J. M. Barnes

Toxic Hazards of Certain Pesticides to Man

Together with a

Select Bibliography on the Toxicology of Pesticides in Man and Mammals

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NOTE

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The mention of manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature which are not mentioned.

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INTRODUCTION

Aim of Report

This report has been prepared upon the lines suggested in the terms of reference drawn up by the World Health Organization, which were as follows:

1. To advise the Director-General, through the medium of a report, on the existing information relative to the chronic and acute toxic effects on man of some of the preparations used as insecticides, anti-parasitics, molluscicides, rodenticides, and herbicides in agriculture and health activities.

2. The study is to be confined to those preparations considered to represent a clear and immediate danger to health in the following spheres:

2.1 Industry, including the danger to labour in the manufacture of the basic product and in the processing of formulations.

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* This report was prepared in accordance with Resolution WHA4.31 of the Fourth World Health Assembly (Off. Rec. Wild Hlth Org. 35, 29) and Resolution EB8.R52 of the Executive Board (Off. Rec. Wild Hlth Org. 36, 17). The author's acknowledgements to all those persons who collaborated in the preparation of the report are contained on page 73. — Ed.
2.2 Application, including the danger to field operators in agriculture and health, and the hazards to which occupants of treated premises might be exposed.

2.3 Residues in food, including the danger to persons handling and consuming processed and fresh foods.

3. In so far as possible, to make recommendations on principles, based on usage and experience, which, it is believed, would define adequate protection under varying conditions and exposures for persons coming in contact with these products in the circumstances described above.

4. The report should contain reference to problems on which insufficient information is at present available and should include recommendations on research which might be initiated towards finding a solution to these problems.

5. The collaboration of the International Labour Organisation (ILO) and the Food and Agriculture Organization of the United Nations (FAO) should be sought throughout the study, either by discussions with the secretariats of these organizations or by consultations with experts recommended by them.

6. The study should be performed on as wide an international basis as possible so that the final report may be applicable to countries in various stages of development.

7. The consultant should be aware that the report will be used as a basis for future study by public-health, agricultural, industrial, and labour experts, so that he may prepare it accordingly."

A somewhat broad interpretation has been put on the opening sentence of paragraph 2 so as to include not only those compounds that present a "clear and immediate danger to health" but also those that might be considered to offer a potential threat to health now or in the future.

There have been a great many papers in recent years in which the real and potential hazards from the use of insecticides, fungicides, and rodenticides have been discussed. Many of them have been written for the guidance of the users of these materials. This report has been prepared with the hope that it may be of value to the medical officer and others with responsibility for public health.

The value of any pesticide that is hazardous to apply must in one sense be only relative. A decision as to whether or not its use should be encouraged may present a problem that a medical administrator may find difficult to resolve. On the one hand he is presented with a threat to the health or even the lives of that small section of the community which will handle the materials. Against this he has to weigh the injury or threat of injury to some or all of the rest of the community that may arise if these materials are not used and the control of pests is, to that extent, inadequate.

Scope of Report

In an attempt to put this problem into perspective for those faced with making any such decision, the report opens with a brief account of the part which chemical control plays both in the suppression of insect-borne diseases of man and in reducing the damage done to his crops by these pests.
An account of the hazards arising from the use of pesticides then follows.

The occupational hazards can be separated into those associated with the manufacture and those associated with the application of the materials. The first group is met with in the restricted environment of the factory, and preventive measures can be much more strictly applied.

The control of hazards related to the application of toxic materials in the field presents special problems. The nature of the work makes it impossible to achieve the degree of control or surveillance that is possible in a factory. For this reason, rules and regulations for personal protection from hazards are less likely to achieve their aim. The emphasis must be on the education and training of the workers handling these materials, rather than on their supervision. This immediately indicates the need for employing only those capable of being trained to handle dangerous materials.

The hazard to the consumer of food which contains traces of foreign chemicals applied during agricultural processes is extremely difficult to assess. This ill-defined risk assumes different proportions in various parts of the world, depending upon the balance that exists between the level of food production and damage by pests and upon the state of development of laws concerning the purity of food.

