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RRAG HOUSE MOUSE RESISTANCE GUIDELINE

1. Introduction

The house mouse (*Mus musculus*) possesses a degree of natural resistance to anticoagulant rodenticides. This means that these chemicals are generally less effective against house mice than they are against Norway rats (*Rattus norvegicus*). However, true resistance to anticoagulants, that conferred by genetical mutation, has been known among house mice in the UK since the 1960s. Resistance is now so widespread it is often said that it is harder to find susceptible house mice than resistant ones. In spite of this, anticoagulants are still widely and successfully used against house mice in the UK.

The study of resistance to anticoagulants in the house mouse has long been a 'poor relation' in comparison to the quantity and quality of available information on anticoagulant resistance in Norway rats. Consequently, there are a number of important unanswered questions about resistance in UK house mice. In particular we remain uncertain about the precise nature of the genetics of the phenomenon and, probably more importantly, no map of the distribution of anticoagulant resistance in house mice has been produced for the whole of the UK, due at least in part to its assumed widespread occurrence.

In Germany, a study of the distribution of resistance in house mice has been conducted using DNA sequencing for the detection of anticoagulant resistant mutations. It revealed that resistant house mice are very widespread and frequent in Germany. More than 90% of the mice examined carried genetical resistance mutations and resistance was found at 29 of the 30 locations sampled. The two resistant house mouse strains found in the German study are also known to be present in the UK. As expected, these two strains of mice have been seen at a similarly high frequency in the UK, however genetic samples have mainly come from London so far.

A study recently published from Ireland detected a high frequency of resistance in house mice in that country, and both mutations commonly found in the UK were also found in Ireland.

Figure 1. The House mouse (*Mus musculus*) is a common pest in the UK

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Produced by the Rodenticide Resistance Action Group

This Guideline has been produced by the Rodenticide Resistance Action Group of the UK to provide a summary of the information we now have available on anticoagulant resistance in house mice and to promote the effective use of anticoagulants, and alternative methods of control, against this ubiquitous and very troublesome pest.

You can find our more about RRAG at www.bpca.org.uk/RRAG.

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2. Taxonomy

The taxonomy of genus *Mus* is still not entirely clear, with taxonomists unable to agree the allocation of species and sub-species names. Recently, the general direction seems to be a reduction in the number of recognised species. The Commonwealth Agricultural Bureau International (CABI) 'Invasive Species Compendium' provides an up-to-date genetical evaluation of the genus *Mus*. The genus comprises four subgenera – *Pyromys*, *Coelomys*, *Mus* and *Nannomys*. Among 8 true species within the subgenus *Mus*, it is the distinct subspecies of *Mus musculus*, M. m. *domesticus*, which occurs in the UK. This will be referred to as simply *Mus musculus* throughout this guideline. For more information on the biology and taxonomy of the house mouse please see 'Further Reading'.

3. Definitions of resistance

The following general definition of anticoagulant resistance was proposed in 1994 by Dr John Greaves, is now widely used and can be appropriately applied to *Mus musculus*.

"Anticoagulant resistance is a major loss of efficacy in practical conditions where the anticoagulant has been applied correctly, the loss of efficacy being due to the presence of a strain of rodent with a heritable and commensurably reduced sensitivity to the anticoagulant".

Some other terms are also used in relation to the resistance phenomenon:

- *Resistance factors* – the factor by which the dose of rodenticide required for a susceptible rodent population must be multiplied to achieve the same affect in a resistant rodent population.
- *Technical resistance* – this term is used in cases where resistance tests identify resistance but where resistance factors for a given anticoagulant are low and the resistance is likely to have no observable practical effect.
- *Practical resistance* – this term is used in cases where resistance tests identify resistance and resistance factors for a given anticoagulant are sufficiently high so that an acceptable level of control is unlikely to be achieved when products containing the anticoagulant are used in practice.
- *Metabolic resistance* – this applies where a physiological change, not directly associated with a major resistance gene, confers a degree of resistance. An example is enhanced elimination of anticoagulants by enzymes of the cytochrome P450 group.

