mins. The acetonitrile extract was separated and evaporated to dryness using a rotary evaporation at 40ºC. The dried extract was re-constituted in HPLC mobile phase B (acetonitrile/water/acetic acid, 50:50:1 v/v/v). HPLC analysis involved separation on a C8 column with programmed elution using mobile phases A (acetonitrile/water/acetic acid, 10:90:1 v/v/v); B and C (acetonitrile + 1% acetic acid). Detection was by ms/ms with electrospray interface (esi), m/z = 308 - >161. Quantitation was by comparison with external standards.
Air (principle of method and LOQ)	LC-MS/MS; LOQ = 0.09µg/m³ Talcum powder (blank-formulation) and Warfarin were spiked on the front filter of the adsorbent tube, filled with Tenax as adsorbent material. Air (humidity > 90%, temperature > 35°C) was sucked through the tube for at least 8 h. Residues were extracted with acetone. An aliquot of the acetone extract was dried by a slight stream of nitrogen and than re-constituted in

	HPLC mobile phase B (acetonitrile/water/acetic acid, 50:50:1 v/v/v). HPLC analysis involved separation on a C8 column with programmed elution using mobile phases A (acetonitrile/water/acetic acid, 10:90:1 v/v/v); B and C (acetonitrile + 1% acetic acid). Detection was by ms/ms with electrospray interface (esi), m/z = 307 ± 2 - >161 ± 0.5. Quantitation was by comparison with external standards.
Water (principle of method and LOQ)	LC-MS/MS; LOQ = 0.05µg/l Samples of drinking and surface (river) water fortified with warfarin in the range 0.05-0.50 µg/l, were acidified with acetic acid (5ml) and applied to SPE C18 tubes at a rate of approx. 1-2 drops per sec. After complete sample application the tubes were dried using the SPE manifold and the warfarin eluted with HPLC mobile phase B (acetonitrile/water/acetic acid, 50:50:1 v/v/v). HPLC analysis involved separation on a C8 column with programmed elution using mobile phases A (acetonitrile/water/acetic acid, 10:90:1 v/v/v); B and C (acetonitrile + 1% acetic acid). Detection was by MS/MS with electrospray interface (ESI), m/z = 308 –> 161. Quantitation was by comparison with external standards.
Body fluids and tissues (principle of method and LOQ)	LC-MS/MS; LOQ = 0.05mg/l blood 0.01mg/kg milk, meat and eggs Blood samples were acidified with 1% acetic acid. Residues were extracted by solid-phase extraction on SPE column and eluted with acetonitrile containing 1% acetic acid. HPLC analysis involved separation on a C8 column with programmed elution using mobile phases A (acetonitrile/water/acetic acid, 10:90:1 v/v/v); B (acetonitrile/water/acetic acid, 50:50:1 v/v/v) and C (acetonitrile + 1% acetic acid). Detection was by MS/MS with electrospray interface (esi), m/z = 307 ± 1 –>161 ± 0.5. Quantitation was by comparison with external standards.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	LC-MS/MS; LOQ =0.01mg/kg Residues of warfarin in cucumbers and citrus were extracted according to module E1 of the multi-method L 00.00-34 (§ 35 LMBG). Residues in wheat grain were extracted according to module E 2 and residues in rape seed were extracted according to module E 9. Clean-up was by GPC, final determination by LC-MS/MS with negative electrospray ionisation. Ions monitored: 307→ 250 amu (quantifier) and 307 → 161 amu (qualifier).
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	LC-MS/MS; LOQ =0.01mg/kg (milk, eggs, meat) Residues were extracted with acetone/water (2:1) followed by partition into cyclohexane/ethyl acetate (1:1) and gel permeation chromatography (mobile phase: cyclohexane/ethyl acetate) according to the modified multi-residue method DFG S 19. HPLC analysis involved separation on a C8 column with programmed elution using mobile phases A (acetonitrile/water/acetic acid, 10:90:1 v/v/v), B (acetonitrile/water/acetic acid, 50:50:1 v/v/v) and C (acetonitrile + 1% acetic acid). Detection was by MS/MS with electrospray interface (esi), m/z = 307 ±

1 –>161 ± 0.5. Quantitation was by comparison with external standards.

CHAPTER 3: IMPACT ON HUMAN HEALTH

Absorption, Distribution, Metabolism and Excretion in Mammals

Rate and extent of oral absorption:	Oral absorption may be considered to occur at effectively 100%
Rate and extent of dermal absorption:	Based on the results of an in-vivo (rat) dermal absorption study with an aqueous 0.5% Warfarin-containing liquid concentrate formulation, the dermal absorption for an 6 and 24-hour exposure amounted to 13.3-14.4% respectively. This is taken into account by assigning a default percutaneous absorption value of 15% in the operator risk assessments
Distribution:	Widely distributed, the liver being the organ with greatest affinity
Potential for accumulation:	Evidence of 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:	Most of the urinary excretion was complete within 2 days. The same metabolites were present in faecal extracts, but in different relative amounts. A prolonged terminal elimination phase was observed in humans (tissue binding).
Toxicologically significant metabolite(s)	Parent compound; warfarin alcohols (anticoagulant activity in humans).

Acute toxicity

Rat LD_{50} oral	5.62 mg/kg bw
Rat LD_{50} dermal	40 mg/kg
Rat LC_{50} inhalation	< 0.005 mg/l air 4 h (below the lowest aerosol concentration)
Skin irritation	Non-irritating
Eye irritation	Non-irritating
Skin sensitization (test method used and result)	Not sensitising (M&K test)

Repeated dose toxicity

Species/ target / critical effect	Prolongation of prothrombin time, haemorrhages (serosanguineous exudate in the pleural cavity, rat)
Lowest relevant oral NOAEL / LOAEL	None established – extrapolation from human clinical use proposed
Lowest relevant dermal NOAEL / LOAEL	Not available
Lowest relevant inhalation NOAEL / LOAEL	Not available

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.

