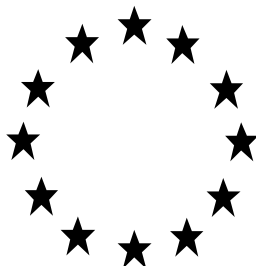


Competent Authority Report
According to Directive 98/8/EC



Bromadiolone (PT14)
The Bromadiolone Task Force

DOCUMENT III-A

Section 5: Effectiveness and intended uses

Rapporteur Member State: Sweden

Final CAR April 2011

Section A5	Effectiveness against target organisms and intended uses	
Subsection (Annex Point)		Official use only
5.1 Function (IIA5.1)	Rodenticide	
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 ; <i>Rattus rattus</i> <i>Rattus norvegicus</i> <i>Mus musculus</i> <i>Mus domesticus</i>	X1
5.2.2 Products, organisms or objects to be protected (IIA5.2)	Humans, animals 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 lose 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.	

Section A5	Effectiveness against target organisms and intended uses	
<p>5.3.2 Likely concentrations at which the A.S. will be used (IIA5.3)</p>	<p>The standard concentration at which the second-generation anticoagulants (including bromadiolone, difenacoum and brodifacoum) 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 and bromadiolone, even at 50 ppm, are, 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 were there is a rodent population that needs to be controlled for public health reasons. In recent years there have been a movement by some formulators (and regulators) to reduce the concentration of brodifacoum to 10 ppm in the final bait. This has potentially serious technical implications since at this level brodifacoum is simply another multi-feed product and the benefit of the single feed kills is lost. This increases the risk of the development of resistance. It would be perhaps preferable to maintain brodifacoum only at 50ppm and limit its use to situations considered “safe”.</p> <p>A disadvantage of reducing the concentration of any of these compounds 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 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.</p>	
<p>5.4 Mode of action (including time delay) (IIA5.4)</p>		
<p>5.4.1 Mode of action</p>	<p>Anticoagulant rodenticides are vitamin K antagonists. The main site of their 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 K₁ epoxide reductase. The anticoagulants accumulate and are 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 K₁).</p>	
<p>5.4.2 Time delay</p>	<p>Within 24 hrs</p>	<p>X2</p>
<p>5.5 Field of use envisaged (IIA5.5)</p>	<p>Include code(s) and term(s)</p>	
<p>MG03: Pest control</p>	<p>Product types PT14; no codes available</p> <p>It is proposed that the active substance will be used as a rodenticide for the control, primarily, of commensal rodent species (<i>Rattus norvegicus</i>, <i>Rattus rattus</i>, and <i>Mus domesticus</i>) by both professional</p>	

Section A5	Effectiveness against target organisms and intended uses	
	and amateur users. The product is intended for use in domestic, industrial and commercial buildings including in and around farm buildings and sewers, but not field use.	
5.6 User (IIA5.6)		
Professional	In and around buildings including domestic, commercial industrial and institutional; sewers, drains and culverts.	
General public	Amateur use proposed, in and around buildings including domestic buildings, drains and culverts.	X3
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	<p>Resistance to the first generation anticoagulants has been widely reported in both <i>Rattus norvegicus</i> and <i>Mus domesticus</i> 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 and bromadiolone 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., 1982a; Lund, 1984; MacNicoll and Gill, 1987). Considerable doubt exists as to the significance of reports of resistance to second-generation anticoagulants and in the UK control failures with the second-generation products are increasingly being attributed to baiting problems rather than physiological resistance (Quy et al. 1992a,b).</p> <p>Mechanisms of Resistance.</p> <p>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 (Misenheimer 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</p>	

Section A5	Effectiveness against target organisms and intended uses	
	<p>rat.</p> <p>This information is relevant to and can be extrapolated for bromadiolone.</p> <p>Behavioural Resistance</p> <p>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.</p> <p>Resistance is of no importance when it is low compared to the field dosage rate of the anticoagulant. In the UK a small but apparently heritable decrease in susceptibility to brodifacoum was detected by means of laboratory tests with bait containing 10 ppm brodifacoum but was not known to have a practical effect on field control when using bait of standard concentration (50 ppm), Gill et al., 1992.</p> <p>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).</p> <p>This information is relevant to and can be extrapolated for bromadiolone.</p> <p>References.</p> <p>Brunton, C.F.A., Macdonald, D.W. and Buckle, A.P. (1993) Behavioural resistance towards poison baits in Brown rats. <i>Applied Animal Behavioural Sciences</i>.</p> <p>Gill, J.E., Kerins, G.M. and MacNicoll, A.D. (1992) Inheritance of low grade brodifacoum resistance in the Norway rat. <i>Journal of Wildlife Management</i> 56, 809-816.</p> <p>Greaves, J. H., Shepherd, D. S and Quy, R. (1982). Field trials of second-generation anticoagulants against difenacoum-resistant Norway rat populations. <i>Journal of Hygiene, Cambridge</i> 89, 295-301.</p> <p>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.) <i>15th Vertebrate Pest Conference</i>. University of California, Davis, pp. 161-164.</p> <p>Lund, M. (1984) Resistance to the second-generation anticoagulant rodenticides. In: Clark, D. O. (ed.) <i>11th Vertebrate Pest Conference</i>. University of California, Davis pp 89-94</p> <p>MacNicoll, A. D. and Gill, J. E. (1987) The occurrence and significance of rodenticide resistance in the UK. In : Lawson, T. J. (ed.) <i>Stored Products Pest Control. British Crop Protection Council Monograph No. 37</i>. BCPC Publications, Thorton Heath, UK, pp. 89-95</p>	<p>X4</p>

