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## Anticoagulant Resistance in the United Kingdom



# History of resistance

Anticoagulants were introduced into the United Kingdom in the early 1950s. Their introduction revolutionized rodent control, providing a far more effective method of controlling rodents compared with the previously available acute rodenticides.

The acute rodenticides (zinc phosphide, alpha-naphthylthiourea, 1080, 1081, thallium) were relatively inefficient as a result of their poor palatability, fast action (mins/hours) and relatively painful impact. Many rodents, either failed to eat the baits or only consumed sub-lethal doses. Those that survived sub-lethal dosing often acquired bait and poison shyness, avoiding further attempts to poison them. Even with pre-baiting it was not easy to average more than 70% mortality in practical situations.

The introduction of warfarin and subsequently other anticoagulants provided a far more effective means of controlling rodent infestations and if applied correctly, 100% mortality could be expected. This increased efficiency was due to the chronic nature of anticoagulants. They were generally far more palatable than the acute rodenticides as they used much lower concentrations of active substance and they had a much slower mode of action and slower onset of symptoms (average time to death 6-7 days). The symptoms were also less painful than those of the acute rodenticides. Due to this, the rodents were not generally aware that they were being poisoned and could continue to feed over several days. This made it far easier to deliver a lethal dose and achieve higher levels of mortality. By the end of the 1950s a number of anticoagulants in addition to warfarin had been introduced to the U.K. market, these included chlorophacinone, diphacinone and coumatetralyl.

Unfortunately, just a few years after these



**above:** Rodents are carriers of at least 45 diseases and 200 human pathogens.

products were launched populations of Norway rats (*Rattus norvegicus*) and House mice (*Mus musculus*) had developed resistance to these early anticoagulants and could consume considerable amounts of bait and survive. These rodents were termed Warfarin-resistant rodents, although a high level of cross resistance existed between all these early anticoagulants.

The spread of resistance stimulated the commercial search for new and more effective anticoagulant rodenticides to which there was no resistance and in the early 1970s difenacoum appeared on the market, soon followed by bromadiolone. At the time of their introduction they were considered to be effective against populations of rodents known to be resistant to the early anticoagulants. To differentiate these new anticoagulants from the older anticoagulants, the term "Second Generation Anticoagulants (SGARs)" was used to describe them

and the term "First Generation Anticoagulants (FGARs)" used to identify the earlier anticoagulants.

In the 1980s and 1990s further SGARs appeared in the U.K. market, these were brodifacoum, flocoumafen and most recently difethialone. By the late 1970s, populations of Norway rats were identified as resistant to difenacoum and also later to bromadiolone. These populations were initially particularly evident in central southern England, but this may reflect sampling patterns.

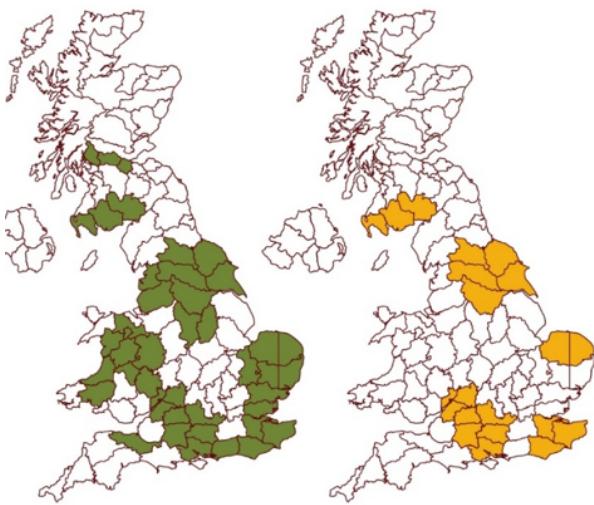
Over the years the resistance to all of the FGARs and to difenacoum and bromadiolone has become more extensive. For a review of the extent of Norway rat resistance in the U.K. see the map in Figure 1. However, the most recent data obtained from genetic analysis can be seen in Figure 2. No resistance to brodifacoum, flocoumafen or difethialone has been identified in the U.K.

## Norway rat resistance to anticoagulants

Where, over 40 years of monitoring, resistance has been recorded at some time to:

first generation rodenticides

second generation rodenticides difenacoum or bromadiolone



Shading does not imply that all rodents in these areas have resistance, nor does lack of shading imply that there is no resistance, as testing may not have been carried out.

There is no evidence of resistance to brodifacoum, difethialone or flocoumafen.

Continuing evidence emerges that the extent of resistance to first and second generation anticoagulants may be more extensive than illustrated. For the latest information on rodenticide resistance, see [www.banca.org.uk/rfrag](http://www.banca.org.uk/rfrag)

