Section A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)			Official use only
5.1	**Function (IIA5.1)**	Rodenticide PT 14	
5.2	**Organism(s) to be controlled and products, organisms or objects to be protected (IIA5.2)**		
5.2.1	**Organism(s) to be controlled (IIA5.2)**	Rats and mice *Rattus rattus* (black rat, ship rat) *Rattus norvegicus* (brown rat, Norway rat) *Mus musculus* (house mouse) *Mus domesticus* (house mouse) Organisms are widespread throughout European continent and are common to all countries in EC.	
5.2.2	**Products, organisms or objects to be protected (IIA5.2)**	Humans, animals, food and feedingstuffs and property to be protected	
5.3	**Effects on target organisms, and likely concentration at which the active substance will be used (IIA5.3)**		
5.3.1	**Effects on target organisms (IIA5.3)**	Signs of poisoning in rodents and other mammals are those associated with an increased tendency to bleed leading ultimately to profuse haemorrhage. After feeding on bait containing the active ingredient for 2 – 3 days the animal becomes lethargic and slow moving. Signs of bleeding are often noticeable and blood may be seen around the nose and anus. As symptoms develop the animal will loose its appetite and will remain in its burrow or nest for increasingly long periods of time. Death will usually occur within 4-5 days of ingesting a lethal dose and animals often die out of sight in their nest or burrow.	x
5.3.2	**Likely concentrations at which the A.S. will be used (IIA5.3)**	The standard concentration at which the second-generation anticoagulants including difenacoum are typically used in ready for use baits is 0.005% w/w. This concentration has been standardised over the last 25 years as the optimal concentration to deliver the benefits of the active substance. Difenacoum is inherently not very palatable and at concentrations above 50 ppm there is a risk that it can be detected by the target species. Difenacoum, even at 50 ppm, is, in practice, multi-feed products and if this concentration was lower then the time to control the target population would be extended to several weeks or even months, which is unlikely to be acceptable where there is a rodent population that needs to be controlled for public health reasons. A disadvantage of reducing the concentration is that it takes longer to accumulate a lethal dose in the target species such that moribund rodents containing residues of the anticoagulants will be active above ground over a longer period. Because of the poisoning effects of general lethargy these are likely	

Section A5 Effectiveness against target organisms and intended uses

		to be the individuals targeted by predators. Maintaining and perhaps limiting the use rate at 50 ppm ensures a lethal dose is quickly ingested and death also follows quickly such that "sick" rodents are available for predators to pick-up for the shortest possible period.	
5.4	**Mode of action (including time delay) (IIA5.4)**		
5.4.1	**Mode of action**	Difenacoum is vitamin K antagonist. The main site of its action is the liver, where several of the blood coagulation precursors undergo vitamin K dependent post translation processing before they are converted into the respective procoagulant zymogens. The specific point of action is thought to be the inhibition of K_1 epoxide reductase. Difenacoum accumulates and is stored in the liver until broken down. The plasma prothrombin (procoagulant factor II) concentration provides a suitable guide to the severity of acute intoxication and to the effectiveness and required duration of the antidoting therapy (vitamin K_1).	
5.4.2	**Time delay**	Within 24 hrs	x
5.5	**Field of use envisaged (IIA5.5)**	MG03: Pest control PT 14	
		The product is intended for use in domestic, industrial and commercial buildings including farm buildings. Use within sewers is restricted to professional users. For rats each bait box will contain up to 10 20 gram blocks. A mouse box will only contain max two 20 gram bait block. Boxes for mice should be placed 5 metres apart, although this can be reduced to 2 metres in areas of high infestation and for rats boxes should be 10 metres apart or to 5 metres apart in high infestation areas. –All distances are perimeter distances around the protected building or area. Boxes should be checked frequently and carcasses removed. Operators should search for all rodent bodies in and around the baited area for disposal. Bait boxes should be removed, in a typical campaign, 6 weeks after initial placement. Wax block baits were chosen as the representative product over, cut wheat, whole wheat, paste bait and pellets. All of these product types have the same active ingredient content. All of the formulation types are available for the general public to use. Bait may be supplied to both professional users and the general public, either as loose bait to refill covered bait points or lockable tamper-proof bait boxes or as pre-baited sealed bait boxes. Additionally, the wax block baits are the only baits that can be used in sewers. In all the other use scenarios, the risks will be similar as the use guidelines are similar. Choosing between dermal and inhalation exposure as the second major route, is justified by the lack of respirable particles in any of the products. Please see the letter reporting the Analysis of Dust Content in Formulations of PelGar Rodenticide, which reports that no material residues from whole wheat, pellets and wax block packaged products passed through a 0.75 mm sieve. The cut wheat product is made from a supply of clean cut-wheat that doesn't contain husks or other smaller particles, and will therefore not	x