4. Tolerance, natural "resistance" and the early anticoagulants

The first anticoagulant extensively tested against house mice was warfarin. Groups of anticoagulant-naïve mice in the laboratory were offered, without choice, 0.025% warfarin bait. Mortality was recorded and is shown in Table 1. It is apparent that, although a substantial proportion of house mice were killed when they consumed bait for 10 days, complete mortality of house mice was not obtained unless the animals fed on warfarin bait for periods longer than that.

The data were used to calculate a series of values for the toxicity of warfarin expressed as lethal feeding periods (LFP). These are defined as a number of days of continuous, no-choice feeding required to kill a given percentage of the mice tested. For example, the LFP_{50}, LFP_{90} and LFP_{99} were calculated, and these values are analogous to the more well-known LD_{50}, LD_{90} and LD_{99} which are based on lethal doses. The analysis revealed that the LFP_{50} for 0.025% warfarin for house mice was 4.8 days and the LFP_{99} was 29.5 days. These results, in comparison with similar results obtained for Norway rats (*Rattus norvegicus*) whose LFP_{50} and LFP_{99} are 1.7 and 5.8 days respectively, showed that house mice possess a remarkable degree of tolerance to warfarin. This does not conform to the definition of resistance given above and is sometimes known as tolerance or "natural resistance".

We also know that the feeding behaviour of house mice is such that they often do not feed consistently from any single food source and this characteristic would make it even less likely that warfarin would be fully effective against house mice.

Research on anticoagulants continued after the invention of warfarin. Other compounds, such as coumachlor, diphacinone, chlorophacinone and coumatetralyl came to the market. However, it is generally accepted that none of these perform significantly better than warfarin against house mice.

Table 1. Mortality of house mice after unrestricted no-choice feeding on 0.025% warfarin baits for different numbers of days. (From Rowe and Redfern, 1964, *Journal of Hygiene, Cambridge* 62: 389-393.)

No. of days feeding	Mortality	Range of days to death
4	6/30	4-23
5	16/35	3-30
6	23/33	3-10
7	36/46	3-13
8	35/41	4-14
10	31/37	4-12
14	41/45	4-30
18	12/12	2-17
21	48/53	3-20
28	13/13	4-10

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5. Resistance to first-generation anticoagulants

In 1961, just ten years after the introduction of warfarin, reports were received of the failure of this compound to control mouse infestations from a number of widely separated locations in the UK. A resistance test was developed in which survival after 21 days of continuous feeding on 0.025% warfarin bait was considered to be indicative of resistance. Using this test, the presence of warfarin resistance was confirmed in mouse infestations from many parts of the UK. Tests of diphacinone and chlorophacinone against mice that had survived the 21-day warfarin resistance test showed that these compounds did not provide a solution to warfarin resistance in mice.