Poisonous pesticides have been in use for 50 years so that many of these problems existed many years before the introduction of the new chemicals for pest control. In many countries where agricultural and public-health services are well developed, the adequate control of the use of these materials should present no serious problem. In describing some of the measures that have been taken in these countries it will be emphasized that their successful application has depended upon the existence of a strong administrative background which may have taken many years to develop and evolve.

After summarizing the principles of such control measures, the report suggests lines upon which further information might be sought and where more research is needed.

A summary of available information on the toxic properties of some pesticides in common use is annexed to the report (Annex 1, page 48). To gain a proper understanding of the hazard involved, the medical man must have some knowledge of how any particular poison exerts its effects. It is possibly because so little is known about the mode of action of some of the commonly used pesticides that so much anxiety exists about their possible dangers. The actual hazards arising from the use of a material may not necessarily be proportional to its intrinsic toxicity as measured by animal experiment. Its chemical and physical properties will play a part.

The type of injury the material produces may also influence views on its undesirability. Many compounds may either kill their victims or
produce a completely reversible condition of intoxication from which recovery is complete. Others—far less poisonous—may kill fewer people, but among their victims there may be some who are left with a permanent crippling injury as a perpetual reminder of the accident. The use of compounds capable of doing this may well be more readily condemned than the use of those in the first group.

1. VALUE OF PESTICIDES IN DISEASE CONTROL AND IN CROP PROTECTION

1.1 Control of Insect Vectors of Disease

Probably nowhere has the use of insecticides shown more dramatic results of irrefutable benefit than in the control of malaria. For many years before the introduction of DDT in 1945, active malaria-control programmes had been conducted in Italy and Greece using drainage and water control, paris green and fish for larva control, and screening for house protection. In 1945 there were 400,000 cases of malaria in Italy with 380 deaths; in Greece during the period 1940-5 there were on an average 4,000 deaths a year and the parasite-rate in schoolchildren averaged 13%. With the widespread use of DDT for house spraying, and in Greece for larvicide work as well, there was a dramatic fall in the incidence of malaria.

In 1951 there were 390 cases of malaria in Italy but no deaths from this disease were recorded in the years 1950-2. In Greece only 7 deaths were attributed to malaria in 1951, most of which on closer inquiry proved to have been due to other causes. The parasite-rate in schoolchildren had dropped to 0.06%. The disease has now been so well controlled in these countries that consideration is being given to a partial or complete abolition of the use of insecticides.

In the State of California, USA, 112 people died of malaria in 1910 and there were several thousand cases of the disease. Intensive control measures against the mosquito had gradually reduced the disease, but it was only after the introduction of DDT that it was virtually eradicated. In many other parts of the world malaria has been eradicated or much reduced by the widespread use of insecticides as the main control measure.

The spread of typhus and plague has also been arrested by the timely use of the new insecticides.

With the disappearance or reduction of widespread and serious diseases, the lesser pestilences assume a new importance. The prevalence of flies,

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*a* The chemical names of the active ingredient of all the pesticides referred to in this report by their abbreviations or common names may be found in the glossary (Annex 3, page 71).
together with imperfect sanitation, may bring a serious incidence of infantile diarrhoea, typhoid fever, and other enteric diseases. The spread of other diseases such as trachoma is believed by some to be associated with the prevalence of flies. The control of flies by hygienic measures is extremely difficult and expensive to achieve. Attempts to control flies by insecticides, which were at first successful, have since met with failure because of the ease with which the flies have developed a resistance to DDT and other insecticides of this group. Nevertheless, the demand for fly control has led to the use of the more-toxic organo-phosphorus insecticides in further control attempts.

The culicine mosquito, unlike the anopheline, has also developed considerable resistance to DDT when attempts have been made to control it where it is a social nuisance and a suspected carrier of equine encephalomyelitis. When chemical methods of control break down, a return to the older methods may be made more difficult if the breeding-places are in agricultural land. The draining or oiling of water in rice fields is not compatible with agricultural requirements.

1.2 Use in Agriculture

Before trying to evaluate the use of insecticides for controlling pests in agriculture, it may be profitable to consider another pest, namely, the locust and grasshopper.