		present an inhalation hazard either. Hence, the choice of the dermal route as the second route of exposure. Considering the potential dermal exposure from each product type, the wax blocks represent the greatest risk of exposure dermally, when applied as instructed, as all the other products are supplied with a scoop for the application of the product, whereas the wax blocks are placed by hand. As the wax block product presents the greatest likelihood of dermal exposure, and covers all proposed uses of difenacoum baits, including use by the general public and use in sewers, it was considered appropriate to use this product type as the representative product.	
5.6	**User (IIA5.6)**		
	Industrial	Manufacture of baits from a master mix concentrate, typically 2.5% w/w a.i.	x
	Professional	In and around buildings including domestic, commercial industrial and institutional; sewers, drains and culverts.	x
	General public	Amateur use proposed, in and around buildings including domestic buildings, drains and culverts.	x
5.7	**Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA5.7)**		
5.7.1	**Development of resistance**	Resistance to the first generation anticoagulants has been widely reported in both *Rattus norvegicus* and *Mus domesticus* since the late 1950's. The incidence of resistance to first generation anticoagulants in areas in which it is established is commonly 25-85%. Some degree of resistance to difenacoum has been reported in the UK and Denmark and other European countries but this is usually only found in certain populations of rodents highly resistant to first generation anticoagulants (Greaves et al., 1982; Lund, 1984; MacNicoll and Gill, 1987). In the UK control failures with the second-generation products are increasingly being attributed to baiting problems rather than physiological resistance (Greaves and Cullen-Ayres, 1988; Quy et al. 1992a,b). Mechanisms of Resistance. The biochemical mechanism of warfarin resistance has been studied in four geographic strains of Norway rat. The mechanism appears to differ in each strain, but in each an altered form of vitamin K-epoxide reductase is involved. In two strains (Welsh and Hampshire) the reductase has both decreased activity and a decreased sensitivity to warfarin inhibition whereas in another two strains (Scottish and Chicago) it is reversibly inhibited by warfarin as compared with irreversible inhibition found in susceptible strains. There is some indication that decreased sensitivity of a second enzyme, vitamin K-quinone reductase, to warfarin inhibition may also be significant in certain strains (Thijssen, 1988; Misenheimer	x

and Suttie, 1990). There appears to be a consensus amongst biochemists that the variants of at least one of these reductases, by their altered affinities for anticoagulants and vitamin K, and supplemented in some cases by subsidiary mechanisms such as faster microsomal clearance of the anticoagulant, are the biochemical basis of resistance in the Norway rat.

Behavioural Resistance

Several elements of behaviour such as neophobia and conditioned or unconditioned aversion to bait can help rodents to avoid ingesting a fatal dose and may explain treatment failures that cannot be accounted for by physiological resistance. The enhancement of such behaviour can constitute a novel defence mechanism and was termed behavioural resistance by Humphries et al. (1992) working with mice. Similarly Brunton et al. (1993) cited enhanced neophobia in the Norway rat as an example of behavioural resistance.

Resistance is of lesser importance when it is low compared to the field dosage rate of the anticoagulant. In the UK a 4x resistance to difenacoum was widely recognised as causing a control problem even though such a low level of resistance would not usually be expected to effect control (Greaves and Cullen-Ayres, 1988). Further studies suggested the presence of behavioural resistance (Brunton et al, 1993). Subsequent investigations indicated that the control difficulty was not due to resistance but to the large size of the infestations and the competing attractions for the rats of cereal stored in the infested area (Quy et al, 1992a,b).

References.

Brunton, C.F.A., Macdonald, D.W. and Buckle, A.P. (1993) Behavioural resistance towards poison baits in Brown rats. *Behavioural Processes.*

Greaves, J. H., Shepherd, D. S and Quy, R. (1982). Field trials of second-generation anticoagulants against difenacoum-resistant Norway rat populations. *Journal of Hygiene, Cambridge* 89, 295-301.

Greaves, J. H. and Cullen-Ayres, P. B. (1988). Genetics of difenacoum resistance in the rat. In ; Suttie, J. W. (ed.) *Current Advances in Vitamin K Research.* Elsevier, Amsterdam, pp. 389-397.

Humphries, R.E., Meeham, A.P. and Sibly, R.M. (1992) The characteristics and history of behavioural resistance in inner-city house mice in the UK. In: Borrecco, J.E. and Marsh, R.E. (eds.) *15th Vertebrate Pest Conference.* University of California, Davis, pp. 161-164.

Lund, M. (1984) Resistance to the second-generation anticoagulant rodenticides. In: Clark, D. O. (ed.) *11th Vertebrate Pest Conference.* University of California, Davis pp 89-94.

