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Some properties of fluoracetamide as a rodenticide

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INTRODUCTION

Fluoracetamide ($F.CH_2.CO.NH_2$) is one of several fluoracetic acid derivatives that produce similar toxic symptoms in rats (Gitter, Blank & Bermann, 1953). It was first suggested as a potential rodenticide by Chapman & Phillips (1955) who pointed out that it is safer to manufacture and handle, and easier to estimate, than sodium fluoracetate. These authors also claimed that the symptoms produced by fluoracetamide were 'milder in form' than those produced by the fluoracetate and that, because of this, cases of accidental poisoning might prove more amenable to treatment if an antidote should be found.

This paper describes the results of an acute toxicity assay of the poison and of observations on three enclosed colonies of wild *Rattus norvegicus* exposed to bait containing fluoracetamide at different concentrations. It also includes some data on the relative speed of onset of 'warning symptoms' in white rats after ingestion of fluoracetamide, sodium fluoracetate and zinc phosphide.

METHODS

The bio-assay consisted of a pilot experiment with twenty-five male Wistar rats and a full assay with fifty-six wild *R. norvegicus* (thirty-one females and twenty-five males). The poison was made into pills with flour and water and presented to the animals on a dissecting needle. This method is very tedious with wild rats.

The observations on the enclosed colonies were made in a building specially designed for watching rodents. In the first experiment sixteen animals were housed together in a nest-box in one room, but allowed access to a second room containing 'Diet 41' (Bruce, 1950). Nine of the animals were marked by means of a depilatory. Both rooms were under continuous illumination, and food was available only during the late morning hours. The animals were thus conditioned to begin feeding within ½ hr. of food having been put down. They were then prebaited for 2 days with damp pinhead oatmeal. On the following day 0·5% of fluoracetamide was added to the oatmeal and the animals were watched through windows of darkened glass.

The second experiment was primarily concerned with palatability and no marking was done. Eleven rats, confined to one room, were offered an excess of damp sausage rusk containing 1% fluoracetamide immediately following 7 days on Diet 41. Food was available for only 2 hr. each morning during the last 2 days

before the observations began. The animals were therefore probably fairly hungry when the poison was offered to them.

In the third experiment, five rats were marked with a depilatory and again shut in a room containing a nest-box and a water point. A tray of crushed Diet 41 was also available for a period of 4–6 hr. during the morning and afternoon of each of the first 5 days, and for $2\frac{3}{4}$ hr. from 9 a.m. on the 6th day. At 9 a.m. on the 7th day a tray containing 2 % fluoracetamide in damp sausage rusk was substituted for the Diet 41 and the animals were kept under observation until 4.50 p.m.—when the poison bait was removed.

The observations on the speed of action of fluoracetamide *vis à vis* sodium fluoracetate and zinc phosphide were based on the technique used by Rjoska (in Chitty & Southern, 1954) and discussed further by Bentley (1958). Twenty-four white rats were trained during about a week to eat flour pills and small pieces of Diet 41 from an aluminium spoon. They were then weighed, divided into three groups of similar weight distribution and returned singly to their cages with rather less than a day's supply of food. Twenty hours later they were given a flour-paste pill containing twice the estimated LD_{50} of one of the three poisons. For this purpose the LD_{50}'s of fluoracetamide, sodium fluoracetate and zinc phosphide were taken to be 13 mg./kg. (see below), 1·5 and 40 mg./kg. of body weight, respectively. All the rats in one group were given the same poison. Five minutes after ingestion of the pill, and at succeeding 5-min. intervals, each rat was offered a piece of Diet 41 weighing approximately 0·05 g. and its behaviour recorded. Every attempt was made to induce a hesitant rat to accept the food and, where it seemed possible that refusal might have been due to bad presentation, it was taken to be definite only after it had occurred three times, consecutively. On final refusal the rats were killed.

RESULTS

The bioassay

In the pilot assay (carried out before the watching experiments) fluoracetamide was administered to five albino rats at each of five dosage levels, viz: 6·6, 10, 15, 22·5 and 33·75 mg./kg. of body weight. The corresponding mortalities were 0/5, 2/5, 3/5, 3/5 and 4/5, respectively, indicating an LD_{50} of about 13–14 mg./kg. Five rats died within 24–48 hr. of poisoning, five during the next 24 hr. and one on each of days 3 and 4. Several died in the rigid position described by Chapman & Phillips (1955) as typical of rats poisoned with sodium fluoracetate.

Two rats that had received 33·75 mg./kg., and which subsequently died, were offered plain flour pills every few minutes for the first hour after the poison had been administered. These offerings were readily accepted, suggesting that the poison had not yet taken noticeable effect.

