

## OBSERVATIONS ON NEW RODENTICIDES\*

BY E. R. KALMBACH

*Wildlife Research Laboratory, Fish and Wildlife Service,  
U. S. Department of the Interior*

In presenting the subject of modern rodenticides it seems appropriate to review briefly the past, at least the recent past. This should be done if for no other reason than to point out that our new developments have stemmed from the lack of adequate supplies of the older, well established rodenticides, a situation brought about largely because of the recent war.

I am not in a position to give a world-wide picture of all that may have been done and I might explain that my presentation will emphasize work done by the agency with which I am connected, the Fish and Wildlife Service of our Department of the Interior.

That agency, as some of you may know, is obligated to conduct research, demonstrations and even direct control operations against rodents when they are jeopardizing products of agriculture, horticulture and forestry. This is in distinction from the responsibilities in the United States of the Federal Public Health Service and those of the Health Departments of our States and municipalities which also conduct research and engage in rat and mouse control primarily because these rodents harbor and transmit, through their parasites, diseases communicable to man. Whereas there are times and places when these two groups of agencies may be working in essentially the same areas, the considerations in the one case largely economic, while in the other they pertain to public health. The Fish and Wildlife Service and its predecessor, The Biological Survey, has, for instance, cooperated extensively with the State of California in areas where the suppression of plague has been the primary objective and with the U. S. Public Health Service in the South where typhus was being combatted. Research findings have been mutually available to all concerned.

In earlier days red squill, barium carbonate, phosphorus, arsenic compounds, strychnine, and, to some extent thallium were relied upon for the control of commensal rats and mice. World War II, however, exerted such a marked effect on the availability of some of these toxic agents that for a few years red squill, strychnine and thallium were in short supply. This condition led directly to the basic research that produced new rodenticides which now assure us ample quantities and guarantee that we will not again be confronted with such a problem.

During those critical times, importations of red squill were interrupted

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from the Mediterranean area and then, when access again was established, much of it was of relatively low quality. Strychnine likewise became scarce when the Japanese intercepted commerce from Malaya and India. American sources had to be relied upon entirely for thallium, which formerly came from Continental Europe, and the latter situation was complicated for a time by certain military demands for this heavy metal. These shortages in the early '40s led to increased use both in the control of rats as well as field rodents of zinc phosphide, which previously had had its greatest use in the control of orchard mice in Eastern States. It quite effectively filled the deficiency in California, where, previously quantities of thallium had been used in the control of ground squirrels in plague areas.

Those were the conditions that prevailed in 1943 when in August of that year, a grant of funds was obtained by the Fish and Wildlife Service from the Office of Scientific Research and Development for intensifying its research for effective new rodenticides. That work, under the supervision of the Denver Laboratory but with the important and able assistance of our Patuxent, Maryland Laboratory, involved the accumulating, synthesizing and testing of all materials that gave some indication of being effective rodenticides. It was a long, tedious, and not particularly promising task, since for many years previous thereto our Service had combed the field of potential rodenticides rather thoroughly and we were reasonably well informed regarding materials that had given some indication of value. In accordance with the division of work agreed upon, the Patuxent Laboratory conducted the initial screening and synthesizing, while the Denver Laboratory confirmed the data on the more promising ones and extended the testing to captive wild animals and even to the field itself, which, after all, provides the acid test for the effectiveness of any rodenticide. In the course of our solicitations for materials, the National Defense Research Council was instrumental in routing to us a large number, some of which had had their origin in the field of chemical warfare. Among those late in 1944 was a sample of sodium fluoroacetate, which, perchance, had attached to it the convenient catalog number of 1080. That is the origin of the now commonly used designation, "1080," for the most widely publicized of recently discovered rodenticides.