Carcinogenicity

Species/type of tumour	None established – extrapolation from human clinical use proposed
lowest dose with tumours	Not available

Reproductive toxicity

Species/ Reproduction target / critical effect	None established – extrapolation from human clinical use proposed
Lowest relevant reproductive NOAEL / LOAEL	None established – extrapolation from human clinical use proposed
Species/Developmental target / critical effect	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); 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). Exposure during the first trimester is associated with FWS and exposure throughout pregnancy or during the second and third trimester is associated with adverse effects on CNS development (human, 2.5 to 20 mg/day).
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	None established Lowest relevant developmental adverse dose levels: NOAEL (Rat): 0.04 mg/kg bw/day LOAEL (Human): 0.04 mg/kg bw/day (Based on effects seen at 2.5 mg/day)

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Not an organophosphorus compound, which is why acute or delayed neurotoxicity studies were not conducted.
Lowest relevant developmental NOAEL / LOAEL.	No evidence for neurotoxic potential from other studies

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

.....	Human long-term therapeutic maintenance dose of 1–13 mg/day (corresponding to 0.0167–0.2 mg/kg bw/day: elevation 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). Reproductive toxicity: Stillbirth or abortion, microcephaly, hydrocephaly, nasal hypoplasia, bone anomalies, growth retardation (human, dose level 2.5 - 12.5 mg/day ≅ (0.04 – 0.2) mg/kg bw/day) In over 40 years of use of Warfarin in rodenticide practice, only one reported case of an operator who suffered poisoning during his work with Warfarin. This illness was attributed to the lack of use of appropriate PPE (gloves).

Summary	Value	Study	Safety factor
Non-professional user			
ADI (acceptable daily intake, external long-term reference dose)	Not relevant	Not relevant	Not relevant
AOEL-S (Operator Exposure)	0.0002 mg/kg bw/day (Repeated dose)	Based on lowest human long-term therapeutic maintenance dose (1 mg/day, 60 kg bw)	100[a]
ARfD (acute reference dose)	0.067 mg kg bw (Acute)	Based on the lowest published lethal dose in humans (6.7 mg/kg bw)	100[b]
Professional user	0.0002 mg/kg bw/day (Repeated dose)	Based on lowest human long-term therapeutic maintenance dose (1 mg/day, 60 kg bw)	100[a]
Reference value for inhalation (proposed OEL)	Not established	Not established	Not relevant
Reference value for dermal absorption	15%	Based on the results of an in-vivo (rat) dermal absorption study	Not relevant

[a]Intra-species safety factor of 10 and 10 for severity of effect (Developmental effects).

[b]Intra-species safety factor of 10 and 10 for severity of effect (lethality).

Acceptable exposure scenarios (including method of calculation)

Professional users	Safe uses were identified for wax block and grain baits when baits were individually wrapped, exposure was limited to the cleanup phase, and PPE was worn. (Modelled using Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2 (June 2002) and results from the CEFIC studies)
Production of active substance:	Not evaluated
Formulation of biocidal product	Not evaluated
Intended uses	Intended for use as the active ingredient in wax block and grain rodenticide baits.
Secondary exposure	Not relevant
Non-professional users	Safe uses were identified for wax block and grain baits when baits were individually wrapped and exposure was limited to the cleanup phase (Modelled using Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2 (June 2002) and results from the CEFIC studies)
Indirect exposure as a result of use	Safe scenarios were modelled for adults, children and infants. (Modelled using Technical Notes for Guidance on Human Exposure to Biocidal Products, Part 3, Section 7.2.1 (June 2002))

CHAPTER 4: FATE AND BEHAVIOUR IN THE ENVIRONMENT

Route and Rate of Degradation in Water

Hydrolysis of active substance and relevant metabolites (DT_{50}).	Warfarin is hydrolytically stable. pH: 4 — Temp/°C: 50 ± 0.5 — % Warfarin remaining after 5 days: 96.2 pH: 7 — % Warfarin remaining after 5 days: 98.9 pH: 9 — % Warfarin remaining after 5 days: 98.9 No significant hydrolysis is expected at temperatures of environmental significance.
Photolytic degradation of active substance and relevant metabolites	No significant degradation was observed following 14 days of continuous irradiation at 313 nm (20-25 °C) A lower limit, $DT_{50} \geq 54$ days in surface water was calculated using the Batelle-UBA computer programme incorporating central European environmental conditions during November.
Readily biodegradable (yes/no)	Yes. (OECD 301 D and EC C.4-E).
Biodegradation in seawater (yes/no)	Not required. "Warfarin and its products are registered in the form of ready-to-use baits for the control of commensal rodents (rats and mice) in open areas, in and around buildings, sewage systems and landfill sites" (Document IIIA dossier section A5). In light of its use pattern and its ready biodegrability, exposure of Warfarin to marine environments is limited.
Non-extractable residues	No data reported – not considered necessary
Distribution in water/sediment systems (active substance)	No data reported – not considered necessary
Mineralisation	No data reported – not considered necessary
Non-extractable residues	No data reported – not considered necessary
Distribution in water / sediment systems (metabolites)	No data reported – not considered necessary

Route and rate of degradation in soil

Mineralisation (aerobic)	Aerobic Mineralisation of Warfarin in laboratory trials Test length/days: 100 — Test Sub.Conc. (mg/kg): 5 — % CO_2 (as % AR): 20 Test length/days: 100 — Test Sub.Conc. (mg/kg): 50 — % CO_2 (as % AR): 10 Test length/days: 134 — Test Sub.Conc. (mg/kg): 550 — % CO_2 (as % AR): 16.4

Laboratory studies (range or median, with number of measurements, with regression coefficient)

DT_{50lab} (20°C, aerobic):

Test Sub.Conc. (mg/kg)	DT_{50lab} Days (1st order).	Range/d	n
2*	2	2–16	3
5-50	61	53–70	2
550	143	135-150	2

*supportive study data. However, this study has been evaluated in the Warfarin monograph prepared under the 91/414/EEC directive. The DT_{50} is listed in the endpoints document of the aforementioned monograph.

