THE ROLE OF INDUSTRY IN DEVELOPING NEW MATERIALS FOR VERTEBRATE PEST CONTROL

G. Hermann, Head of Vertebrate Control Laboratory, Farbenfabriken BAYER, Germany, and W. M. Zeck, Research Director of Vero Beach Laboratories

In the first paper presented to you today by Dr. Spencer, an expert in the Animal Biology field and an official authority at the same time, you heard about the requirements imposed on a chemical in order to pass the different official hurdles before it ever will be accepted as a proven tool in wildlife management. Many characteristics have to be known and highly sophisticated tests have to be run. In many instances the governmental agency maintains its own screening, testing or analytical programs according to standard procedures. It would be impossible, however, for economic and time reasons to work out all the data necessary for themselves. They, therefore, depend largely on the information furnished by the individual industry which naturally has to be established as conscientiously as possible. This, among other things, Dr. Spencer has made very clear; and this is also what makes quite a few headaches for the individual industry, but I am certainly not speaking only for myself in saying that Industry fully realizes this important role in developing materials for vertebrate control and the responsibilities lying in this.

This type of work - better to say cooperative work with the official institutions - is, however, only one part and for the most of it, the smallest part of work which Industry pays to the development of compounds for pest control. It actually refers only to those very few compounds which are known to be effective. But how to get to know about their properties in the first place? How does Industry make the selection from the many thousands of compounds synthesized each year? This, by far, creates the biggest problems, at least from the scientific and technical standpoint. Let us rest here for a short while and think about the possible ways of screening and selecting effective compounds.

Basically there are two different ways. One is the empirical way of screening as big a number of compounds as possible under the supposition that with the number of incidences the chances for a "hit" increase, too. You can also call this type of approach the statistical or the analytical one, the mass screening of new, mostly unknown candidate materials. This type of testing can only be performed by a producer of many new materials, that means by big industries. It requires a tremendous investment in personnel, time and equipment and is based on highly simplified but indicative test methods, the results of which would have to be reliable and representative for practical purposes.

The other extreme is the intellectual way of theorizing effective chemical configurations. Defenders of this method claim to now or later be able to predict biological effectiveness on the basis of the chemical structure or certain groups in it. Certain pre-experience should be necessary, that means knowledge of the importance of certain molecular requirements, then the detection of new and effective complete molecules is a matter of coordination to be performed by smart people or computers. You can also call this method the synthetical or coordinative method.

It would be interesting to compare the successfulness of both approaches. Yet, accurate information in this respect is hard to obtain. Naturally, the latter way of coordinating chemical groupings to biological efficacies and vice versa has much more challenge to it, would finally be cheaper and more direct; and much progress has already been made along those lines. But I think we are still far away from making any reliable predictions of the biological efficacies of molecules. The majority of the biological screening work is therefore still done in the empirical way of mass screening molecules as they are synthesized. However, more and more emphasis is given and even more will be given in the future to principles and combinations found to be effective and in this very important field fruitful cooperation is under way with industries engaged in Biological Research and governmental, university or local institutions.

In the following I will try to give you a view into the efforts and problems Industry has to face in screening out those compounds which finally reach the Experiment Station for further development in the vertebrate control field.