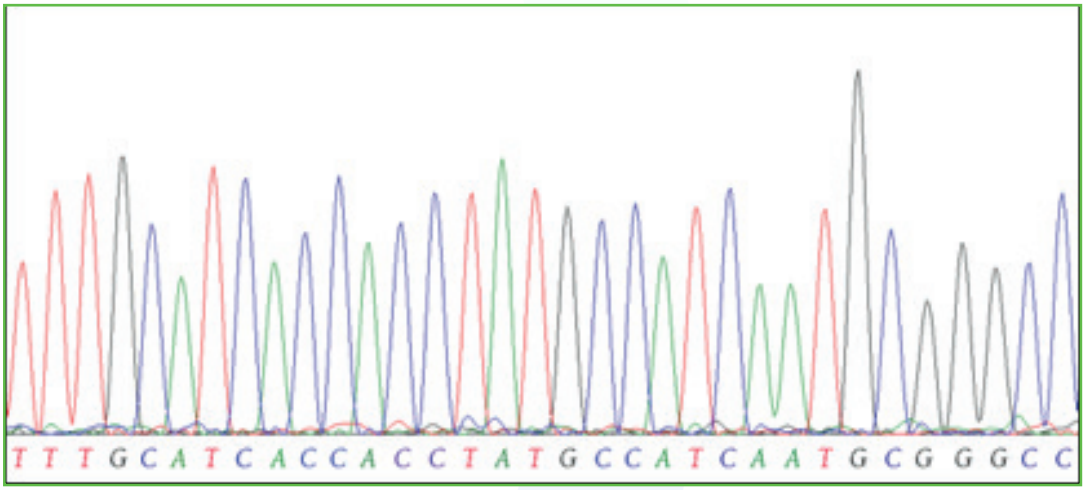
Some time later, a population of resistant house mice was discovered in Cambridge. These had a distinctive coat colour and it appears that the gene for this attribute was linked to that of resistance. These 'Cambridge Cream' mice were held in the laboratory and much subsequent assessment of the activity of anticoagulants against resistant house mice relied on tests on the progeny from this original breeding stock.

6. Resistance to second-generation anticoagulants

The second-generation anticoagulants were developed with the express purpose of controlling resistant rodents. Difenacoum and bromadiolone were the first active substances to be tested against resistant house mice. Laboratory tests showed a useful level of activity of these compounds and both appeared to be substantially more effective than warfarin. Two days of no-choice feeding of 0.005% difenacoum resulted in 87% mortality and ten days of similar testing of bromadiolone gave 80% mortality. Subsequently, a series of pen tests was carried out using families of warfarin-resistant house mice and field trials against natural infestations were also conducted.

A result observed in these trials was the frequent inability of difenacoum and bromadiolone to provide complete control, both in the case of resistant family groups in pen tests and of wild infestations in the field. Indeed, mice survived in five of the 12 field trials conducted. These survivors were removed to the laboratory and later offered either 0.005% bromadiolone or difenacoum for 21 days. Respectively 43% and 18% of the mice survived in these bromadiolone and difenacoum tests. These results appeared to show that some mice, substantially resistant to bromadiolone and difenacoum, were present in field infestations even before these two compounds came into widespread use in the UK. It is not clear whether this was just another manifestation of tolerance or whether resistance mutations were already present in some mouse populations, although it is likely that the latter was true. The tests also showed that, for whatever reason, control was likely to be more problematic in the case of bromadiolone than difenacoum and this has subsequently proved to be the case.

Two more second-generation anticoagulants, brodifacoum and flocoumafen, were subsequently introduced and these were shown to be substantially more potent than bromadiolone and difenacoum against house mice. In the laboratory, complete mortality of resistant house mice was achieved with both these compounds after both one- and two-day periods of no-choice feeding. Six field trials of brodifacoum



DNA sequence traces like this one are used to determine the genetic resistance status of house mice

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against wild house mouse infestations resulted in an average of 98.8% control and ten of flocoumafen gave an average of 97.2% control.

An advantage of these two compounds for resistant house mouse control is that only small quantities of bait are required to achieve a lethal dose, even of resistant mice, and this characteristic is important for house mice because of their sporadic feeding behaviour.

7. The genetics of anticoagulant resistance in House mice

The genetics of anticoagulant resistance in the house mouse is not well understood. It was initially thought that resistance in mice was similar to that in Norway rats, there being a single gene governing anticoagulant resistance. However, the outcome of classical genetical breeding studies failed to confirm this and it may be that house mouse resistance is complicated by the involvement of several genes, and perhaps even several different resistance mechanisms, including metabolic resistance.