From biblical times to the present day, locusts have presented an indirect threat to the lives of large numbers of people. For years chemical methods have been used to control the movements of locusts and grasshoppers. Some of the newer compounds have proved very effective and their use will continue and expand. There have been no reports of ill-effects among the workers who have applied these compounds, often under conditions of extreme simplicity and with apparent risk of exposure. Even if some casualties had occurred the measure of the disaster would have been relatively negligible in comparison with that affecting whole groups of people suddenly deprived of large parts of their food-supply by the uncontrolled insects. Insecticides are likely to be used in increasing quantities for locust control and no one is likely to gainsay their value for this purpose.

In considering the use of insecticides in agriculture it becomes somewhat more difficult to compare the risks to which workers handling dangerous chemicals are exposed, on the one hand, and the ultimate benefits conferred on the community as a result of their work, on the other. In communities where there is a peasant agriculture with many small plots of different crops, pesticides are not widely used and in many cases the cultivator could not afford them. A relatively low standard of produce is generally acceptable for internal consumption where it meets no competition. It is
only when agriculture has been intensified and developed on a vast scale that the problems become much more serious. But it seems only reasonable to suppose that the provision of an adequate diet for the millions of undernourished people in the world today, and for the millions more tomorrow, will depend upon the development of agricultural practices on the scale and intensity now seen, for example, in North America.

The population will only be adequately fed when it proves possible to obtain high yields of many different crops on the fertile land available in the world. It does not seem unreasonable, therefore, to examine the American situation and to learn from experience gained there.

In some parts of the world, additional factors have intensified the insect and other pest problems. Intense cultivation favours multiplication. The non-rotation of crops and the persistent use of special crops for soil replacement help to establish pests. Irrigation and similar projects may favour breeding.

Insecticides and fungicides have been used since 1880, so that it is impossible to say what would happen if their use were to be abandoned. However, many of the special crops—for example, fruit—and some staple foods, such as potatoes, could not be produced in anything approaching adequate amounts without the use of pesticides. Special circumstances in the USA make it imperative for the farmer to use pesticides: the United States Food and Drug Administration (FDA) may condemn food found to contain insect parts as "produced under filthy conditions". Also, in the USA—a country where particular fruits, vegetables, or other foods are frequently raised in great quantities in a relatively small area and shipped to a large market, and where competition has made the profit margin very small—a premium has been placed on products which are free from blemishes. These conditions are peculiar to North America, but they do not detract from the fact that some use of pesticides is absolutely essential in the production of adequate crops under conditions of intensive cultivation.

Insecticides are also widely used for the protection of livestock. Insect pests by harassing cattle will reduce milk production and retard growth (meat production). Other pests ruin hides and wool.

Stored food, especially grain, is liable to very serious depredations by insect pests. In this particular case, as much could probably be gained by general hygiene and better cleanliness in storage places as by the use of chemicals.

Cotton crops can also be seriously reduced by pests, and a great number of insecticides have been used on cotton because there is no fear of residue hazards as there is in the case of food crops.

Finally, there may be the problem of the transfer of insect pests in shipments of food from one country to another.
A very strong case can be made for the need to use chemicals for pest control in agriculture. It is perhaps worth considering whether the sale of pesticides for agricultural use has developed into an abuse in the same way as the sale of patent medicines for the alleged benefit of human ills. Two important factors prevent this: First, the economic margin on many crops, especially cereals, is so small that the cost of applying anything at all would be completely prohibitive unless the increased yield at least paid for this application. Secondly, in many countries where insecticides are widely used the farmer is protected by a government licensing system which only permits the sale of compounds of proven efficacy capable of doing what their labels claim for them.

1.3 Developments in Pesticide Production and Application

The comparatively rapid development and introduction of new insecticides may sometimes be viewed with suspicion by those who are apprehensive of the dangers to health that may arise from their use.

As will be discussed later (page 46), new pesticides are introduced only after extensive trials have proved their worth, and their ultimate success will depend upon their efficiency in relation to those already in use. The toxic hazard is an important factor but if the use of a more toxic material results in a great increase in efficiency by increasing the effectiveness, reducing the cost, and economizing the manpower needed for application, it may be worth while to spend more on developing a careful method of application.