Section A5	Effectiveness against target organisms and intended uses	
	<p>Misenheimer, T.M. and Suttie, J.W. (1990). Warfarin resistance in a Chicago strain of rats. <i>Biochemical Pharmacology</i> 40, 2079-2084.</p> <p>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. <i>Crop Protection</i>. 11, 14-20.</p> <p>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 Heath, UK, pp. 291-300</p>	
5.7.2 Management strategies	<p>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.</p> <p>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.</p> <p>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.</p> <p>Prevention of Resistance.</p> <p>The following are considered the most feasible to limit the development of resistance to anticoagulants:</p> <ol style="list-style-type: none"> 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 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. 	X5
5.8 Likely tonnage to be placed on the market per year (IIA5.8)	This information is regarded as commercially sensitive. Please refer to Appendix XIA 'Information claimed as confidential' to review this information	

Section A5	Effectiveness against target organisms and intended uses	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	February 2008	
Materials and methods		
Conclusion	<p>X1: Not all the specified strains have been tested. Efficacy data have been submitted for <i>Mus domesticus</i> and <i>Rattus norvegicus</i>. This is however considered enough to claim efficacy against rats and mice.</p> <p>X2: Death usually occurs within 4-5 days.</p> <p>X3: For non-professionals the use will be in and around buildings.</p> <p>X4: The mechanism for resistance for warfarin may not be identical for bromadiolone.</p> <p>X5: It is recommended that the label states that any instances of resistance are referred to the manufacturer of the a.s.</p>	
Reliability		
Acceptability	The information is acceptable	
Remarks	Table 5.3: The summarised results from laboratory trials with bromadiolone wax block are missing. No field studies have been submitted. The results from the laboratory tests can be found in Doc IIIB 5.10.	

Table 5.3: Summary table of experimental data on the effectiveness of the active substance against target organisms at different fields of use envisaged, where applicable

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*
Include respective code(s) for function type(s) given in section 5.1	Include respective code(s) for product type(s) given in section 5.5	Describe specification if deviating from that given in section 2	Specify species, strain, sex, weight, growth stage etc. as appropriate	Shortly describe test system and application method used in the tests	Shortly describe test conditions including concentrations applied and exposure time	Describe relevant results; quantify the effects on target organisms; indicate the dependence on the concentrations of the A.S. and the possible existence of a threshold concentration. Also describe if results indicate the mode of action and/or the development of resistance.	Only author(s) and year of publication/ report; full bibliographic data in footnote
No codes	No code	Bromadiolone	rats	Field	Field / various	100% control	E1
No code	No code	Bromadiolone	mice	Field	Field / various	100% control	E1

The potency of bromadiolone, a second-generation anticoagulant, again commensal rodents is well documented. It is well known that both formulation type and age of the formulation can affect palatability and potency. This is particularly true in situations where a control programme is being carried out in a situation where there is an excess of highly attractive, alternative foodstuffs for the rodents to feed on. In this situation control can be extremely difficult to achieve simply because the target rodents do not eat the rodenticide bait preferring other foodstuffs in the vicinity. Because of the over-riding importance of palatability in the ultimate effectiveness of a bait it is normal during the development of bait formulations to carry out either laboratory choice tests or field trials to establish their effectiveness in controlling the target species.

Standard test protocols have been developed for the evaluation of baits. Laboratory test guidelines have been issued by the OEPP/EPPO and US EPA. The standard protocol compares the test bait with a highly palatable standard bait formulation for which the detailed composition and storage conditions are clearly laid down (standard EPA meal). The test bait is then considered effective when acceptance by the target species is not significantly less than 33% compared to the standard EPA meal and mortality in the test is not less than 90%.

The Bromadiolone Task Force have carried out extensive laboratory trials on its standard wax block formulation (20g block containing 0.005% w/w bromadiolone). Efficacy reports are presented for the laboratory evaluation of this formulation against *Rattus norvegicus* and *Mus musculus*. The results are summarised below: