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## RODENTICIDES - PROBLEMS AND CURRENT RESEARCH

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**ABSTRACT:** Regarded from both the economic and health aspects, the control of rodents is a pressing world wide problem. Continued improvements in food storage facilities, crop husbandry and environmental control are likely to do much in the long-term to help reduce rodent populations and damage. Looking ahead again, it is possible that biological control methods involving for example the use of reproduction inhibitors or rodent predators or diseases may ultimately be developed for rodent control purposes. In the immediate future however it is likely that rodent control operations will continue to be based on the use of rodenticides.

The rodenticides in current use (standard compounds) are either of the single dose, acute type or of the multiple-dose, chronic-acting anticoagulant type. The relative paucity and shortcomings of existing acute poisons and the emergence, particularly in Europe, of anticoagulant resistant rodent populations, emphasizes the need for alternative rodenticides of both the acute and chronic types. A search for new rodenticides is now being conducted at the Infestation Control Laboratory, Tolworth, U. K. in co-operation with various chemical and pharmaceutical companies and in collaboration with the World Health Organization. Candidate rodenticides provided by Industry are evaluated in a programme employing laboratory and wild rats *Rattus norvegicus* and mice *Mus musculus*. The tests procedures that have been developed and the rodenticidal performance of standard and candidate compounds are considered.

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Rodents of one kind or another are a world-wide problem. Although there is little quantitative information as to the losses they cause to crops, both in the field and in storage, there can be little doubt that improved control measures could make a significant contribution to the protection of world food supplies. Further, rodents and their ectoparasites can transmit a number of diseases which pose a threat to both humans and livestock.

It is probable that future improvements in storage facilities, proofing techniques and crop husbandry will do much to reduce levels of rodent damage and, in the long term, biological control techniques involving anti-fertility agents or predators and diseases may also be developed to limit rodent populations. In the foreseeable future however it is likely that rodenticides will remain the principal means of control.

The rodenticides in current use are either of the single-dose, quick-acting, acute type or of the multiple-dose, slow-acting, chronic type, the latter at present comprising only the anticoagulants. Each type has its merits and demerits. Acute poisons, being quick-acting, are most gainfully employed in situations demanding a quick knock-down of rodents as, for example, when infestations reach epidemic proportions or during outbreaks of plague. Unless a period of prebaiting is required, treatments employing acute poisons are less costly in terms of bait and labour and for these reasons too their use is often preferred to that of anticoagulant rodenticides in large-scale operations. With the exception of norbormide however acute poisons are toxic to a wide range of animals including man, and in various circumstances the risks of accidental poisoning whether by ingestion, inhalation or percutaneous absorption may be considerable. There is also, to varying degree, a latent danger of a secondary poisoning to other animals that may encounter and eat the bodies of poisoned rodents. The use of acute poisons is therefore often precluded by considerations of hazard. Moreover, many of the acute poisons are not completely satisfactory from the view point of efficacy. Most difficulties arise as a result of the consumption by rodents of only sublethal doses with the consequent development of either avoidance of the poison or bait for many weeks afterward or of tolerance to the poison.

The development, as rodenticides, of anticoagulant compounds such as warfarin marked a major advance in rodent control and since their appearance some 20 years ago these poisons have become the most extensively used of all rodenticides in many parts of the world. The use of anticoagulants as first choice rodenticides has stemmed from their unique combination of general effectiveness and comparative safety. Anticoagulants are readily accepted by rodents when they are included in bait at low concentrations and their effect is cumulative when ingested over a period of days. Relatively few cases of primary or secondary poisoning in other animals are reported as a result of their use and vitamin K<sub>1</sub> is strongly antidotal. The occurrence of warfarin resistance in some rat (*Rattus norvegicus* Berk.) and mouse (*Mus musculus* L.) populations in various European countries is now a matter of some concern in

view of the paucity and shortcomings of existing alternative poisons. There is therefore a clear need for new rodenticides that are both safe and effective.

#### THE CHARACTERISTICS REQUIRED OF RODENTICIDES

A rodenticide should preferably be attractive to rodents or, if not tasteless and odourless, then at least readily acceptable to them at the concentration at which it is to be employed in bait. Most compounds irrespective of their toxicity, tend, with increasing concentration, to make bait less palatable. It might generally be expected therefore that a highly toxic compound which could be included at low concentrations in bait, would stand the best chance of being most readily accepted. Though this may often be true it is not invariably so, since it is quite possible for extreme toxicity and unpalatability to be combined in the same compound. Most of the acute rodenticides in use today however have an LD50 to the target species of less than 50 mg/kg of body weight and it is probable that such considerations as palatability and cost would set a practicable upper limit in this respect little higher than 100 mg/kg of body weight.