DT_{90lab} (20 °C, aerobic): 2 mg/kg soil: 6 days (range 6–7 days) n = 1
[supportive study data, see*]

DT_{50lab} (10 °C, aerobic): not relevant

DT_{50lab} (20 °C, anaerobic): not required

Field studies (state location, range or median with number of measurements)

No data reported/not considered necessary as no significant soil contamination should arise.

Anaerobic degradation:

No data reported/not considered necessary.

Soil photolysis

Not required as the amount of active substance deposited to the surface is expected to be insignificant.
However a supportive study presented in the dossier, document III A 7.2.2.4/02 found that Warfarin did not undergo significant degradation when treated with polychromatic light (290-800 nm, Xe lamp source) for 29 days.

Non-extractable residues (in soil after)

Warfarin Conc. (mg/kg soil)	Test length/days	% Residual radioactivity in soil at the end of test period
5	100	41.7
50	100	33.3
550	134	13.6

Adsorption/desorption

K_f, K_d

For Warfarin

Soil type	Ka (=K_F)	Ka_{OC} (=K_{FOC})	K_d (for 2nd desorption)
silty clay loam	0.66	18	3.64
sandy silt loam	8.51	247	8.56
silty clay loam	0.65	42	3.44
clay loam	46.77	390	50.39

K_a (average) 14.15 , range 0.66-46.77, n=4.
K_{aOC} (average) 174, range 18-390, n=4.

K_{foc}, K_{doc}

pH dependence (yes/no) (if yes type of dependence)

Yes
Warfarin adsorption strongly depends on pH and organic matter content. Adsorption increases with decreasing soil

	pH and increasing organic matter content.

Fate and behaviour in air

Direct photolysis in air	According to spectral data no quantitatively relevant degree of photolysis is to be expected
Quantum yield of direct phototransformation	Not available
Photochemical oxidative degradation in air	QSAR estimation, Atkinson method, AOPWIN version 1.90). DT_{50} (Ozone) = 2.015 hr DT_{50} (OH·) = 2.4 h (12-hour day, 1.5 x 10^6 OH·/cm³) DT_{50} (OH·) = 7.2 h (24-hour day, 0.5 x 10^6 OH·/cm³)
Volatilisation	Medium to low volatility ($p \leq 3 \times 10^{-5}$ hPa at 20 °C; Henry law constant = 2 x10^{-4} Pa m^3/mol [QSAR, Henrywin Program (SRC) version 3.00]

Monitoring data, if available

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

CHAPTER 5: EFFECTS ON NON-TARGET SPECIES

Toxicity Data for Aquatic Species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity
Fish			
Salmo gairdniri	96 h	Mortality, LC_{50}	LC_{50} =65 mg/L
Salmo gairdniri	21 day	Mortality NOEC	NOEC = 2 mg/L
Invertebrates			
Daphnia magna	48 h	immobility and mortality	EC_{50} >105 mg/L
Daphnia magna	21 day	immobility and reproduction rate	NOEC = 0.059 mg/L
Algae			
Scenedesmus subspicatus	72 h	Cell density	E_bC_{50} and E_rC_{50} >83.2 mg /L
Microorganisms			
Activated Sludge	175 min	Inhibition of oxygen consumption	EC_{20}>400 mg/L

Effects on earthworms or other soil non-target organisms

Acute toxicity to ……..	Not required
Reproductive toxicity to ……	Not required

Effects on soil micro-organisms

Nitrogen mineralization Carbon mineralization	At 550 mg/kg soil, clear inhibition of microbial activity (dehydrogenase activity)

Effects on terrestrial vertebrates

Acute toxicity to mammals	Mice LD_{50}=374 mg/kg bw Rabbit LD_{50}=800 mg/kg bw Pig LD_{50}=1-5 mg/kg bw Dog LD_{50}=20-50 mg/kg bw
Acute toxicity to birds	LD_{50} > 2000 mg/kg bw LOAEL=1000 mg/kg bw NOAEL=500 mg/kg bw
Dietary toxicity to birds	LC_{50} > 5000 ppm
Reproductive toxicity to birds	Based on a 6-week dietary study with technical grade coumatetralyl (Racumin® S, purity 99.9 %) performed with adult Japanese Quail: NOEC for parental toxicity = 20 mg a.s./kg food (= 2 mg

	a.i./kg bw/day). NOEC for the reproductive toxicity = 60 mg a.s./kg food. (= 6 mg a.i./kg bw/day).
Secondary toxicity to birds	NOAEL in predatory birds = 17.1 mg/kg (dietary exposure)

Effects on honeybees

Acute oral toxicity	Not required
Acute contact toxicity	Not required

Effects on other beneficial arthropods

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

Bioconcentration

Bioconcentration factor (BCF)	≤21.6
Depuration time(DT_{50}) (DT_{90})	In the depuration phase the warfarin concentration decreased rapidly to levels at or below the detection limit so that after 11 days (the first day of warfarin measurement after termination of exposure) warfarin was no longer detectable in any of the test groups. Valid estimates of DT_{50} and DT_{90} can therefore not be provided. In conclusion DT_{90}≤11 days
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable

CHAPTER 6: OTHER ENDPOINTS

Not applicable.

APPENDIX II: LIST OF INTENDED USES

Product-type:

Rodenticide (PT14)

Claim of the participant:

For the control of rats and mice.

Target organisms:

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

Concentration:

The active substance is used at a nominal concentration of 790 mg/kg.

Categories of users:

Professionals and non-professionals.

Type of application:

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

The active substance is used in three, partly cereal-based, products.
• Block bait (green blocks, ready for use), supplied loose or in protective sachets
• Paste bait (blue paste, ready for use), supplied in sachets made of paper
• Pellet bait (blue cereal pellets, ready for use), supplied loose and in protective sachets

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

Formulated products containing Warfarin are not applied directly on food or feeding stuffs.Products are not intended to be applied directly on surfaces intended for contact with food or feeding stuffs. However, Warfarin containing products are intended to be used in premises were food or feeding stuffs are prepared or stored.