As part of the rodenticidal history of sodium fluoroacetate, mention should be made of the publishing in The Onderstepoort Journal of Veterinary Science and Animal Industry in September, 1944 of the findings of J. S. C. Marais, a pharmacologist, with respect to the toxic principle of a West African plant long used as a rat poison. Under the name of "ratbane" this plant technically known as *Chailletia toxicaria*, not only had been used to kill rats, but also had been employed in an aboriginal version of chemical warfare in that it had been used by the natives to poison the water supplies of hostile tribes. Marais' findings released at

about the same time that sodium fluoroacetate was proven in the United States to be an effective rodenticide, disclosed that the toxic principle of ratbane was none other than monofluoroacetic acid. This leads one to think that other plants also may have hidden in their vegetative structure the bases of toxic agents useful in rodent control. It must be candidly admitted, however, that throughout the years of our research in this field, vegetative poisons other than those derived from *nux vomica* have not proved acceptable to and effective against rodents.

Subsequent to the demonstration of the effectiveness of "1080" as a raticide against laboratory rats, personnel of the Denver Laboratory carried the studies into the field. There, during the fall and winter of 1944-45, compound "1080" was subjected to field testings in cooperation with the operating force of our Service and with other agencies in nearly a score of States and in more than a hundred cities and smaller towns. Conspicuous in this cooperative effort was the U. S. Public Health Service and the Health Departments of States and municipalities. Along the line helpful corroborative work was carried out by sanitarians in the Army and Navy, the Typhus Commission, and, if I remember correctly, some foreign workers associated with the Pan-American Sanitary Bureau. It was on such a foundation that the first recommendations for the use of sodium fluoroacetate as a control agent against rats and mice was based.

Concurrently the field workers of the Fish and Wildlife Service were subjecting the new rodenticide to trials against field rodents. Tests were carried out against two species of prairie dogs and four species of ground squirrels. Additional experiments were conducted against a number of the smaller forest rodents and the initial information was accumulated regarding the toxicity of "1080" to various game, seed-eating, and predatory birds which might be endangered by feeding on poisoned baits or on the rodent victims of "1080." That was the picture of the utility and selectivity of this poison against field rodents up to the close of 1945. Since then research has added many details to the story of 1080 as an implement for the control of both rodents and predators. These facts are of current nature and cannot be construed as part of the earlier history of research with 1080; they will be discussed in later portions of this paper.

Almost concurrently with the research which led to the demonstration of the value of "1080" as an effective rodenticide, Dr. Curt P. Richter of Johns Hopkins University made a notable discovery in his studies of the taste responses of rats. While testing a series of the thioureas, he discovered that some were definitely toxic to rats. This led to more extended investigations, which ultimately resulted in the demonstration that one of these related compounds, alpha-naphthyl-thiourea, not only was highly toxic to rats, but that it was also well accepted in a variety of

food baits. Much of the early history of alpha-naphthyl-thiourea and the course of events associated with its demonstration as a rodenticide have been recorded in the restricted documents that emanated from the Office of Scientific Research and Development.

Several events associated with a formerly well-established rodenticide red squill, are worthy of mention in connection with its war-time history. The scarcity of squill has been alluded to, but even before the acute shortage of the war period was upon us, progress had been made toward the utilization of the lower grade chips and powders with which the American market was being flooded. On the basis of work carried out at the Denver Laboratory of the Fish and Wildlife Service, there was presented at the 1941 meeting of the American Chemical Society, a paper by Crabtree, Ward and Garlough on the "fortification" of red squill by means of extracts obtained from similar low grade material. As pointed out in that paper, "squill powders bioassayed within the last two years (1940-1941) have varied in killing power from 400 mg/kg. to approximately 3000 mg/kg. The price has never been an index of toxicity and red squill powder practically useless for rat control has often been more expensive than better material."

Through this process of fortification in which the "counter current" principle of extraction is used, red squill powder of a potency to male rats of 2000 mg/kg. is readily converted into a powder, the toxicity of which may be in the 200-400 mg/kg. range for male white rats. The degree or intensity of fortification is dependent, of course, on the quantity of the toxic extract that is added to a stipulated quantity of the same low-grade powder. The procedure is adaptable to large scale operations and at the present time all red squill used by the Fish and Wildlife Service is fortified in this manner at the plant of the Louisiana State Health Department at Abbeville, Louisiana. Likewise, all the principal squill processors in the United States market a similarly fortified product either in powder form or as liquid extracts, which have been similarly treated.