Since the early genetical studies, a very limited amount of research work has been done on house mouse resistance in the UK. However, a major advance was made in the science of anticoagulant resistance with the development of a method by which it is possible to examine the genetic make-up of individual rodents and to discover whether they possess mutated genes that might confer anticoagulant resistance. Some samples of UK house mice have been studied in this way and two different genetic mutations have been found. The first mutation is the one occurring in the Cambridge Cream resistance strain, held at the Central Science Laboratory (no longer operational), that has been used in resistance research in the UK since the 1980s. This is known as the leucine128serine mutation, or may be referred to by its abbreviated name L128S. It is likely that this mutation occurs widely in the UK, as it does in Germany.

In the 1990s, a population of resistant mice was discovered in the Reading area and studies were conducted on them which resulted in the development of a pure laboratory strain of resistant house mice. The mutation later found in this strain was tyrosine139cysteine (or Y139C). Once again, this resistance mutation was found in the geographical survey of resistance conducted recently in Germany. This strain is considered to be fully resistant to the first-generation anticoagulants and to the second-generation compound bromadiolone.

Additionally, a distribution map of mouse resistance has been produced for the UK (Prescott et al. 2018), although the tissue samples collected to date are mainly from the Greater London area and a few neighbouring counties. The two known strains were identified at similar frequency (50.9% L128S and 47.2% Y139C) and over 88% of the samples analysed had one or both of these resistance mutations. This indicates a very high degree of selection for anticoagulant resistance in the house mice that were sampled. There were a few mice that possessed both L128S and Y139C mutations.

Thus, we can say with reasonable certainty that we have in the UK at least two different house mouse resistance mutations in the UK. Little is known of their wider geographical distribution and there are few studies of the degree of resistance that these mutations confer. But both confer a degree of practical resistance to anticoagulants including, in the case of mice carrying the Y139C mutation, resistance to at least one of the second-generation compounds.

8. Recommended use of anticoagulants against resistant house mice

The first-generation anticoagulants

It has long been a regulatory policy that anticoagulants such as warfarin, chlorophacinone, diphacinone and coumatetralyl should not be used for the control of house mice in the UK. However, this decision has been qualified and there is now a coumatetralyl UK product authorisation for a foam formulation containing a high concentration of coumatetralyl which permits use against mice.

Anticoagulant rodenticides are reviewed under the rules of the Biocidal Products Regulations (BPR), both in the UK and across the European Union (EU). Proof of efficacy is required in order to obtain product authorisations. The successful completion of laboratory choice tests, in which at least 90% mortality is obtained, together with demonstrable efficacy in pen trials or field evaluations is likely to be sufficient to obtain product authorisations in the European Union, and consequently in the UK. It is possible to obtain such evidence of efficacy for first-generation anticoagulants when using susceptible strains of mice. Resistant strains of mice are only needed if a resistance claim is to be made. However, “resistance claims must be considered on a case by case basis in discussion with the Member States” (ECHA 2018).

Despite the permitted use of a foam formulation of coumatetralyl in the UK it is the advice of RRAG that first generation anticoagulants more generally should not be used for the control of house mice. This is because the occurrence of resistance to them would be likely to render them ineffective and because the use of these substances is likely to increase the severity and spread of resistance among house mice.

Bromadiolone and difenacoum

We know that one of the two strains of resistant mice present in the UK (Y139C) shows a significant degree of resistance to bromadiolone. There are also many anecdotal reports of the failure of bromadiolone to control house mice. While it is likely that some infestations may be controlled, at least in part, by applications of bromadiolone, the use of this active substance against house mice

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Table 2.

ED_{50} and ED_{99} values, derived from blood clotting response tests, for the second-generation anticoagulants against anticoagulant-susceptible house mice. (From Prescott et al., 2009, *International Journal of Pest Management* 53(4): 265-272.)

		Mean effective dose (mg/kg^{-1})				
Sex	Effective dose	bromadiolone	difenacoum	difethialone	flocoumafen	brodifacoum
Male	50%	1.96	0.85	0.83	0.51	0.39
	99%	2.72	1.27	1.46	0.74	0.51
Female	50%	1.68	0.56	0.83	0.44	0.35
	99%	1.87	0.84	1.46	0.63	0.46

in UK is not recommended as it may not result in an adequate level of control and will exacerbate resistance problems.