In the full assay, with wild rats, the poison was administered at mean dosages of 6·23, 10, 16 and 25·6 mg./kg. of body weight and the mortality figures were 1/15, 7/14, 6/14 and 11/13, respectively. There was no obvious difference in susceptibility between the sexes. When the data were analysed in terms of log dose and probit mortality an LD_{50} of 13·0 mg./kg. ($\log LD_{50} = 1{\cdot}1406 \pm 0{\cdot}0565$) was ob-

tained. The slope of the regression line was 3·1 giving an LD_{95} of approximately 43 mg./kg.

The test animals were kept under very close observation for several hours after being dosed. Seven died within 24 hr., eleven on day 2, four on day 3, two on day 4 and one on day 6. Almost all the animals showed symptoms similar to those described by Gitter *et al.* (1953).

The period that elapsed between dosing and the onset of convulsions appeared to be related to the dosage level. At 6·23 mg./kg. the mean period for ten animals was 201 min. The corresponding figures for 10, 16 and 25·6 mg./kg. were 174 min. (ten animals), 136 min. (six animals) and 96 min. (three animals), respectively. Some rats had but one spasm; others up to seven. Most convulsions lasted for about 4–10 sec. and seemed to be about as frequent in rats that recovered as in rats that died.

Observations on the enclosed colonies

In the first 'watching' experiment the poison bait (containing 0·5 % fluoracetamide) was laid at 10.05 a.m. and the first rat began feeding 24 min. later. Other rats quickly joined it. There was no sign that the rats found the bait unpalatable. Those animals that approached the bait-trays seemed to feed quite freely—except that one animal made numerous journeys, always by the same circuitous route, to pick up a single mouthful of food, which it carried back to the nest-box in the next room. Two animals seemed reluctant to examine the trays and for some time confined their activities to scavenging food dropped by others. Feeding became rather intermittent after about an hour, though several rats were active outside the nest-box for a little longer.

At 11.50 a.m.—81 min. after the first rat began to eat—one of the animals showed convulsions. This plainly alerted the whole colony; for every rat that was outside the nest-box, except one, promptly withdrew to it. The rat that stayed outside 'froze' for about 15 min. and then joined the others. Thereafter various rats in turn were overcome by similar spasms, lasting a few seconds. Some animals seemed to recover very quickly and then usually rejoined the nest-box. Others lay, as if dead, for periods of an hour or more.

All the rats had eaten a lethal dose of poison and died in less than 24 hr.—eleven of the sixteen dying outside the nest-box. Recording the behaviour of the nine marked rats was hindered by the amount of activity that occurred after feeding began; also by difficulties of identification and the impossibility of knowing what happened in the nest-box. However, it seems clear that the poison did not affect any individual animal until more than an hour after it had begun to feed. One female rat of 175 g. that fed over a period of 34 min. was active and apparently well 66 min. after beginning to eat and showed convulsive movements at 101 min. For two females of 169 and 155 g. the corresponding times were 55, 82 and 102 min. and 52, 67 and 153 min., respectively. Two more females weighing 125 and 129 g. were apparently unaffected 52 and 63 min. after first taking the bait.

Altogether the sixteen animals, weighing about 2800 g., ate 129 g. of damp

oatmeal or about 4·5 % of their total body weight. On the average, therefore, each rat ingested about 18 LD_{50}'s.

In the second experiment, with 1 % fluoracetamide, similar results were obtained. Rats visited the baiting point within 10 min. of its being put in place. During a further 10 min. they spent more time smelling at and scratching the bait than eating it and then fed, seemingly without hesitation, for about 40 min. The last rat to visit the food-tray did so 80 min. after the first. Between them the eleven rats made thirteen visits to the water point during this period. Signs of poisoning began 42 min. after the last visit of a rat to the baiting point and thus 122 min. after feeding began. Since none of the rats was marked it is impossible to be more precise about the time of onset of visible warning symptoms. All eleven rats were alive and showing occasional convulsive movements 6 hr. after feeding began. At this point the animals were killed. Between them the rats ate 393 g. of damp sausage rusk and as their total body weight was about 3000 g., each animal, on the average, ate the equivalent of 100 LD_{50}'s.

In the experiment with 2 % fluoracetamide some initial reluctance to feed was again evident: but this appeared to be the result of general suspicion of the new baiting tray and the changed bait-base. When feeding did begin there was no indication that the bait itself was unpalatable, though the average consumption was less than in the tests with 0·5 and 1·0 % fluoracetamide. The five animals, weighing 1084 g., ate only 34 g. of damp sausage rusk, or 3·1 % of their body weight. Nevertheless, on the average, each rat still received the equivalent of about 48 LD_{50}'s and died in less than 24 hr.