As a further aid in assuring operators of the adequacy of red squill being marketed, a program is now being formulated whereby a reference squill powder of adequate and known potency will be maintained at a point where it will be available to bioassay laboratories and others at a nominal cost. This reference powder, hermetically sealed in cans of convenient size, will have its potency tested from time to time and all replacements will be of similar strength. By the use of this reference powder the adequacy of squill of unknown quality may be determined by a simple process of direct comparison.

\* Another development with respect to red squill as a raticide in the Western Hemisphere will be of more than average interest to those gathered here for the reason that it pertains, in part at least, to Mexico.

It had its beginning in limited experiments carried out by the Denver Laboratory of the Fish and Wildlife Service to determine where red squill (*Urginea maritima*) could be successfully grown in the United States. Field plantings were made at numerous points in our Southern States from Florida to Southern California and as far north as the State of Washington on the West Coast. In addition, greenhouse plantings at other points afforded opportunity to study flower and seed production under controlled conditions. These exploratory attempts to produce red squill in our country demonstrated that, when climatological factors were favorable and the flowers are fertilized, a viable seed could be produced in quantity and toxic bulbs grown. A prerequisite for the favorable growth of red squill in the field are a dry season of considerable length during which the bulbs undergo a period of dormancy; a relatively cool, wet season, during which vegetative growth is stimulated; and the absence of frequent winter freezing. These conditions prevail throughout much of the native range of red squill in the Mediterranean region and are most closely duplicated in North America only in the coastal region of Southern California and the adjacent parts of Baja California in Mexico.

Armed with those facts our Foreign Economic Administration imported in 1944 some 1500 mature squill bulbs from Algeria. At our Denver Laboratory a sample was taken from each by removing a cylindrical plug which did not injure the growing qualities of the bulbs. These samples later served as the basis of determining the toxicity of each bulb so that this might be traced in subsequent cultural treatments. The bulbs were then sent to Ensenada in Baja California, where, through the generous cooperation of former President Abelardo Rodriguez of Mexico, they were planted on his estate and given individual care. At the close of the war when our Foreign Economic Administration terminated its activities, most of the bulbs were transferred to one of our own experimental stations in Southern California, where the selective cultural development of the bulbs is under the guidance of the Department of Agriculture. Through selection and proper breeding and culture, a uniformly toxic bulb is being sought. Because of the slow development of squill this project necessarily will have to extend over a number of years. If our cooperative efforts are crowned with success, the Western Hemisphere will be assured of an independent source of usable red squill, which, it is believed, can be grown to a more uniform and higher degree of toxicity than that of the Mediterranean product, which is harvested largely from the wild. Reference to this and related research in red squill is included in the bibliography attached to this paper.

So much for the recent history of three important rodenticides. Now let us turn to the utilization, the advantages and disadvantages, and

the future outlook with respect to these and certain other rodenticides, the development of which is still in the formative stage.

Probably no other rodenticide has so vitally concerned those obligated to control commensal rats and mice as compound "1080." One might even say it has had more than its warranted share of publicity. This statement is made not only because it has aroused public demand for its use beyond the point of safe and sound procedure, but this same clamor has tended to obscure the many real hazards associated with its use. Although the toxicity of "1080" to man is somewhat greater than that of certain other economic poisons now in use, it possesses several characteristics wholly apart from its toxicity, that make it particularly dangerous. It has no distinguishing odor nor readily recognized taste; it has the appearance of baking powder, flour, or powdered sugar; solutions of it are indistinguishable in appearance from water; its high solubility makes for rapid absorption by the digestive tract and there is, at the present time, no effective antidote.