The necessity of mass screening of the several hundred compounds synthesized each week in the laboratories of a single major chemical company as such creates a multitude of problems. Naturally, in reaching out into the unknown and creating new substances Industry aims at finding areas of useful and lucrative application for them. That is what keeps Industry growing and people working. A compound not only could be a rodenticide; it could be a herbicide, or an insecticide, a repellent or a fungicide, a nematocide or defoliant as well. Therefore, a multitude of different tests have to be run and they should allow one to instantly and with a high degree of reliability pick out the effective compounds and reject the ineffective ones. This requires highly specialized test methods in which time, space and specimen are absolutely limiting factors. To determine the toxicity level of a compound on an animal species is relatively easy, because the criteria are easily definable: the occurrence of sickness or death after administration of a certain dose. In case of repellents, however, it is much more difficult since it is not any more a physiological reaction, but the behavior of the test animal which has to be evaluated. This can be influenced by adaptability or individual variation, or modifiability of the individual test animal by moods and emotions, pre-experience and seasonal changes and so on. Frequently the economically important species is not available in large quantities, therefore another, maybe closely related, species has to be substituted. This touches one of the main problems Industry has to face in the systematic development of compounds for vertebrate control: to what extent can a result achieved on one species be regarded as representative for other harmful species, too. We have learned in recent years that extreme caution has to be observed in this respect. The roof rat, for instance, is 30 times less sensitive to ANTU than the Norway rat, a close relative of her. A similar situation can be found with the Hydroxycumarius in case of long and short tail mice or voles. The situation is still worse in case of compounds which influence the behavior of the animal, like repellents or attractants, where individual and species differences count even more. Theoretically, therefore, each compound would have to be tested on each harmful species. This is impossible, as everybody will agree, in view of the many problems and the many compounds to be tested. Also, Industry is tight in its efforts to economic

feasibilities. We must admit that in the past the incident was helping where systems failed. How this will be in the future? Who knows! But as I explained to you earlier, there will be more of the direct or intelligent approach in the future. As long as no definite progress is made in this concern, however, screening facilities in industrial laboratories have to be extended to satisfy the biological facts as well as the need for more and better compounds. In order not to get lost in the multitude of problems, Industry will also have to concentrate on a few of the pests of major importance. This certainly requires close contacts to the people in the field and again underlines the importance of cooperation between industrial and local researchers.

I will now give you a brief review on the contributions Industry has so far made to the Vertebrate Pest Control in developing effective compounds. The chemical control of harmful vertebrates reaches far back in history but not until relatively recently any organized attempt was made in controlling them, and this, I would like to say, is coincidental with the chemical industry getting involved in it. For many centuries Arsenic and yellow phosphorus have been in use for the control of rats. Also other highly toxic materials like Strychnine or some alkaloids entered into the picture relatively early. Such compounds actually were known from pharmacology to be highly toxic drugs and were bought in drug stores as such or they were sold through quacks who also made the rodenticidal applications, mostly with dubious success but catastrophic side effects on domestic animals. Even organized control actions, for instance against rats in cities, until very recently have been partially effective at the best. Too little was known about biology and behavior of the animals in question. Not until zoologists and application specialists took part in solving the problems was any progress made. Then the time was ripe for the chemical industry to step into the picture. Biological screening methods were developed, fundamental research was done, and compounds were systematically screened as to their rodenticidal potential. That was in the first two decades of this century. The first true rodenticide commercially sold in Germany was the 3 - Methylxanthine in 1920. As in most cases of the early rodenticidal developments, also in this case a loan was made from pharmacology: this compound was known to crystallize in the renal ducts and clog them up. This property was evaluated controlling rats. Soon other compounds were evaluated for rodent control like the Thallium compounds and industrial biologists took more and more active part in working out the requirements for the successful application of rodenticides, for instance so far as formulation and bait preparations are concerned.

Soon the vertebrate control research took on more sophisticated attitudes. The newly developed Thallium products, as well as the older arsenics, had the disadvantage of poisoning also those animals and birds which fed on the rodents killed with such products, which created a dangerous hazard by itself. Search therefore went on for compounds without the danger of secondary poisoning. Such a compound was developed in 1930: the zinc phosphide. It is relatively unstable, particularly when formulated as bait, and is soon inactivated inside the poisoned animal and therefore eliminates the danger of secondary poisoning. Yet the compound was still highly toxic after application as such to birds. Broad scale control operations, therefore, could not be undertaken until additional progress was achieved. This

was done with the development of Chloro-dimethyl-aminomethyl-pyrimidin in 1937. This compound, which was a true industrial development inasmuch as it resulted from systematic screening as the compound best suitable for the purpose out of a series of homologues, was outstanding since it is stable enough for field use, it is readily decomposed under the physiological condition of the intestines so that secondary poisonings are eliminated; and a similar decomposition takes place in the crop of birds before the compound reaches vital organs. This all means that from then on large scale control operations were possible in agriculture and forestry without disastrous impact on fur and feather game.