One rat stopped feeding after 37 min. and the others after 39, 43, 47 and 52 min. Two were apparently unaffected at 66 and 155 min. after beginning to feed. The next time they appeared (273 and 389 min., respectively, after beginning to feed) they were obviously ill. The remaining three rats behaved somewhat abnormally (adopting a slightly flattened posture, for example) at 67, 82 and 159 min. and they were undoubtedly ill at 216, 122 and 194 min., respectively.

The onset of warning symptoms

In the experiments on the speed of onset of warning symptoms, a note was made not only of the time of occurrence of final refusal of food, but also of the interval that elapsed between ingestion of the poison and 'hesitation' (Rzoska, in Chitty & Southern, 1954). Table 1 summarizes the data so obtained. Sodium fluoracetate brought about hesitation in an average of 47 min. and refusal in 70 min. The corresponding averages for fluoracetamide were 157 and 233 min. These figures may be somewhat misleading however; for while hesitation and other symptoms of discomfort appeared simultaneously in rats dosed with sodium fluoracetate, hesitation in the rats poisoned with fluoracetamide was often preceded by abnormal posturing. Such behaviour was observed up to 30 min. before feeding was affected. Even so, fluoracetamide still seems to be much slower than sodium fluoracetate to affect behaviour at the dosages studied.

The figures for zinc phosphide in Table 1 need even more careful interpretation. Two of the poisoned rats were still regularly accepting food when recording was

discontinued, 365 min. after dosing. The average intervals before hesitation and refusal in the other six animals were 165 and 215 min., respectively. However, the abnormal posturing behaviour between feeds shown by five of the rats, and also the marked immobility of the remaining three, suggested that all eight were experiencing discomfort within 25–40 min. after ingestion of the poison. Had it been practicable to use wild rats in the tests, the hesitation and refusal times for zinc phosphide might easily have been as short therefore as for sodium fluoracetate. Whether the behaviour of the rats between feeds is regarded as important or not, the data in Table 1 indicate that zinc phosphide can be more variable in its effect on feeding than the other two poisons, at dosages that can be expected to give a kill of well over 50 %.

Table 1. *Time of onset of 'hesitation' (H) and 'refusal' (R) in twenty-four rats*

Poison	Behaviour	Minutes after ingestion of poison								Average (min.)
Fluoracetamide (26 mg./kg.)	H	140	130	109	185	200	205	115	175	157
	R	240	195	224	275	275	225	145	285	233
Sodium fluoracetate (3 mg./kg.)	H	65	85	34	34	40	35	30	50	47
	R	115	115	39	49	45	45	50	105	70
Zinc phosphide (80 mg./kg.)	H	220	235	39	234	55	205	365+*	365+*	—*
	R	240	315	44	289	60	345	365+*	365+*	—*

* See text.

DISCUSSION

The estimate of 13 mg./kg. for the oral LD_{50} of fluoracetamide for wild *R. norvegicus* that was obtained in the bioassay agrees well with the figure of 15 mg./kg. reported by Phillips & Worden (1956) for white rats. The surprisingly low figure of 19–20 mg./kg. quoted by these authors for the so-called 'LD_{100}' was not confirmed, however.

The LD_{50} of zinc phosphide for white rats has been estimated by workers at the Bureau of Animal Population, Oxford (Chitty & Southern, 1954) to be 41·3 mg./kg. and the corresponding LD_{95}, calculated from the figure of 6·611 quoted for the slope of the probit mortality/log dosage regression line, is about 73 mg./kg. Comparing these figures with those found by us for fluoracetamide, baits containing 1–1½ % of the latter poison would seem to be about as toxic to *R. norvegicus* as baits containing zinc phosphide at 2·5 %—the strength normally used in Britain for control. It does not follow that they would be equally effective in practice; for other factors such as their acceptability to rats and the speed with which they bring feeding to a stop may affect their rodenticidal efficiency.

The importance to be attached to good acceptability in an acute rodenticide depends on the manner in which the poison is offered. It is very great in direct poison treatments—and less so where 'prebaiting' has been carried out. However, even with prebaiting it must often arise that some rats in the population are inadequately conditioned to the bait-base when the poison is laid.

In the experiments with 1 and 2 % fluoracetamide the rats were probably more suspicious of the bait than they would be in a normal control operation with prebaiting. Nevertheless, they ate more LD_{50}'s per head than, experience shows, would be expected in a treatment with 2·5 % zinc phosphide (see also, Thompson in Chitty & Southern, 1954). This suggests that rats find 1 and 2 % fluoracetamide the more palatable. They certainly appeared to eat the bait without hesitation once they had picked it up. However, the large amount of poison bait eaten may also have been due, in part, to the appearance of warning symptoms later than would be expected with zinc phosphide. The observations made during the tests, the results of which are summarized in Table 1, suggest this possibility, but are not conclusive, since the test animals received the equivalent of only 2 LD_{50}'s. More convincing evidence is provided by Rzoska, Table 9 (in Chitty & Southern, 1954), who obtained refusal times of only 20, 20, 25 and 35 min. for four white rats dosed with zinc phosphide at 320 mg./kg. This dosage is equivalent to about 8 LD_{50}'s and is much nearer to what might be ingested by the average rat in a successful control treatment.