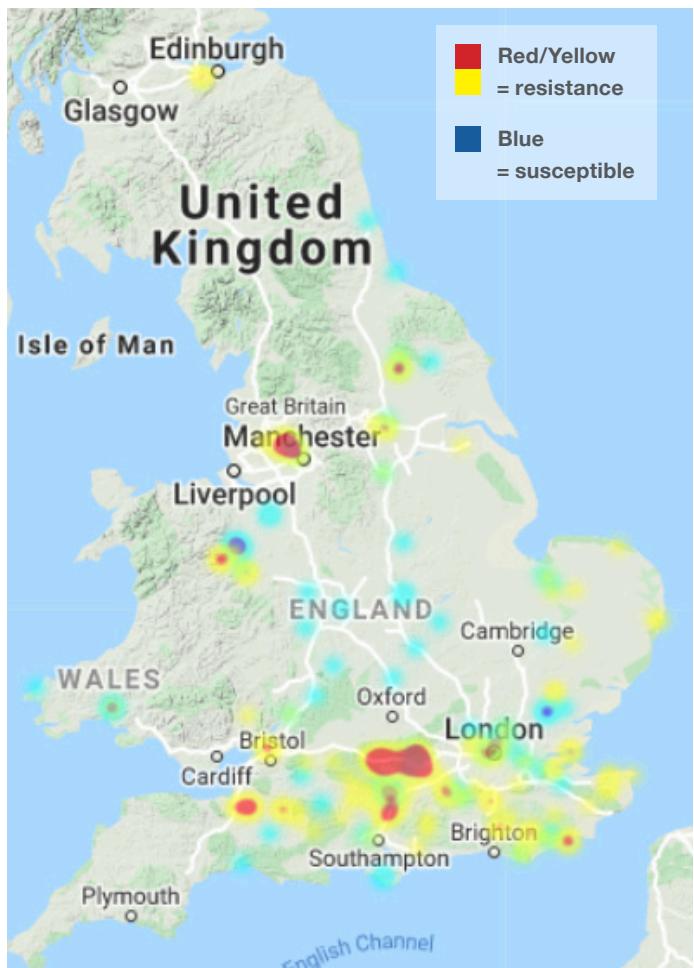


Figure 1:

Norway rat resistance within the U.K. as obtained from the Rodenticide Resistance Action Committee: [www.rrac.info](http://www.rrac.info)

Figure 2:

Norway rat resistance within the U.K., determined by genetic analysis, as obtained from the Rodenticide Resistance Action Committee: [www.rrac.info](http://www.rrac.info)

## Impact of resistance

In the early stages of resistance development in a rodent population, when heterozygous resistant individuals are first appearing, control treatments can fail and damage a technician's reputation. Identifying resistance as the reason for failure is often difficult as resistance testing is expensive and not readily available. Persistent treatment of populations that are resistant to the anticoagulant being used is expensive in terms of labor and materials and control cannot be achieved. The rodents will continue to cause damage and spread disease.

Additionally, continued treatment of these populations with the anticoagulants to which they are resistant leads to continued selection

for resistance, as over time homozygous resistant individuals begin to become more prevalent. Finally, when these resistant individuals emigrate to other areas it leads to the spread of resistance.

Frustration at the failure to achieve control may lead to less safe use of anticoagulants and over-baiting. This increases environmental risk. In resistant populations, the long term, extended use of anticoagulant baits increases the risk of non-target access to the anticoagulants and damage/contamination to the human food chain. In addition, the ongoing consumption of anticoagulants by resistant rodents increases their anticoagulant load and leads to the risk of the contamination of

the food chains of scavengers and predators.

The CRRU guidelines recommend that the less hazardous anticoagulants are used preferentially.

**Heterozygote resistant individuals have one allele for resistance and the other for susceptibility.**

**Homozygote resistant individuals have both alleles for resistance.**

## Managing resistance with Selontra® rodent bait

To control anticoagulant resistant rodents and to reduce the growth potential of resistance in the U.K. and elsewhere, non-anticoagulant rodenticide bait such as Selontra® should be considered as a first choice in most situations.

- The mode of action is fundamentally different to the anticoagulants and will not lead to potential continued selection for anticoagulant resistance.
- The active in Selontra® rodent bait, cholecalciferol, is not persistent in the environment, does not bioaccumulate and is readily metabolized by rats and mice. Furthermore, studies on birds (quail and mallard) have shown that compared to rats and mice, they are approximately 50-times less sensitive to cholecalciferol
- In most resistance management strategies for species other than rodents (insects, weeds, fungicides and even with antibiotics) the recommendation is to use pesticides with alternative modes of action, to reduce the chance of further selection for resistance. I see no reason why this argument is not also relevant to cholecalciferol.



### Innovation for a Better Tomorrow

In 2050, nearly ten billion people will live on Earth. While the world's population and its demands will keep growing, the planet's resources are finite. Though faced with huge global challenges, BASF sees many opportunities, especially emerging from chemistry. To keep pace with the ever-evolving and growing needs of our global customers, we have set out to strengthen our foundation. For example, BASF continues to dedicate substantial resources to drive innovation and sustainable solutions:

- Around 3,000 projects are in our research pipeline
- 10,000 employees are involved in research and development
- 100,000 molecules tested on average for one patent
- Major research centers in Limburgerhof, Germany, Research Triangle Park NC, USA and Thane, India and testing stations in the US, Brazil, Spain, Germany, India, and the Philippines

BASF continues to create chemistry to meet the huge global challenges for a better tomorrow.

**above:**

Adrian Meyer, United Kingdom

Master of Science degree in ecology and population dynamics, University of Durham.

Joined the U.K. Government Ministry of Agriculture, Fisheries and Food (MAFF) in the mid '70s as a vertebrate pest specialist. Extensive practical knowledge of the problems of applying pest control strategies. Extended his pest control experience into the food industry, as a specialist consultant, through managing the Food Protection Association, and in developing the Modular Pest Control programme. Field Advisor for ADAS (U.K.'s largest independent provider of agricultural and environmental consultancy). Left MAFF in 1994 and co-founded the Acheta consultancy. 1994 – today. Working as an independent pest control consultant Member of the British Rodenticide Resistance Action Group. Other publications are the 1993 and 2001 National Rodent Surveys and a WHO booklet of rodent control.