The situation of difenacoum is more equivocal. This active substance is widely used in successful mouse control treatments. However, mice carrying the Y139C mutation possess a degree of resistance to difenacoum. The situation with L128S is more uncertain. What is certain, however, is that 30 years ago some individuals within mouse infestations were practically incapable of control with difenacoum baits, and it is unlikely that this situation has improved in the intervening period. It would therefore be prudent, in areas where resistance in house mice is suspected, not to use products that contain difenacoum.

Brodifacoum and flocoumafen

Studies on the intrinsic activity of the second-generation anticoagulants, measured as the dose of anticoagulant that produces an effect, i.e. effective dose (ED), demonstrate that brodifacoum and flocoumafen are the most potent active substances against susceptible house mice (Table 2). There is also good evidence from early field studies that brodifacoum and flocoumafen are effective against anticoagulant-resistant house mice. Furthermore, laboratory studies conducted on mice carrying the Y139C mutation at the University of Reading have confirmed that brodifacoum baits are effective against this type of resistant house mouse.

Currently, there are no anecdotal reports of the failure of either of these compounds to control infestations of house mice in the UK. Therefore, products containing brodifacoum and flocoumafen should be the rodenticides of choice when carrying out control treatments against house mice in the UK. This is because they offer the promise of the highest levels of control and are the least likely to result in anticoagulant-resistant mice surviving treatments.

Baits containing brodifacoum, difethialone and flocoumafen in the UK had previously carried a restriction on their use to “indoors” only. In 2017, these restrictions were revised and now these compounds can be used “in and around buildings”. Generally, house mouse infestations are known to live and feed predominantly indoors and this allows the use of brodifacoum and flocoumafen baits to be used against them indoors with limited risk to non-target wildlife.

Some reports have been published, however, on studies conducted in Denmark and Canada that show a reduced susceptibility to brodifacoum of some house mouse populations, although no information is available on the nature of any resistant mutations that may be present. It would be useful, therefore, if practitioners using brodifacoum and flocoumafen for house mouse control were on the alert for infestations that are more difficult to control than normal using products that contain these active substances. These should be reported to RRAG if they are discovered.

Difethialone

Baits carrying the second-generation anticoagulant difethialone are relatively new to the market in the UK. Literature produced by the manufacture claims that there is ‘no known resistance in mice’. Such claims, however, fall short of proof that difethialone is effective for the practical control of resistant house mice and RRAG is aware of no difethialone field trials conducted in the UK against these animals.

The study mentioned earlier on the potency of difethialone and the other second-generation active substances against anticoagulant-susceptible house mice (Table 2) showed that difethialone falls somewhere between bromadiolone and difenacoum in terms of intrinsic activity. It should be held in mind,

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however, that difethialone baits contain 0.0025% of the active substance, while those carrying brodifacoum and flocoumafen contain twice that concentration, namely 0.005%.

Low- strength baits

Recently some manufacturers have introduced products that contain lower concentrations of the active substances than have been used in the past. These so-called "low-strength baits", containing less than 30 ppm of the anticoagulant active substances, are available both to the general public and to professional pest control practitioners having the advantage that they not labelled "toxic to reproduction". In use scenarios where this classification is not a significant factor, formulations containing the highest available concentration of an active substance should always be used because resistance in house mice, conferred by the Y139C and L128S mutations, is apparently widespread. The use of full-strength baits will ensure that treatments are conducted quickly and efficiently, and the risk of partial treatment failure will not increase the severity of resistance and promote its spread.

9. Other resistance management measures

A range of alternative measures is available by which anticoagulant resistance in house mice may be combated.