There is normally no big advantage in using a poison that is slower than others to produce warning symptoms at dosages well above those necessary to ensure death. It is otherwise at sublethal dosage levels, and it was this fact that dictated the choice of twice the LD_{50} for the tests on hesitation and refusal. It can be inferred from these tests that, on the whole, survival of rats as a result of the too rapid onset of warning symptoms is less likely to occur in control treatments with 1 or 2 % fluoracetamide than when 2·5 % zinc phosphide is used—given that the latter is not more palatable.

The demonstration that ingestion of fluoracetamide at lethal and sublethal dosages produce convulsions in *R. norvegicus* does not support the claim that the action of this poison is noticeably milder than that of sodium fluoracetate—if comparison is made at levels that produce similar mortality. And unfortunately, it is not difficult to imagine situations where the onset of convulsions might lower the efficiency of control treatments with fluoracetamide. This could occur, for example, where the individuals of a crowded colony of rats tended to 'stagger' their feeding times. However, it is not at all certain that fluoracetamide is different from zinc phosphide in this respect: for Chitty & Southern (1954) report that white rats often attempt to break out of their cages, and also exhibit terminal convulsions, within as short a time as 1 hr. after ingestion of zinc phosphide.

Little or no information is available about the toxicity of fluoracetamide to species other than the common rat and the rabbit. It is wise therefore to assume for the present that it is at least as toxic to man and domestic animals. This militates against its use as a rodenticide at concentrations above about 1 %, except in special environments such as sewer systems. On the other hand, it would seem that comparative field trials between 1 % fluoracetamide and 2·5 % zinc phosphide, using the prebaiting method, would be well worth while.

The most promising role of fluoracetamide in sewers is as an alternative to the use of 0·25 % sodium fluoracetate for 'direct' poisoning of rats (i.e. poisoning without prebaiting). The choice of a suitable concentration for field trials, however,

is partly a matter of guess work—as there is no unanimity on the value of the LD_{50} of sodium fluoracetate for *R. norvegicus*. Different authors give values ranging from 0·22 mg./kg. (Dieke & Richter, 1946*a*) to 7 mg./kg. (U.S. Public Health Service, 1949). Moreover, further work may show that the present disagreement is not due to variations in bioassay technique but to real, constant differences in the susceptibility of different strains of *R. norvegicus* or, for example, to age effects such as have been found for alpha-naphthylthiourea (Dieke & Richter, 1946*b*).

A compromise that we have adopted for field trials in sewers that are now in progress is to assume an LD_{50} of 1·5 mg./kg. for sodium fluoracetate and a constant relative toxicity *vis à vis* fluoracetamide. On this basis the concentration of fluoracetamide that is equivalent in toxicity to 0·25 % sodium fluoracetate is 2 %. It has been shown above that at this strength in damp rusk, fluoracetamide seems to be reasonably palatable to the common rat and is therefore unlikely to be very much less acceptable than 0·25 % sodium fluoracetate, whatever the acceptability of this may be. And the tests summarized in Table 1 show that at equivalent toxicities, fluoracetamide is less likely than sodium fluoracetate to lead to poison-shy rats through the ingestion of sublethal amounts of bait.

SUMMARY

1. The average lethal dose of fluoracetamide for wild *R. norvegicus* was found to be 13 mg./kg. of body weight and the LD_{95}, about 43 mg./kg.

2. Wild rats offered bait containing 0·5, 1 and 2 % fluoracetamide, after a period of conditioning, seemed to find it palatable and, on the average, ingested the equivalent of 18–100 LD_{50}'s. Warning symptoms appeared in about an hour or longer and included short convulsive spasms.

3. The speed of onset of warning symptoms leading to cessation of feeding was studied in albino rats dosed with the equivalent of 2 LD_{50}'s of sodium fluoracetate, zinc phosphide or fluoracetamide. Feeding ceased soonest in the case of sodium fluoracetate. Zinc phosphide gave very variable results, but it is thought that if wild rats had been used, feeding would have stopped nearly as soon as with sodium fluoracetate.

4. It is considered that field trials to compare the efficiency of 1 % fluoracetamide and 2·5 % zinc phosphide, both with 'prebaiting', would be well justified.

5. Fluoracetamide at 2 % may also prove to be a good alternative to 0·25 % sodium fluoracetate as a 'direct' poison for controlling rats in sewers.

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