From the very beginning those who have been associated with the development of "1080" as a rodenticide, have been aware of its hazards and have urged the utmost caution in its use. Equally concerned about the dangers connected with its careless use has been the sole manufacturer in the United States, the Monsanto Chemical Company of St. Louis, Missouri. Great credit is due this firm in the sincere efforts it has made to keep "1080" in responsible hands. Their sales agreement demands that it may be purchased only by governmental agencies (Federal, State, and Municipal) and duly insured and competent professional pest control operators; there is also a prohibition against the resale or distribution to unauthorized individuals. Despite these precautions and repeated warnings from those who have developed "1080" there have been a number of fatal cases of human poisoning.

Because of its high solubility, compound "1080" has been extensively used in water solutions exposed either in small open waxed paper cups of about  $\frac{1}{2}$  ounce capacity or in self-feeding water founts similar to those used in supplying poultry with water on many farms. The former of these procedures is used in the intermittent treatment of premises by many pest control operators and after exposure for a day or two, these temporary containers are collected and effectively disposed. Exposure of such containers must be made only during periods when the buildings are not occupied, since the small paper cups often are an attraction to children. The supplying of "1080" solutions in the permanent time of water found is resorted to in places where attempt is made to prevent reinfestation after a building has been freed of rats. To lessen the possibility of accidental poisoning of human beings, I may point out that at the present time arrangements are being made with the manufacturer of "1080" to incorporate with it an aniline dye which will discolor not only the original "1080" but also any solution prepared with it.

I know you will be interested to know that in the very near future there will be available from our National Research Council, 2101 Constitution Ave., in Washington, D. C. a recently revised brochure on compound "1080." This brochure will set forth all the currently known facts regarding its toxicity to various creatures; safeguards regarding its handling; and precautions and limitations in its use. It also will outline procedures for the preparation of effective baits (both water solutions and food baits) and methods for the proper and safe placement of such material for rat and mouse control. In addition to such pertinent information concerning the use of "1080," it also comments briefly on its use in the control of field rodents and certain predators. Lastly, it includes helpful suggestions to the attending physician who may be called upon to treat accidental victims of this poison.

This brochure sets forth the combined knowledge of all agencies that have had research contact with this new and highly effective, but hazardous rodenticide. I am sure that a request for a copy of the revised edition will bring it to you in the very near future.

Alphanaphthylthiourea, more commonly referred to under the abbreviated designation of ANTU also has had wide application in rat control in the United States. It is manufactured by the Dupont Company of Wilmington, Delaware, and has given effective results in the control of rats in areas where the Norway rat (*Rattus norvegicus*) is the sole or dominant species. It has been much less effective against rats of the *Rattus rattus* group, and for that reason cannot be used to advantage in the southern part of our country, where those forms are most abundant. There are other disadvantages with respect to ANTU among them being a rapid build-up of tolerance when sub-lethal doses are ingested and its insolubility in water which precludes the use of water solutions as bait which has proved so convenient and effective with "1080." The tolerance which may be created among a colony of rats within a few days may persist for several months, thus preventing the follow-up treatment so often needed to remove the survivors of initial treatments. ANTU, on the other hand, is well accepted except in those cases where repeated use may have created an aversion. ANTU also has a much more favorable record with respect to accidental poisoning of human beings than "1080" although there have been some losses of domestic pets attributed to it.

A mimeographed brochure setting forth facts concerning ANTU was published a few years ago by the Nationale Research Council. This information was based largely on the work done by Drs. Richter and Diecke of Johns Hopkins University, but supplemented by data obtained from experiences of field operators of the U. S. Public Health Service, The Fish and Wildlife Service, several units of the Armed Services, and other agencies.

Red squill, thanks to the improvement obtained through the fortified article, still remains the one most selective and safe poison for use by the layman. It is the poison most frequently used in municipal rat control programs in which the individual property owner handles his own problem. Whereas red squill is about as toxic to most domestic animals including pets as it is to rats, there is a marked unwillingness on the part of these creatures to ingest appreciable quantities of this poison. Furthermore, the emetic properties of red squill tend to safeguard many animals which might accidentally swallow substantial quantities of such rat baits.

Should it ever prove possible to analyze and synthesize the toxic principle or principles of red squill so that this or some closely analogous poison could be created in the chemical laboratory, probably the ideal in rat poison would have been attained. Whereas research of this type has been done, the solution still appears to be distant.