APPENDIX III: LIST OF STUDIES

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. For studies marked Yes(i) data protection is claimed under Article 12.1(c) (i), for studies marked Yes(ii) data protection is claimed under Article 12.1(c) (ii). These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was, however, not possible to confirm the accuracy of this information.

Section No /Reference No	**Author(s)**	**Year**	**Title. Source, Report No. GLP / (Un)Published**	**Data Protection Claimed (Yes/No)**	**Owner**
A3.1.1/01	Krips, H.J.	1998	Determination of the melting temperature of warfarin technical NOTOX, s'Hertogenbosch, NL, Report No.: 240672GLP, Not Published	Y (New/First)	Task Force
A3.1.2/01	Sendor, T.	2004	Model calculation of the boiling point of warfarinEBRC Consulting GmbH, Hannover, Germany, 08.01.2004, Not GLP, Not Published	Y (New/First)	Task Force
A3.1.3/01	Krips, H.J.	1998	Determination of the density of warfarin technicalNOTOX, s'Hertogenbosch, NL, Report No.: 240683GLP, Not Published	Y (New/First)	Task Force
A3.11/01	Krips, H.J.	1998	Determination of the flammability of warfarin technicalNOTOX, s'Hertogenbosch, NL, Report No.: 240694GLP, Not Published	Y (New/First)	Task Force
A3.11/02	Krips, H.J.	1998	Determination of the relative self-ignition temperature of warfarin technicalNOTOX, s'Hertogenbosch, NL, Report No.: 240705GLP, Not Published	Y (New/First)	Task Force
A3.13/01	Krips, H.J.	1998	Determination of the surface tension of an aqueous solution of warfarin technicalNOTOX, s'Hertogenbosch, NL, Report No.: 240716GLP, Not Published	Y (New/First)	Task Force
A3.15/01	Battersby, R.V.	2004	Explosivity of warfarin technicalEBRC Consulting GmbH, Hannover, Germany, 13.01.2004, Not GLP, Not Published	Y (New/First)	Task Force
A3.2.1/01	Battersby, R.V.	1998	Model calculation of Henry's Constant WarfarinEBRC Consulting GmbH, Hannover, Germany, 11.06.1998, 6 p., Not GLP, Not Published	Y (New/First)	Task Force
A3.2/01	Schleich, W.	2001	Warfarin. Determination of the vapour pressureInfracor GmbH, Marl, Germany, Report No.: AN-ASB 0172GLP, Not Published	Y (New/First)	Task Force
A3.5/01	Walter, D.	1998	Water solubility of warfarinGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 98304/01-PCSBGLP, Not Published	Y (New/First)	Task Force

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A3.6/01	Heintze, A.	2003	Ionisation constant of warfarin in waterGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20021048/01-PCDCGLP, Not Published	Y (New/First)	Task Force
A3.7/01	Walter, D.	1998	Solubility of warfarin in organic solventsGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 98304/01-PSBOGLP, Not Published	Y (New/First)	Task Force
A3.9/01	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, Report No.: 12003186GLP, Not Published	Y (New/First)	Task Force
A4.1/01	Mende, P.	2003	Validation of a confirmatory method for analysis of warfarin in warfarin technical grade materialGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20021065/01-RVFGLP, Not Published	Y (New/First)	Task Force
A4.1/02	Persson, D.; Borgkvist, M.	1995	Specification and routine tests for active substancesPharmacia, Malmö, Sweden, Report No.: S 385; 46 98 50Not GLP, Not Published	Y (New/First)	Task Force
A4.1/03	de Ryckel, B.	1999	Analysis of 5 batches of Warfarin technical products, and of 2 batches of Warfarin Sodium salt technical products (without chapter 5+6)Departement de Phytopharmacie, Belgium, Report No.: EBRC/PJ/BA 9318/Ch.1703 to Ch.1709/1998/212GLP, Not Published	Y (New/First)	Task Force
A4.2/01	Mende, P.	2001	Residue analysis of warfarin in soil. Method validationGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20011279/01-RVSGLP, Not Published	Y (New/First)	Task Force
A4.2/03	Heintze, A.	2002	Validation of an analytical method for the determination of warfarin from air or airborne warfarin containing dust (Curattin Haftstreupuder) from airGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20021045/01-CMLUGLP, Not Published	Y (New/First)	Task Force
A4.2/07	Mende, P.	2001	Residue analysis of warfarin in drinking water and surface water. Method validationGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20011279/01-RVWGLP, Not Published	Y (New/First)	Task Force