Necessary though toxicity and palatability may be, these qualities are in themselves insufficient. A third, extremely important attribute, that has a considerable bearing on the usefulness of a rodenticide, is the speed of onset of its toxic effects. It is highly advantageous for a rodenticide to have a naturally delayed action, preferably of several hours or more. Such a delayed action increases the chance of a rodent consuming a lethal dose of poison before the onset of symptoms leads to the cessation of feeding, and also makes it more difficult for any sublethally dosed rodents to become poison- or bait-shy by learning to associate consumption of the poisoned bait with its after effects. If the latent period before the development of symptoms affecting feeding behaviour can be measured in days these advantages become more marked. In addition it becomes possible, as with the anticoagulants, to exploit any subacute or cumulative toxicity by choosing for use in bait a concentration of the compound that, while high enough to ensure that a lethal dose is consumed by rodents over a period of days, is yet too low to be acutely toxic to non-target species. In this context, low acute toxicity combined with high subacute or cumulative toxicity may constitute a further valuable attribute by reducing hazards to other animals.

Considering further the safe use of rodenticides, information on the relative toxicity to both rodent and non-rodent species is extremely important. Ideally a rodenticide should be selectively toxic either to rodents generally or to a particular genus or species, and harmless to man and other animals. Failing this, even a small degree of selectivity can be useful. As yet however no compound is known that combines high rodenticidal effectiveness with a substantial degree of specificity; norbormide though remarkable for its selective toxicity to *Rattus norvegicus* has been disappointing as far as its efficacy against this species is concerned. Although selective toxicity is a very desirable attribute in a rodenticide, it is not the sole prescription for safe use, and the lack of it should not preclude the examination of any compound that goes far in meeting other rodenticidal requirements. A candidate rodenticide may, for example, prove acceptable to rodents but not to equally susceptible non-target species. Clearly, with non-selective rodenticides the availability of effective antidotal treatment to counteract accidental poisoning would be distinctly advantageous. Other characteristics that are important in determining the usefulness of a rodenticide are cost, stability, purity, particle size, ease of formulation, fungicidal and insecticidal properties which would improve the keeping qualities of bait, and last, but not least, humaneness.

#### THE SEARCH FOR NEW RODENTICIDES

Since the introduction of the anticoagulants there has been little activity in the development of new rodenticides by Industry, in contrast to the situation with other pesticides. This relative lack of interest in rodenticides can be attributed to various factors - the possibility of high research costs coupled with market uncertainties, a disinclination on the part of some pharmaceutical houses to be involved in the production of rat poisons, an inadequate knowledge of the characteristics required of rodenticides and an unawareness of the need for research in this field. However Industry has available a wide range of toxic compounds of varied pharmacological activity, that have been rejected from further development for the purposes originally envisaged but which might nevertheless prove suitable for use as rodenticides. This situation combined with the experience of Infestation Control Laboratory, Tolworth in the rodenticide field has proved to be the basis of a mutually advantageous research collaboration.

Cooperation with interested companies has been developed along the following lines. First the principles underlying the control of rodents and the characteristics ideally required of candidate rodenticides are explained in discussion with company staff. Each company is then asked to provide samples of compounds whose properties, as far as they are known, go some way towards meeting these requirements. Compounds are accepted only if their chemical structures are given, and on the understanding that promising compounds will be made available for further development. Donated compounds are examined for rodenticidal activity at Infestation Control Laboratory, and the results reported back to the company concerned. All work is carried out on the basis of complete confidentiality.

#### EVALUATION PROCEDURES

Candidate rodenticides are first examined in a 3-stage screening procedure employing laboratory strains of rats and mice. At each stage in turn the compound either meets more exacting criteria, which are related to the performance of standard rodenticides in similar tests, or is rejected from further consideration. Compounds are evaluated as both acute and chronic rodenticides.

Stage I consists of range-finding tests in which each candidate compound is administered by stomach tube at two dosage levels. Single (acute) or four daily (chronic) doses of the compound are given, the chronic dosage levels being chosen after examination of the acute toxicity test results. The approximate oral LD50 values and time of onset of signs of poisoning are used to determine which compounds shall be examined in free feeding trials.

In Stage II animals are given a standard bait without alternative food containing concentrations of the candidate compound derived from LD50 values calculated in Stage I. Tests are continued for one day (acute) or four days (chronic). Compounds performing satisfactorily are then further examined in Stage III, in which animals are given a choice between plain and toxic baits.

Promising compounds are next investigated more intensively in laboratory feeding trials aimed at detecting any marked variation in toxicity and acceptability to anticoagulant resistant and wild rodents of both sexes and various age classes and establishing, where appropriate, optimum concentrations of compounds for use in field trials.

#### CURRENT PROGRESS

Not unexpectedly in view of the hit-or-miss nature of this work the vast majority of compounds are rejected at different test stages. Up to the present two compounds, both of the chronic type and representing about one per cent of the total number examined, have performed sufficiently well in all the laboratory tests to be given field trials, which are now in progress. \

It is recognised that our approach has many limitations, particularly in gaining access to the full range of the compounds potentially available and it could conceivably turn out that our main contributions will have been to the methodology of rodenticide evaluation and to stimulating the interest of others able to add to our efforts in this field. We have however been greatly encouraged both by the extent to which Industry has participated in this work and the results to-date. It is considered, though this remains to be proved, that the chances of identifying new classes of compounds with a useful degree of rodenticidal activity are reasonably good.