Research in the development of still more effective and selective rodent poisons is still progressing. A number of recently developed poisons have been given trial but none is at the present time in a state of perfection warranting use on an operational scale. Some of the organic phosphates designed originally as insecticides have been found to be highly toxic to laboratory rats. These include hexmethyl tetraphosphate, "HTP," and tetraethyl pyrophosphate, "TEPP," and another organic phosphate of highly involved chemical composition, known as "Parathion" or "Thiophos, 3422." Despite the toxicity of these compounds to laboratory rats, a pronounced objection to their use as rodenticides rests in the fact that their toxic properties may be readily absorbed through the unbroken skin and hence would constitute a distinct hazard to all handlers of rat baits prepared with them.

"Castrix" (2-chloro-4-dimethylamino-6-methylpyrimidine) was developed by the Germans during World War II as a raticide to replace thallium sulphate, which became short in supply. Following the War, samples of this substance were prepared in the United States and subjected to tests to ascertain its utility as a rodenticide. In rats, mice, guinea pigs, rabbits and dogs, Castrix produces symptoms typical of central nervous system stimulants. Convulsions occurred 15-45 minutes after oral or intraperitoneal injection. Castrix appears to be more toxic to rats than sodium fluoroacetate (1080). With the recent discovery that Castrix may be antidoted (up to 10 LD<sub>50</sub> doses) with sodium pentobarbital, the Wildlife Research Laboratory is reviewing previous data obtained with Castrix and extending experiments to field trials against rats and mice. Since it can be antidoted, it may prove to be of advantage to use Castrix as a raticide rather than sodium fluoroacetate (1080) in many instances.

At the present time one of our field biologists is investigating the utility of thiosemicarbazide, which has given satisfactory results with laboratory rats. It is now being tested against orchard mice with the hope that it might serve as a substitute or alternate poison for zinc phosphide in areas where that poison seems to have lost its effectiveness. .

In the meantime the methodical, laborious, and to a large extent fruitless search continues in the laboratory for potential rodenticides. It probably will continue for many years to come and it is somewhat questionable whether the "ideal" or ultimate rodent ever will be revealed. I say this for the reason that experience has shown that wild creatures appear to have an unexplainable ability to meet adversity, even though that be a subtle and virulent poison. We have seen that happen in the case of strychnine and field rodents, when at one time it was highly effective against most species. Gradually, especially in California, strychnine became less effective and the entrance of thallium seemed to be the answer. Even this seemed to be lessening in efficiency when the war caused a shift to zinc phosphide, followed closely by the introduction of compound "1080" which is now the vogue of the operators and the bane of the rodents. Will it continue forever against virile, resourceful and fecund species? Our experiences of the past indicate that it may now be enjoying its heyday and eventually it also will give way to a successor, and we hope a safer poison.

#### BIBLIOGRAPHY

- Crabtree, D. Glen: Red Squill—Most specific of the raticides, *Economic Botany*, 1 (4): 394-401, 1947.
- Crabtree, D. Glen; Ward, Justus C.; and Garlough, F. E.: The fortification of red squill (*Urginea maritima*) by means of an extract of red squill, *Jour. Am. Pharm. Assn.*, XXXI (5): 142-144, 1942.
- Kalmbach, E. R.: Birds, rodents, and colored lethal baits, *Trans. Eighth N. Am. Wildlife Conf., Am. Wildlife Inst., Washington, D. C.*, 408-415, 1943.
- Kalmbach, E. R.: "Ten-Eighty," a war-produced rodenticide, *Science* 102 (No. 2644): 232-233, 1945.
- National Research Council: Instructions for using Antu (alpha-naphthylthiourea) as a rat poison (mimeographed brochure) 2101 Constitution Ave., N. W. Washington, D. C. (undated).
- National Research Council: Directions for using sodium fluoroacetate (compound 1080) as a rodent poison (mimeographed brochure), 2101 Constitution Ave., N. W. Washington, D. C., 1948.
- Richter, Curt P., and Emlen, Jr., John T.: Instructions for using Antu as a poison for the common Norway rat, *Pub. Health Rep.*, 61 (17): 602-607, 1946.
- Storer, Tracy I., and Mann, Margery P.: Bibliography of Rodent Control, National Research Council, 2101 Constitution Ave., N. W., Washington, D. C., Rodent Control Subcommittee, Insect Control Comm. Report 182, IV, 324 pp. and III, 57 pp. 1946.
- Storer, Tracy I., and Mann, Margery P.: Bibliography of Rodent Control, (first supplement) and bibliography of Antu, U. S. Public Health Service,