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A4.2/12	Mende, P.	2002	Residue analysis of warfarin in animal tissues and body fluids: Method, development and validationGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20011279/01-RVATGLP, Not Published	Y (New/First)	Task Force
A4.2/26	Lang, D.; Böcker, R.	1995	Highly sensitive and specific high-performance liquid chromatographic analysis of 7-hydroxywarfarin, a marker for human cytochrome P-4502C9 activityJ. Chromatogr. B 672, 305-309, Not GLP, Published	N	
A5.2/01	Chambers, C.M.; Chambers, P.L	1983	Warfarin and the grey squirrelArch. Tox. Suppl. 6, 214-221, Not GLP, Published	N	
A5.2/02	Bradfield, A.A.G.; Gill, J.E.	1984	Laboratory trials of five rodenticides for the control of Mesocricetus auratus WaterhouseJ. Hyg. 93, 389-394, Not GLP, Published	N	
A5.2/03	Gill, J.E.; Redfern, R.	1980	Laboratory trials of seven rodenticides for use against the cotton rat (Sigmodon hispidus)J. Hyg. 85, 443-450, Not GLP, Published	N	
A5.2/04	Taniguchi, N.; Kato, T.; Ikeda, Y.	1985	Rodenticidal activity of warfarin against wild Norway rat Rattus norvegicus, collected from some locations in JapanJpn. J. Sanit. Zool. 36, 107-110, Not GLP, Published	N	
A5.2/05	Bäumler, W.; Asran, A.A.	1987	Susceptibility of house mice (Mus musculus) of different origin to anticoagulantsAnz. Schaedlingsk., Pflanzenschutz, Umweltschutz 60, 1-6, Not GLP, Published	N	
A5.2/06	Gill, J.E.; Redfern, R.	1977	Some laboratory tests of five rodenticides for the control of Arvicanthis niloticusPANS 23, 33-37, Not GLP, Published	N	
A5.2/07	Mahmoud, W.; Redfern, R.	1981	The response of the Egyptian spiny mouse (Acomys cahirinus) and two other species of commensal rodents to anticoagulant rodenticidesJ. Hyg. 86, 329-334, Not GLP, Published	N	
A5.2/08	Gill, J.E.; Redfern, R.	1983	Laboratory tests of seven rodenticides for the control of Meriones shawiJ. Hyg. 91, 351-357, Not GLP, Published	N	
A5.2/09	Balasubramanyam , M.; Purushotham, K.R.	1988	The susceptibility of the indian field mouse Mus-booduga Gray to anticoagulant rodenticidal baitsPestic. Sci. 23, 209-213, Not GLP, Published	N	
A5.2/10	Balasubramanyam, M.; Christopher, M.J.; Purushotham, K.R.	1984	Laboratory trials of three anticoagulant rodenticides for use against the Indian field mouse, Mus booduga GrayJ. Hyg. 93, 575-578, Not GLP, Published	N	

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A5.2/11	Arshad, M.I.; Khan, R.A.; Khaliq, A.	1988	Strategies for the control of indian crested porcupine, Hystrix-indicaPak. J. Sci. Ind. Res. 31, 784-785, Not GLP, Published	N	
A5.2/12	Balasubramanyam, M.; Shobarani, D.; Maddaiah, G.P.; Purushotham, K.R.	1988	Responses to warfarin by the Indian gerbil Tatera indica from Tirupati, IndiaIndian J. Exp. Biol. 26, 694-696, Not GLP, Published	N	
A5.2/13	Advani, R.; Prakash, I.	1987	Variations in the rodent populations in response to four anticoagulant rodenticides in the residential habitat of the Indian desertPesticides 21, 18-22, Not GLP, Published	N	
A5.2/14	O'Brien, P.H.; Lukins, B.S.	1990	Comparative dose-response relationships and acceptability of warfarin, brodifacoum and phosphorus to feral pigsAust. Wildl. Res. 17, 101-112, Not GLP, Published	N	
A5.2/15	Saunders, G.; Kay, B.; Parker, B.	1990	Evaluation of a warfarin poisoning program for feral pigs (Sus scrofa)Aust. Wildl. Res. 17, 525-533, Not GLP, Published	N	
A5.7/01	Pelz, H.-J.; Hänisch, D.; Lauenstein, G.	1995	Resistance to anticoagulant rodenticides in Germany and future strategies to control Rattus norvegicusPestic. Sci. 43, 61-67, Not GLP, Published	N	
A5.7/02	Boyle, C.M.	1960	Case of apparent resistance of Rattus norvegicus Berkenhout to anticoagulant poisonsNature 188, 517, Not GLP, Published	N	
A5.7/03	Myllymäki, A.	1995	Anticoagulant resistance in Europe: appraisal of the data from the 1992 EPPO questionnairePestic. Sci. 43, 69-72, Not GLP, Published	N	
A5.7/04	Jackson, W.B.; Ashton, A.D.	1995	Extended summary RRAC symposium anticoagulant resistance in North AmericaPestic. Sci. 43, 95-96, Not GLP, Published	N	
A5.7/05	Misenheimer, T.M.; Suttie, J.W.	1990	Warfarin resistance in a Chicago strain of ratsBiochem. Pharm. 40, 2079-2084, Not GLP, Published	N	
A5.7/06	Greaves, J.H.	1970	Warfarin-resistant rats in BritainAgr. Sci. Rev. 8, 35-38, Not GLP, Published	N	
A5.7/14	Greaves, J.H.	1995	Managing resistance to anticoagulant rodenticides: an appraisalPestic. Sci. 43, 79-82, Not GLP, Published	N	
A6.1.1/01	Bai, K.M.; Krishnakumari, M.K.; Majumder, S.K.	1992	Single dose toxicity (oral) of a chronic anticoagulant rodenticide-warfarin in albino ratsComp. Physiol. Ecol. 17, 75-82, Not GLP, Published	N	

