Active Insight: Rodenticides

by Steve Broadbent

The development of the modern anticoagulant rodenticides is a fascinating story, and quite different to what one might expect. For centuries 'physicians' had proposed that 'thinning' the blood was an effective treatment for various maladies. In earlier centuries the prescription of leeches was common for this purpose.

With this in mind, the story of the development of modern oral anticoagulants starts with haemorrhagic disease in cattle in the Midwest of the USA in the 1920s. This disease was characterised by severe internal bleeding. The cause was eventually traced back to the ingestion of spoiled sweet clover. Scientists worked to determine what the substance was that was causing the bleeding. This was eventually extracted and identified as a coumarin compound. This work by Dr Karl Paul Link and his team, working at the University of Wisconsin went on to show that it was actually a fungal metabolite that had developed in the spoiled sweet clover.

This lead to the development and commercialisation of dicoumarol in 1941 for the medicinal 'thinning' of blood. A few years later, in 1945, while recovering from a recurrence of tuberculosis, Link was reading about the history of rat control. Rodents were a serious problem for the farmers he had worked with in the isolation of dicoumarol, and he wanted to help them out. He considered dicoumarol, but thought it better to avoid its use as a rodenticide as he felt it would detract from its human therapeutic uses. He therefore looked at the range of products his lab had developed from the coumarin work overall.

These efforts to develop an effective rodenticide resulted in the synthesis of warfarin (Wisconsin Alumni Research Foundation). Warfarin was first introduced as a rodenticide in 1952 and, oddly enough, two years later it was approved for human medical use, despite this having been Link's concern with dicoumarol!

Coumarins, as these compounds are known, block the chemical reduction of vitamin K, which is an essential component in the clotting of blood. The 'K' in vitamin K comes from the German word *koagulation*. Today warfarin is probably most well known as a therapeutic agent given to humans to prevent thrombosis, the formation of potentially life-threatening clots in veins or arteries.

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Warfarin has a strong taste deterrent that has to be disguised to ensure the rodents are not deterred from feeding, and will eat poisoned feed for several days; or at least until the symptoms of poisoning set in. Rodent death from warfarin typically takes up to six days. It causes a slow death through the gradual onset of internal bleeding. Further first generation rodenticides entered the market over time and still remain in use. In the 1950s came fumarin from Amchem, a subsidiary of Union Carbide. Then in the late 1950s came a more potent group of products starting with diphacinone, patented by Upjohn Corporation; coumatetralyl from Bayer was developed in 1956; and in 1961 chlorphacinone came from

Liphatech. These latter products offer greater toxicity to rodents, but also to non-target species. Diphacinone is very poor as a mouse killer.

Later, in the 1960s the rodenticidal value of pindone was recognised. Pindone had been developed as an insecticide by Motomco Ltd. Pindone is therefore an effective anticoagulant rodenticide, that also exhibits insecticidal and mould inhibiting qualities, even in its commercial form

at 0.025%. All these products are multi-feed, so the rodent has to feed over several days to incur a lethal dose.

Within a decade of warfarin's introduction, rats and mice resistant to the poison were discovered. The demise of warfarin in rodent control programs though is more attributable to the development of the more effective, second-generation anticoagulant rodenticides. Ward Benkinsop in the United Kingdom, the company that became Sorex (now part of BASF), developed the first of these second-generation products, difenacoum, quickly followed by brodifacoum; while Liphatech developed bromadiolone, and later difethialone. As a small UK based company, Ward Benkinsop licensed brodifacoum and difenacoum to ICI for worldwide development. Later, when Shell bought out Sorex, they were asked to develop a further compound. This lead to the development of flocoumafen. These are also coumarin derived compounds and all are available in the Australian market. They remain highly effective, though genetic mutations conferring resistance to them has been identified in both rats and mice.

Active	Acute LD50 * *Rattus norvegicus*
Warfarin	10.0 – 20.0 mg/Kg
Fumarin	125.0 mg/Kg
Diphacinone	2.3 – 43.0 mg/Kg
Chlorphacinone	20.5 mg/Kg
Pindone	10.0 mg/Kg
Coumatetralyl	16.0 mg/Kg
Difenacoum	1.8 mg/Kg
Brodifacoum	0.22 – 0.27 mg/Kg
Bromadiolone	1.1 – 1.8 mg/Kg
Flocoumafen	0.25 – 0.56 mg/Kg
Difethialone	0.56 mg/Kg

Second generation actives are used at much lower dose rates, but have raised concerns over secondary poisoning, especially of raptors, which feed on the rodents killed by the poisons. This has lead to use again of first generation products in some sensitive areas, though recent studies indicate these too are of concern with respect to the poisoning of birds, especially diphacinone.
It is the single-feed aspects of these second-generation anticoagulants that has conferred the greatest benefits. Technically, only brodifacoum and flocoumafen are true 'single feed' products, as their potency allows for control of all rodents under *all conditions* through a single feed. The reality though is that all the second generation products are single feed in *most* conditions on *most* species. Whilst death may occur from a single ingestion, it usually takes 3 – 4 days for the rodents to actually die, which minimises the onset of bait shyness. Mice are much harder to kill with anticoagulants which has given brodifacoum an edge as the best mouse killing compound.
The major control technology for rodents is the use of baits formulated from proprietary mixtures of cereals and wax based substances. An important aspect of bait development is the presence of both olfactory compounds that will draw the rodents to the bait; and then the presence of high quality cereal and protein feed to ensure rodent feeding. The wax component is a trade-off in block baits. Higher wax content baits will keep their form better in high temperature environments, but this is 'traded off' against palatability.
This has lead to the development of extruded baits, which are compressed and therefore use less wax; and more recently, soft baits, often referred to as pasta baits, which have the highest palatability. The single-feed action of these second-generation baits is dependent upon a highly attractive feed component, which usually means a more expensive product.