In 1948 another progress was made. RICHTER of the John Hopkins University in cooperation with DuPont developed alpha-naphtyl-thiourea, a compound particularly effective on rats and well accepted. It had a so-called built-in safety mechanism inasmuch as the active deteriorates rapidly when the bait, into which it is mixed, becomes spoiled.

The alpha-napthyl-thiourea is a good example to show that industry and state or governmental research had to go together to arrive at real achievements.

In the next big step forward research people of the Wisconsin University were the pioneers.

The compounds so far named were all strong acting poisons. The intoxication happens relatively quickly, yet there are always a few survivors which develop an appropriate protective reaction, a poison or bait shyness against such compounds, the effects of which they experienced. These few survivors build up new populations thereby making total success impossible. Eradication programs were successful only after the so-called "Anticoagulants" were available.

Following up on first investigations into the nature of "sweet clover disease" of cattle, by SCHOFIELD AND BRODERICK in 1922, scientists of the Wisconsin State Experiment Station - together with USDA workers - were able in 1939 to isolate the anticoagulant Dicoumarol in spoiled sweet clover hay, and in 1941 STAHMANN, HUEBNER and LINK were successful in synthesizing this compound, which was replaced one year later by another cumarin derivative, when the Wisconsin Alumni Research Foundation introduced Warfarin which was considerably more effective than Dicoumarol in the inhibition of blood clotting.

The agents were there, what was needed now were methods of application to make them work. SCHEEL and WU, I suppose also from Wisconsin University, in 1947 proved the usefulness of Warfarin as a rodenticide and an English worker, O'CONNER developed the multiple dose technique, based on the excellent acceptance of cumarin compounds and their cumulative action inside the rodents. Now the anticoagulants were in business as rodenticides and quickly conquered markets. Other derivatives were developed and reached the market in rapid succession. Geigy developed Cumachlor in 1949; another company brought Fumarin in 1952; and in 1957 Bayer brought the Cumatetralyl.

With these compounds which are relatively safe from hazards to humans, large scale eradication programs against rats have been run covering big city areas in Germany like Hamburg, with a population close to 2 million. The compounds were disseminated through pest control operators, the success was checked periodically and guaranteed for 2 years, the total cost amounted to roughly 25 cents per person living in the area. I am willing to give further details on this later on when so desired.

Simultaneously with the development of the Hydroxy cumarin substances another group of compounds with anticoagulant effects was introduced, the Indandion derivatives. Kilgore, in 1942 in England, found Pivalylindandion to be an effective insecticide, yet too expensive for practical use. In the following years this substance was discovered to possess anticoagulant properties and the experiences gathered with the hydroxy cumarins plus the efforts of several American industries in cooperation with the Wildlife Research Service helped this substance to become a rodenticide in 1952.

That much about rodenticides.

There are other fields of Vertebrate Control to which Industry has successfully contributed, like rodent repellancy, bird repellancy, bird toxicants, protection of construction and packing materials. Their path of development is even shorter and less filled with historical landmarks in comparison to the rodenticides. I think I can spare you and myself the elaboration on the role Industry maintained in these disciplines. I already have spelled out a few of the major problems in development, others are of the same general nature as in case of the rodenticides.

Instead I feel it more appropriate and interesting to you, as well as helpful for the chemical industry, to name a few of the practical problems with which Industry, at least on the other side of the ocean, is concerned. I will be glad to learn afterwards or in the sessions to follow what can be cut from or should be added to this list.

So far as rodenticides are concerned, it is felt that a true selective compound is needed, one which is virtually not dangerous for men and domestic animals as well as game and birds. Although tremendous progress has been achieved for instance with the anticoagulants versus the toxic materials from earlier days, none of the presently used chemicals is harmless or safe enough.