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.1.1/02	Back, N.; Steger, R.; Glassman, J.M.	1978	Comparative acute oral toxicity of sodium warfarin and microcrystalline warfarin in the Sprague-Dawley ratPharmacol. Res. Commun. 10, 445-452, Not GLP, Published	N	
A6.1.2/01	Daamen, P.A.M.	1994	Assessment of acute dermal toxicity with warfarin technical in the ratNOTOX, s'Hertogenbosch, NL, Report No.: 110464GLP, Not Published	Y (New/First)	Task Force
A6.1.3/01	Biesemeier, J.A.	1985	Acute inhalation LC50 of warfarin technical in Sprague-Dawley ratsFood & Drug Research Laboratories, Inc., Report No.: 8359GLP, Not Published	Y (New/First)	Task Force
A6.1.4/01	Pels Rijcken, W.R.	1994	Primary skin irritation/corrosion study with warfarin technical in the rabbit (4-hour semi-occlusive application)NOTOX, s'Hertogenbosch, NL, Report No.: 110475GLP, Not Published	Y (New/First)	Task Force
A6.1.4/02	Pels Rijcken, W.R.	1994	Acute eye irritation/corrosion study with warfarin technical in the rabbitNOTOX, s'Hertogenbosch, NL, Report No.: 110486GLP, Not Published	Y (New/First)	Task Force
A6.1.5/01	Daamen, P.A.M.	1994	Assessment of contact hypersensitivity to warfarin technical in the Albino Guinea pig (Maximization-Test)NOTOX, s'Hertogenbosch, NL, Report No.: 110497GLP, Not Published	Y (New/First)	Task Force
A6.12.2/01	Gallerani, M.; et al.	1995	Non-haemorrhagic adverse reactions of oral anticoagulant therapyInt. J. Cardiology 49, 1-7, Not GLP, Published	N	
A6.12.2/03	DeFranzo, A.J.; Marasco, P.; Argenta, L.C.	1995	Warfarin-induced necrosis of the skinAnn. Plast. Surg. 34, 203-208, Not GLP, Published	N	
A6.12.2/04	Cole, M.S.; Minifee, P.K.; Wolma, F.J.	1988	Coumarin necrosis - a review of the literatureSurgery 103, 271-277, Not GLP, Published	N	
A6.12.2/09	Martin-Bouyer, G.; Linh, P.D.; Tuan, L.C.; Barin, C.; Khanh, N.B.; Hoa, D.Q.; Tourneau, J.	1983	Epidemic of haemorrhagic disease in vietnamese infants caused by warfarin-contaminated talcsLancet (Jan. 29), 230-232, Not GLP, Published	N	
A6.12.2/16	Fristedt, B.; Sterner, N.	1965	Warfarin intoxication from percutaneous absorptionArch. Environ. Health 11, 205-208, Not GLP, Published	N	
A6.2.1/01	Barker, W.M.; Hermodson, M.A.; Link, K.P.	1970	The metabolism of 4-C14-warfarin sodium by the ratJ. Pharm. Exp. Ther. 171, 307-313, Not GLP, Published	N	

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.2.1/03	Breckenridge, A.; L'E Orme, M.	1972	The plasma half lives and the pharmacological effect of the enantiomers of warfarin in ratsLife Sci. 11, 337-345, Not GLP, Published	N	
A6.2.3/01	King, S.-Y.P.; Joslin, M.A.; Raudibaugh, K.; Pieniaszek, Jr. H.J.; Benedek, I.H.	1995	Dose-dependent pharmacokinetics of warfarin in healthy volunteersPharm. Res. 12, 1874-1877, Not GLP, Published	N	
A6.2.3/06	O´Reilly, R.A.; Aggeler, P.M.; Leong, L.S.	1963	Studies on the coumarin anticoagulant drugs: the pharmacodynamics of warfarin in manJ. Clin. Invest. 42, 1542-1551, Not GLP, Published	N	
A6.2.3/09	Sutcliffe, F.A.; MacNicoll, A.D.; Gibson, G.G.	1987	Aspects of anticoagulant action: a review of the pharmacology, metabolism and toxicology of warfarin and congenersRev. Drug Metab. Drug Interact. 5, 225-272, Not GLP, Published	N	
A6.3.1/01	Hayes, W.J., Jr.; Gaines, T.B.	1959	Laboratory studies of five anticoagulant rodenticidesPublic Health Rep. 74, 105-113, Not GLP, Published	N	
A6.4.1/01	Hayes, W.J. Jr.	1967	The 90-dose LD50 and a chronicity factor as measures of toxicityTox. Appl. Pharm. 11, 327-335, Not GLP, Published	N	
A6.6.1/01	van de Waart, E.J.	1994	Evaluation of the mutagenic activity of warfarin technical in the ames salmonella/microsome test (with independent repeat)NOTOX, s'Hertogenbosch, NL, Report No.: 110508GLP, Not Published	Y (New/First)	Task Force
A6.6.2/01	van de Waart, E.J.	1994	Evaluation of the ability of warfarin technical to induce chromosome aberrations in cultured peripheral human lymphocytesNOTOX, s'Hertogenbosch, NL, Report No.: 110521GLP, Not Published	Y (New/First)	Task Force
A6.6.3/01	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, s'Hertogenbosch, NL, Report No.: 110519GLP, Not Published	Y (New/First)	Task Force
A6.6.4/01	Grötsch, W.	1999	In vivo micronucleus test of warfarin in miceL+S AG, Bad Bocklet, Germany, Report No.: 06287188/1GLP, Not Published	Y (New/First)	Task Force
A6.6.5/01	Leuschner, J.	1999	Unscheduled DNA synthesis (UDS) test of warfarin, sodium salt after oral administration to Sprague-Dawley ratsLPT, Hamburg, Germany, Report No.: 11731/98GLP, Not Published	Y (New/First)	Task Force

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.8.1/01	Mirkova, E.; Antov, G.	1983	Experimental evaluation of the risk of prenatal pathology with the application of the coumarine rodenticide warfarinHig. Zdrav. 25, 476-482, Not GLP, Published	N	
A6.8.1/02	Howe, A.M.; Webster, W.S.	1992	The warfarin embryopathy: a rat model showing maxillonasal hypoplasia other skeletal disturbancesTeratology 46, 379-390, Not GLP, Published	N	
A6.8.1/04	Feteih, R.; Tassinari, M.S.; Lian, J.B.	1990	Effect of sodium warfarin on vitamin K-dependent proteins and skeletal development in the rat fetusJ. Bone Miner. Res. 5, 885-894, Not GLP, Published	N	
A6.8.1/05	Kronick, J.; Phelps, N.E.; McCallion, D.J.; Hirsh, J.	1974	Effects of sodium warfarin administered during pregnancy in miceAm. J. Obstet. Gynecol. 118, 819-823, Not GLP, Published	N	
A7.1.1.1.1/01	Heintze, A.	2002	Abiotic degradation of Warfarin - Hydrolysis as a function of pHGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20021048/01-PCHYGLP, Not Published	Y (New/First)	Task Force
A7.1.1.1.2/01	Kloepffer, 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, Frankfurt, Germany, Report No.: BE-P-78-91-PHO-01GLP, Not Published	Y (New/First)	Task Force
A7.1.1.2.1/01	Dengler, D.	2004	Assessment of the ready biodegradability of Warfarin with the closed bottle testGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20031401/01-AACBGLP, Not Published	Y (New/First)	Task Force
A7.2.1/01	Bieber, W.-D.; Kroehn, R.	1991	Degradation (metabolism) of warfarin in soilNATEC, Hamburg, Germany, Report No.: NA 89 9252Not GLP, Not Published	Y (New/First)	Task Force
A7.2.2.4/01	Kurth, H.-H.	1999	Aerobic soil degradation of warfarinFraunhofer Institut für Umweltchemie und Ökotoxikologie, Schmallenberg, Germany, Report No.: SPI-001/7-15GLP, Not Published	Y (New/First)	Task Force
A7.2.2.4/03	Todt, K.; Niemann, I.; Thiele, E.	1989	Degradation of warfarin in soilNATEC, Hamburg, Germany, Report No.: NA 89 9719Not GLP, Not Published	Y (New/First)	Task Force
A7.2.2.4/04	Kellner, G.	1991	Degradation of warfarin in soilNATEC, Hamburg, Germany, Report No.: NA 91 9072GLP, Not Published	Y (New/First)	Task Force