MacNicoll, A. D. and Gill, J. E. (1987) The occurrence and significance of rodenticide resistance in the UK. In : Lawson, T. J. (ed.) *Stored Products Pest Control. British Crop Protection Council Monograph No. 37*. BCPC Publications, Thorton Heath, UK, pp. 89-95.

Misenheimer, T.M. and Suttie, J.W. (1990). Warfarin resistance in a

Chicago strain of rats. *Biochemical Pharmacology* 40, 2079-2084.

Quy, R. J. , Shepherd, D. S. and Inglis, I. R. (1992a) Bait avoidance and effectiveness of anticoagulant rodenticides against warfarin- and difenacoum-resistant populations of Norway rats. *Crop Protection.* 11, 14-20.

Quy, R. J., Cowan, D. P., Haynes, P., Inglis, I. R. and Swinney, T. (1992b) The influence of stored food on the effectiveness of farm rat control. In: *Pests and Diseases*. British Crop Protection Council Monograph No. 42. BCPC Publications, Thornton Health, UK, pp. 291-300.

Thijssen, H. H. W. (1988) Warfarin inhibition of vitamin K epoxide reductase of Scottish resistant rats is reversible. In: Suttie, J. W. (ed.) *Current Advances in Vitamin K Research.* Elsevier, Amsterdam, pp 429-434.

5.7.2 Management strategies

A control strategy should be developed both in terms of reducing rodent numbers but also in terms of managing the environments, i.e. Integrated Pest Management (IPM). The three main components are:

1) Habitat management
2) Control of rodent movement through proofing
3) Control of the rodent population using appropriate chemical and physical control measures.

The immediate aim of resistance management is to prevent or retard the development of resistance to a given anticoagulant while, as far as is not counterproductive, permitting its continued use. The ultimate aim is to reduce or eliminate the adverse consequences of resistance.

The use of a suitable arsenal of alternative rodenticides is necessary for the management of resistance. Even out-moded compounds such as zinc phosphide were beneficial when anticoagulant resistance first appeared in the UK. The newer rodenticides to which resistance has not yet developed including the anticoagulants brodifacoum, flocoumafen and difethialone and the non-anticoagulants calciferol and bromethalin, all appear to have a role in resistance management.

A consistent selection differential that places resistant individuals at a disadvantage, large or small, is needed to eliminate resistance. The most practical way to achieve this is first to stop using rodenticides to which the rodenticides are resistant and then to eliminate the resistant population by the exclusive use of non-selective or counter selective control techniques, both chemical and non-chemical.

A contrary strategy is that of withholding or saving effective rodenticides while continuing to use a given anticoagulant until resistance exhausts its usefulness is sometimes put forward as a means of limiting the development of resistance. However it is generally accepted that this strategy is likely to accelerate the development and spread of resistance.

Prevention of Resistance.

The following are considered the most feasible to limit the development of resistance to anticoagulants:

1. Maximum use of non-chemical control techniques.
2. Preferential use of rodenticides and formulations to which resistance rarely develops.
3. Ensure the complete eradication of the target population

Section A5 Effectiveness against target organisms and intended uses

whenever a rodenticide is used.

4. Avoid the use of first generation anticoagulants, to which resistance develops relatively easily.
5. Maintain uncontrolled, susceptible populations in refugia from which emigration can occur.

Anticoagulant Resistance Management Strategy for Pest Management Professionals, Central and Local Government and Other Competent Users of Rodenticides. Technical Monograph 2003. Rodenticide Resistance Action Committee. CropLife International, Brussels, Belgium.

5.8 Likely tonnage to be placed on the market per year (IIA5.8)

See Annex Confidential Data and Information.

Evaluation by Competent Authorities	
Date	8.12.2006
Materials and methods	-
Conclusion	-
Reliability	Not relevant
Acceptability	Acceptable

Section A5 Effectiveness against target organisms and intended uses

Remarks	5.3.1: The dependence of the effect on the concentration is missing. 5.4.2: A clarification is needed. Does 'within 24 hours' refer to the intended effect or onset of symptoms. The time delay for both symptoms and death should be given. 5.6: Industrial production of the active substance or manufacture of rodenticide baits is not biocidal use. 5.6: Agricultural buildings should be added to professional and/or amateur use. 5.7.1: Resistance incidence and resistance factors for difenacoum are missing.
	COMMENTS FROM …
Date	Give date of comments submitted
Results and discussion	Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion. Discuss if deviating from view of rapporteur member state
Conclusion	Discuss if deviating from view of rapporteur member state
Reliability	Discuss if deviating from view of rapporteur member state
Acceptability	Discuss if deviating from view of rapporteur member state
Remarks	