It seems probable that the use of pesticides will increase considerably, especially, for example, on cereal crops and for soil treatment. To keep potential health hazards to a minimum there would seem to be a place for more expert guidance in their use and application.

The attitude towards the use of insecticides differs widely in different parts of the world. Many factors unconnected with the control of pests probably contribute to these differences. In some places there is a tendency to standardize the pest-control practices and, in consultation with the proper experts, spraying programmes are carried out at fixed and regular times during the growing season. In contrast to this, some growers may either refuse to handle a pesticide at all because they have been told it is poisonous, or refuse to buy any until they have direct visual evidence that a pest is destroying their crop. An ideal would seem to lie somewhere between these extremes, and to achieve it the role of the consultant entomologist would seem to be crucial.

It is not considered that at the present time an excessive number of active principles are used in pesticides. Although there are a number of pesticides which have a similar broad spectrum of activity against several
pests, each compound may be especially effective against one or two different pests.

The widespread use of and reliance on chemicals to control living pests is viewed with some misgiving by biologists not primarily concerned with toxic hazards to man or animals. This misgiving must be shared by those familiar with the unfortunate results that have sometimes followed the use of the powerful modern antibiotics as prophylactics against human infection. The gonococcus learnt to accommodate itself to the sulfa drugs applied in this way with the same facility as the fly learnt to live with DDT. The development of some form of natural control of these pests is obviously desirable and many people are studying the problem.

The development of biological control is often very slow and extremely difficult. The breeding of resistant strains of plants may be successful, but the parasite may also learn to adapt itself. Again, the resistant strain may remain free of pests but produce a crop that is markedly inferior in quality or quantity from the original strain. Attempts have been made to build up reservoirs of parasites and predators but this system of control usually means that a percentage of the crop must be sacrificed to allow these natural processes to continue. Though possible with a low-price crop, it may be difficult to carry out with a high-priced one. Control by proper cultivation is not always practical. Even if the virtues of natural manure were established, supplies are totally inadequate. Although there are a few pests that invade only damaged crops, the majority will flourish in direct proportion to the growth and activity of the host. There is much to be said in favour of the concept of biological control for agricultural pests. It is a matter of regret that such methods have to date been of such limited value to the ordinary farmer.

General hygiene measures have played an overwhelming part in the control of human disease, and it seems almost certain that the reliance on chemicals for the control of agricultural pests will continue with modifications from time to time. Experience with DDT for fly control has provided a warning of things to come; but, in the meanwhile, the widespread use of chemicals for the control of pests that would otherwise inflict very serious damage on staple food and other supplies continues to be accepted by the great majority of practical entomologists.

SUMMARY

There can be no doubt that pesticides have proved of great value both in the control of insect-borne diseases of man and in the protection of his crops. Their use will probably expand at least for a number of years in the absence of better methods for controlling the pests against which they are directed. New chemicals are expected to appear but are likely to be submitted to increasingly rigorous experimental testing before they can supersede those in use today.
2. HAZARDS AND THEIR CONTROL DURING MANUFACTURE

It is convenient to consider the hazards arising during the production of toxic pesticides under two headings:

1. Manufacture of the primary active ingredients.

2. Formulation of the active ingredients into material suitable for field use.

As in most branches of the chemical industry, it is among the users rather than the manufacturers of toxic chemicals that the majority of accidents take place.

2.1 Manufacture of Primary Active Ingredients

The active ingredients of the many pesticide preparations are made by very few manufacturers. In almost every case the company is a well-established chemical manufacturer with experience in the handling of compounds possessing all degrees of toxicity. The possession of a high degree of toxicity by a chemical compound is not an absolute bar to its production or use as an intermediate in chemical manufacture.