Another problem, particularly in Europe, is the replacement of the highly toxic and residual chlorinated hydrocarbons, which are still used in grassland spray treatments against common voles and water voles. Aside from the high acute toxicity of such materials they are highly persistent and require special precautions even after the treatment and holding times until the treated areas can be used again.

Industry will also have to continue efforts towards improvement of methods for application of the presently used materials in order to increase their effectiveness or make the applications safer.

Naturally industry will participate as it did in the past in studying the habits of damaging rodent species, since still many details are unknown, what often betrays the intended effect of the treatments.

Coming to the rodent repellents, a field still scarcely touched but wide open for promising candidates Industry (and particularly here in cooperation with the Wildlife Research Service) is trying hard to advance. From my earlier remarks you know about the difficulties in routine screening on that subject. The problem is aggravated by the fact that in developing compounds for protection of plants or seeds a new factor enters the picture, the plants with all their reactions and sensitivities. Search therefore is continuing for a non-toxic repellent which can be applied to the leaf or seed and guarantees long enough protection. Such a compound has therefore also to be residual, phytotolerant and most likely at least to some degree systemic, so that after seed treatment also the growing seedling is protected. There was a compound developed in 1948 in Germany, the Tetra methylen disulfotetramin with the common name Tetramin. This compound has been under investigation since 1951 with the Fish and Wildlife Service and has proved to render the leaves of trees repellent to rodents for years after application to the soil and uptake through the roots. Yet, this compound is so powerful a poison that it looks like it will have no chance to be marketed despite the fact that an antidote is known and well functioning methods of application were developed.

Search also is continuing for effective repellents to be used in packing and construction materials. This also is a very tricky problem, since the treated materials are not eaten by the rodents, but only scrapped. A compound for this purpose would have to exhibit an alarming odor or color or something.

So far as bird control is concerned an ever increasing demand is felt for chemical agents to manipulate problems like exploding pigeon populations in big cities, or to cut down on overpopulations of certain bird species like weaver birds in Africa which intrude by the millions in grain growing areas and completely destroy the crop, or starlings becoming a nuisance and a pest in many agricultural and urban areas. Applications to nesting places of 25% Parathion in kerosene were successful yet the fact that a highly toxic material is used in high concentrations limits its use considerably. New, less toxic compounds are under development; you may hear about them in a later paper. Work is also continuing on bird repellents, highly effective on many species and harmless from the toxicity standpoint.

The list of presently acute problems should not be finished without referring to one, the nature of which is almost as much psychological as it is real.

You know and everybody knows that we want to have safe chemicals in every aspect. That much is real and also in my paper today I had to refer to the respective efforts frequently. Yet there are the unreal things which hurt. Efforts were made in the last year or year and a half by poorly informed journalism to say the least, to play down the role of Industry in the pesticide field, namely to serve mankind with better and safer products. Arguments have gone forth and back, experts of both sides have spoken to the issue and new legislations were put into effect. There is no need to tune in on all that again. Yet by looking over the achievements and the programs now in effect with both government and Industry I cannot help but say that the attendants of this meeting as well as the organizations they represent have

not been on trial. We have reason to welcome all the commotion stirred up because it brought into the open what efforts toward safety and safer compounds actually were already in effect. It looks, however, as if through new regulations the development of new pesticides will be more expensive in the future and more time consuming.

In the foregoing I have tried to brief you on the problems of developing chemicals for vertebrate control in the view of chemical industry. I have tried to do that

> by elaborating on the problems of screening vast numbers of compounds and then making the proper selections,
>
> by reviewing achievements in the history of rodenticides and
>
> by listing the major acute problems for the future, as we see them.

I had often to refer to the importance of the cooperation of Industry with officials in the USDA and FDA, the research people in the Fish and Wildlife Service, and the local people in the vertebrate control field. I think I am speaking for my colleagues of other companies as well in spending high praise for the wonderful understanding of these people concerning our problems and in assuring them our sincere gratefulness for their valuable cooperation and assistance, without which progress was and is not possible. Together with this statement naturally goes the pledge for continuation and improvement of these relations to the benefit of everybody.