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A7.2.3.1/01	Kurth, H.-H.	1999	Adsorption/desorption of warfarin on soilFraunhofer Institut für Umweltchemie und Ökotoxikologie, Schmallenberg, Germany, Report No.: SPI-001/7-13GLP, Not Published	Y (New/First)	Task Force
A7.2.3.2/01	Warncke, U.	1993	Investigation of the leaching behaviour of warfarin and sulfachinoxalin in "Cumarax Koeder- und Streumittel - Neu" (SPI 87930 R)Urania Agrochem GmbH, Hamburg, Germany, Report No.: C 93 VSR 01GLP, Not Published	Y (New/First)	Task Force
A7.3.1/01	Battersby, R.V.	1998	Predictive model calculation of the atmospheric oxidation behaviour (AOP) WarfarinEBRC Consulting GmbH, Hannover, Germany, 11.06.1998, 6 p., Not GLP, Not Published	Y (New/First)	Task Force
A7.4.1.1/01	Günther	1984	Fish toxicity, rainbow troutsÖkolimna, Burgwedel, Germany, Not GLP, Not Published	Y (New/First)	Task Force
A7.4.1.1/02	McAllister, W.A.; Cohle, P.	1984	Acute toxicity of warfarin technical to Bluegill sunfish (Lepomis macrochirus)Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri, USA, Report No.: 32460GLP, Not Published	Y (New/First)	Task Force
A7.4.1.1/03	Günther	1984	Fish toxicity, OrfeÖkolimna, Burgwedel, Germany, Not GLP, Not Published	Y (New/First)	Task Force
A7.4.1.2/01	Hertl, J.	2001	Acute toxicity of warfarin techn. to Daphnia magna in a 48-hour immobilization testIBACON, Rossdorf, Germany, Report No.: 12001220GLP, Not Published	Y (New/First)	Task Force
A7.4.1.2/02	Forbis, A.D.; Georgie, L.; Burgess, D.	1984	Acute toxicity of warfarin technical to Daphnia magnaAnalytical Bio-Chemistry Laboratories Inc., Columbia, Missouri, USA, Report No.: 32462GLP, Not Published	Y (New/First)	Task Force
A7.4.1.2/03	Günther	1984	Daphnia toxicityÖkolimna, Burgwedel, Germany, Not GLP, Not Published	Y (New/First)	Task Force
A7.4.1.2/04	Kady, M.M.; Brimer, L.; Furu, P.; Lemmich, E.; Nielsen, H.M.; Thiilborg, S.T.; Thastrup, O.; Christensen, S.B.	1992	The molluscicidal activity of coumarins from Ethulia conyzoides and of dicumarolPlanta Med. 58, 334-337, Not GLP, Published	N	
A7.4.1.3/01	Hertl, J.	2001	Toxicity of warfarin techn. to Scenedesmus subspicatus in an algal growth inhibition testIBACON, Rossdorf, Germany, Report No.: 12002210GLP, Not Published	Y (New/First)	Task Force

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A7.4.1.4/01	Alexanderson, T.	1992	A study of how wastewater suppresses respiration in active sludgeANOX AB, Sweden, Report No.: TA/920602Not GLP, Not Published	Y (New/First)	Task Force
A7.4.2/01	Battersby, R.V.	2003	Estimation of the bioconcentration factor (BCF) of WarfarinEBRC Consulting GmbH, Hannover, Germany, 10.09.2003, 4 p., Not GLP, Not Published	Y (New/First)	Task Force
A7.4.3.1/01	Dommröse, A.-M.	1989	Investigation of the test substance warfarin in a prolonged toxicity test on fish (rainbow trout)NATEC, Hamburg, Germany, Report No.: NA 88 9867/3.3GLP, Not Published	Y (New/First)	Task Force
A7.4.3.3.1/01	Dommröse, A.-M.	1990	Bioaccumulation (flow-through test) with the test substance warfarin in fish (rainbow trout)NATEC, Hamburg, Germany, Report No.: NA 88 9867/3.4GLP, Not Published	Y (New/First)	Task Force
A7.5.3.1.1/01	Beavers, J.B.	1985	An acute oral toxicity study in the bobwhite with warfarinWildlife International Ltd.,, Report No.: 205-103GLP, Not Published	Y (New/First)	Task Force
A7.5.3.1.2/01	Beavers, J.B.	1985	A dietary LC50 study in the mallard with warfarinWildlife International Ltd., Report No.: 205-102GLP, Not Published	Y (New/First)	Task Force
A7.5.3.1.2/02	Beavers, J.B.	1985	A dietary LC50 study in the bobwhite with warfarinWildlife International Ltd., Report No.: 205-101GLP, Not Published	Y (New/First)	Task Force
A7.5.5.1/01	Bode, M.	2003	Estimation of the bioconcentration factor (BCF) of WarfarinEBRC Consulting GmbH, Hannover, Germany, 19.11.2003, 4 p., Not GLP, Not Published	Y (New/First)	Task Force
A9/01	European Economic Community	1993	EEC, Anhang zur Richtlinie 93/72/EWG, Band II, L258, p. 872, Not GLP, Published	N	
B7.1/02	Odam, E.M.; et al.	1979	A study of the persistance of warfarin on wheat bait used for the control of grey squirrels (Sciurus carolinensis)Ann. Appl. Biol. 91, 81-89, Not GLP, Published	N	
B7.8.7.2/01	Townsend, M.G.; et al.	1981	An assessment of the secondary poisoning hazard of warfarin to tawny owlsJ. Wildl. Manage. 45, 242-248, Not GLP, Published	N	
B7.8.7.2/02	Townsend, M.G.; et al.	1984	Assessment of secondary poisoning hazard of warfarin to least weaselsJ. Wildl. Manage. 48, 628-631, Not GLP, Published	N	