Habitat modification is an essential component in any balanced rodent control strategy. This includes the removal of foodstuffs that might sustain mouse infestations, the prevention of ingress into structures by use of proofing measures and the denial of harbourage. However, those who engage in practical mouse control know how difficult it is to implement these measures thoroughly to prevent infestation. House mice are capable of living from very limited food resources. They are also adept at getting into buildings through very small apertures and finding harbourage where none appears to exist. So, while all these measures always require consideration and often implementation, none is likely to preclude mouse infestation and is still less likely to remove existing infestations of house mice.

Unlike rats, house mice generally do not exhibit strong aversion to novel objects ('neophobia'). Therefore, in most circumstances, house mice are readily trapped. Trapping is a very useful tool in the control of mouse infestations, particularly where the operator has a good level of experience and skill and, when the infestation is substantial, large numbers of traps can be deployed.

Some non-anticoagulant rodenticide active substances are available in the UK for the control of house mouse infestations. The use of the narcotising/sedative agent alphachloralose may provide good control of house mice, although it is known that efficacy can be adversely affected as ambient temperatures increase. Baits nominally have an active ingredient content of 4% and are restricted to indoor use (which is a minor consideration in most circumstances for house mouse control). Also, carbon dioxide is dispensed as a gas within a proprietary trapping device against mouse infestations indoors.

More recently, rodenticide baits containing the active substance cholecalciferol has been authorised for use against house mice in the UK. Cholecalciferol, otherwise known as vitamin D3, exerts a rodenticidal effect by disrupting calcium metabolism when consumed by rodents in baits that contain 0.075% of the active substance. Baits are authorised for use by professionals (i.e. those able to prove competence according to the requirements of the UK Rodenticide Stewardship Regime, see: https://www.thinkwildlife.org/training-certification/) and can be applied both indoors and outdoors around buildings (i.e. in and around buildings). Cholecalciferol is also authorised for use in permanent baiting.

The use of these alternative measures carries the very important benefit that they do not select for the anticoagulant resistance genetic trait because they act equally effectively against both susceptible and resistance house mice. Their use within a wider strategy of the control of house mice will serve to prevent the spread of anticoagulant resistance in house mice, as well as the removal of resistant infestations in some favourable situations.

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Appendix

Rodenticide Resistance Action Group: Classification of Active Substances for Resistance Management

The use of ONLY effective active substances against resistant infestations of house mice and Norway rats has important benefits:

(1) Rodent infestations are controlled quickly and efficiently.

(2) The spread and increases in severity of resistance are prevented.

(3) Unnecessary and often high emissions to the environment of rodenticide active substance are avoided.

The classification of rodenticide active substances that are authorised in the UK given below will help users to decide which active substances to use when they encounter resistant rodent infestations.

Group		Sub-Group		Compounds	Recommended uses
1	Anticoagulants	A	FGAR	warfarin, coumatetralyl	For use against Norway rats when there is no resistance to anticoagulants.
		B	SGAR	bromadiolone, difenacoum	For use against Norway rats when there is no resistance to anticoagulants, and against rats carrying mutations (L128Q and Y139S).
		C	SGAR	brodifacoum, difethialone, flocoumafen	For use against house mice, and all strains of resistant rats (L128Q, Y139S, L120Q, Y139C, Y139F).
2	Calciferols	-	-	cholecalciferol	Recommended against house mice, and all strains of rats.
3	Narcotics	-	-	alphachloralose	Recommended for control of all strains of house mouse.
4	Gases	-	-	carbon dioxide, aluminium phosphide, hydrogen cyanide	Specific applications by trained professionals only. Species restrictions may apply.

FGAR - first-generation anticoagulant rodenticide; SGAR - second-generation anticoagulant rodenticide

General guidance:

- Always know the name of the active substance you are using and follow the instructions on the product label.
- The use of full-strength baits (i.e. containing 50 ppm if it is a Group 1B and 1C active ingredient) will ensure that treatments are conducted quickly and efficiently, and the risk of partial treatment failure will not increase the severity of resistance and promote its spread.

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