Washington, D. C., Div. of Research Grants and Fellowships, R. G.-273, 64 pp. and 11 pp., 1948.

Ward, Justus C., and DeWitt, James B.: Hazards associated with handling the new organic phosphates. Pests and their Control, Kansas City, Mo., March, 1948.

Ward, Justus C., and Spencer, D. A.: Notes on the pharmacology of sodium fluoroacetate—compound 1080, Jour. Am. Pharm. Assn., XXXVI (2)·59-62, 1947.

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### OBSERVACIONES SOBRE NUEVOS RODENTICIDAS (*Sumario*)

El A. presenta primeramente una breve historia del curso de los acontecimientos que durante la última guerra condujeron a la crisis originada por la escasez, mala calidad o imposibilidad de obtener los raticidas más importantes, como el talio, de Europa; la escila roja, de la región del Mediterráneo, y la estricnina, del Lejano Oriente. Esa escasez dió lugar a una pesquisa intensificada en busca de nuevos materiales o sustitutos y cuyo costo fué sufragado con ayuda de los fondos de la Office of Scientific Research and Development asignados al Fish and Wildlife Service del Departamento del Interior.

Muchos raticidas potenciales fueron sometidos a pruebas severas y como resultado de ello se descubrió una substancia notable: el fluoroacetato de sodio, cuyo número de serie en el catálogo es "1080" lo que dió origen al nombre que actualmente lleva ese veneno.

El ANTU (alfanaltitiourea) que según demostró el Dr. Curt P. Ritcher de la Universidad de Johns Hopkins, es un raticida eficaz, fué descubierto aproximadamente en esa misma época mientras realizaba sus estudios sobre el sentido del gusto en las ratas. Aunque el ANTU ha sido empleado extensamente en las zonas donde predomina la rata Noruega, es menos eficaz contra la rata negra (*Rattus rattus*).

La escila roja, raticida sumamente específico, se desacreditó con anterioridad y durante la guerra debido a la escasa toxicidad del material importado en aquella época, mucho del cual era inservible para el control de la rata. Para vencer esa deficiencia, el Laboratorio de Denver, del Fish and Wildlife Service, perfeccionó un procedimiento de fortificación de la escila en polvo de baja calidad, consistente en extraer el principio tóxico de una cantidad de polvo de grado bajo, agregándolo a una cantidad estipulada de polvo del mismo grado. Ese procedimiento que permitía el empleo de escila en polvo, que de otro modo resultaba inservible, está siendo utilizado ahora por los grandes manufactureros de escila en polvo en Estados Unidos. Para ayudar en el bioensayo general de la escila en polvo se ha establecido una substancia de referencia, de potencia uniforme, contra la cual son comparados los polvos de potencia desconocida.

El compuesto "1080," a pesar de su eficacia, es considerado sumamente peligroso, debiendo ser empleado solamente por personas expertas en ello. La venta de ese veneno se halla limitada en Estados Unidos, a las agencias del Gobierno y a los operadores responsables del control de la peste. El ANTU, utilizado en forma adecuada, resultará valioso en las zonas en que predomina la rata Noruega. La escila roja, en su forma más efectiva, fortificada, continuará siendo el veneno de rata de elección para ser empleado por personas inexpertas y será siempre de gran valor en las zonas densamente pobladas. Se está ensayando cierto número de otras substancias que prometen utilidad.