Section No /Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
B7.8.7.2/03	Townsend, M.G.	1992	A study of the toxicity of warfarin to magpies (Pica pica) consuming warfarin-fed miceContract Report No C87/0584, Not GLP, Not Published	Y (New/First)	Task Force
B7.8.7.2/06	Cioloca, T.; et al.	1972	Comments on warfarin poisoning of pigs, sheep and wild birdsDeut. Tieraerztl. Wochensch. 79, 37-39, Not GLP, Published	N	
B7.8.7.2/07	Prier, R.F.; Derse, P.H.	1962	Evaluation of the hazard of secondary poisoning by warfarin-poisoned rodentsJAVMA 140, 351-354, Not GLP, Published	N	
B7.8.7.2/11	Aulerich, R.J.; et al.	1987	Primary and secondary toxicity of warfarin, sodium monofluoroacetate, and methyl parathion in minkArch. Environ. Contam. Toxicol. 16, 357-366, Not GLP, Published	N	

Reference List Doc. IIB-1 (Wax Block)

Section No / Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.1.4/01	Pels Rijcken, W.R.	1994	Primary skin irritation/corrosion study with warfarin technical in the rabbit (4-hour semi-occlusive application)NOTOX, s'Hertogenbosch, NL, Report No.: 110475GLP, Not Published	Y (New/First)	Task Force
A6.1.4/02	Pels Rijcken, W.R.	1994	Acute eye irritation/corrosion study with warfarin technical in the rabbitNOTOX, s'Hertogenbosch, NL, Report No.: 110486GLP, Not Published	Y (New/First)	Task Force
A6.1.5/01	Daamen, P.A.M.	1994	Assessment of contact hypersensitivity to warfarin technical in the Albino Guinea pig (Maximization-Test)NOTOX, s'Hertogenbosch, NL, Report No.: 110497GLP, Not Published	Y (New/First)	Task Force
A6.2.1/01	Barker, W.M.; Hermodson, M.A.; Link, K.P.	1970	The metabolism of 4-C14-warfarin sodium by the ratJ. Pharm. Exp. Ther. 171, 307-313, Not GLP, Published	N	
A6.2.1/03	Breckenridge, A.; L'E Orme, M.	1972	The plasma half lives and the pharmacological effect of the enantiomers of warfarin in ratsLife Sci. 11, 337-345, Not GLP, Published	N	
A6.2.2/01	Leuschner, J.	1999	Absorption study of 14C-labelled warfarin by topical administration for 6 or 24 hours in Sprague-Dawley ratsLPT, Hamburg, Germany, Report No.: 11687/98GLP, Not Published	Y (New/First)	Task Force
B3.1/01	Braun, H.-J.	2004	Written communication, Vetyl-Chemie GmbH, Not GLP, Not Published	Y (New/First)	Task Force
B3.6/01	Wilfinger, W.	2004	Relative density of the solid bait "Tox-Vetyl Festköder"GAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20041109/01-PCTDGLP, Not Published	Y (New/First)	Task Force
B3.7/02	Wilfinger, W.	2004	Interim Report: Physico-chemical properties of the solid bait "Tox-Vetyl Festköder" before and after accelerated storage at 30 C for 18 weeks and 40 C for 8 weeksGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20041109/01-PCASGLP, Not Published	Y (New/First)	Task Force
B3.7/03	Wilfinger, W.	2004	Physico-chemical properties of the solid bait "Tox-Vetyl Festköder" when stored in commercial packaging material over a period of 2 years at 20 C - starting date reportGAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20041109/01-PCTYGLP, Not Published	Y (New/First)	Task Force
B4.1/01	de Ryckel, B.	1999	Validation of an analytical method for the determination of warfarin content in three types of formulationDepartement de Phytopharmacie, Belgium, Report No.: EBRC/P.J./B.A. 9297/Ch.1696-1698-1701/1998/211GLP, Not Published	Y (New/First)	Task Force

Section No / Reference No	Author(s)	Year	Title. Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
B4.1/02	Wilfinger, W.	2004	Development and validation of an analytical method for the determination of the content of active ingredient in the solid bait "Tox-Vetyl Festköder"GAB/IFU, Niefern-Öschelbronn, Germany, Report No.: 20041109/01-PCVEGLP, Not Published	Y (New/First)	Task Force
B6.6/01	Sendor, T.	2004	Estimation of human exposure to Warfarin from application of "Tox-Vetyl Festköder" wax blockEBRC Consulting GmbH, Hannover, Germany, 07.02.2004, 16 p., Not GLP, Not Published	Y (New/First)	Task Force
B7.1/01	Sendor, T.	2004	Estimation of environmental exposure to Warfarin following application of "Tox-Vetyl Festköder" -EUBEES calculations-EBRC Consulting GmbH, Hannover, Germany, 14.02.2004, 8 p., Not GLP, Not Published	Y (New/First)	Task Force
B7.1/02	Sendor, T.	2004	Estimation of predicted environmental concentrations of Warfarin following application in sewage systems -EUSES report-EBRC Consulting GmbH, Hannover, Germany, 16.02.2004, 23 p., Not GLP, Not Published	Y (New/First)	Task Force