By comparison with many other chemicals manufactured in bulk, DDT appeared to be comparatively non-toxic. Although a certain amount of caution was advised in the early days because of ignorance of its possible remote effects, in the rush of wartime production arising from the obvious strategic importance of the material, large quantities were produced under conditions allowing scant protection to those who handled it. No ill-effects were reported, and many thousands of tons of DDT have since been manufactured in various parts of the world without any reports of any ill-effects among the plant operatives. In one case a special investigation was carried out by one of the biggest manufacturers among its employees who had been exposed for ten years to DDT.

One of the principal manufacturers of BHC has carried out regular examinations of the workers exposed to it, and has found no evidence of ill health resulting from this exposure. There have been a number of cases of dermatitis among those handling BHC powders but not among those making liquid preparations.

When a new pesticide of this group is being considered for manufacture, a comparative toxicity test on animals will indicate whether the new material is much more or much less toxic. On the basis of such preliminary findings, coupled with a knowledge of the physical properties of the material, it should be possible to decide what type of manufacturing plant will be needed to ensure that the worker is not dangerously exposed. Although some of the newer chlorinated-hydrocarbon insecticides—chlordane, aldrin, and dieldrin—have been manufactured under conditions where there was some exposure to dusts, the men were warned of possible hazards and proper medical supervision was established.
In the case of the organo-phosphorus group of insecticides, their history of association with powerful chemical-warfare agents warned most potential manufacturers of the possible hazards they might encounter. As soon as field tests indicated that there was likely to be a persistent and heavy demand for parathion, some manufacturers took special steps to see that it was going to be possible to produce large quantities without danger to the workers. A number of accidents in the early years made it more than ever necessary to be able to demonstrate that the material could be made safely. One producer in the USA constructed a specially designed plant based on the findings of the firm’s industrial hygiene division; this plant was placed in what is designated as a special area into which no one may go without changing into regulation clothing. No exposure to parathion can take place at any stage of manufacture. A special team of workers has been assembled for the work but they are not paid “danger money”. The firm considers that they are in no danger and this money has been spent in ensuring that this is in fact the case. Although production has doubled each year since 1949, no accidents have taken place during the operation of this plant. This illustrates two points: First, the inherent toxicity of a compound need be no bar to its manufacture on a large scale. Secondly, the cost of making the production of a substance like parathion really safe is such as to exclude any but large companies or those with very big potential markets from undertaking its manufacture.

In contrast to this experience, a large European manufacturer states that they have taken no special precautions to safeguard their workers during the manufacture of parathion and some of the other organo-phosphorus insecticides. In an experience extending over several years, they have had only two accidents, neither of which were fatal and both of which were due to gross carelessness. During 1952, routine blood cholinesterase determinations have been made and the results provide no evidence that such workers have been unduly exposed. It should be emphasized that where manufacturing conditions are satisfactory, the organo-phosphorus compound may be made without danger to the workers.

Special dangers certainly exist in the research and development laboratories of those manufacturers searching for new pesticides. Several serious accidents have occurred, but the number of persons exposed is few and they are all qualified people who should be able to appreciate the risks attached to their work and to safeguard themselves accordingly.

2.2 Formulation of Active Materials into Preparations Suitable for Field Use

Although the active principles of pesticides used the world over probably number less than fifty, the number of preparations which contain them and can be purchased for use in any one country probably run into several
thousand. This indicates that there must be many formulating companies operating in a highly competitive field. For many, the turnover or profit margin must be small; it is not, therefore, surprising that the worst hazards of manufacture arise at this stage. Formulating is carried out by every type of company in every stage of development. Many are small and employ few workers. In some cases the preparation of a given pesticide is carried out only during part of the year, depending on seasonal demand. Many of these firms had handled arsenic, lead, and nicotine for years without apparently running into serious difficulties; vast quantities of DDT and BHC have also been handled without producing illness among the operatives in formulating plants.

The advent of parathion presented a new danger and there were one or two deaths in formulating plants during the early years of its introduction. Because there is no uniform factory legislation in the USA, the special problems posed by the production and handling of parathion in so many widely scattered plants led the Industrial Hygiene Division of the United States Public Health Service (USPHS) to issue a special circular to provide "uniform information to state and local industrial hygiene units and to industry so that co-operative action will be taken in preventing illness from parathion". Recommendations were given in some detail and emphasized the need for proper exhaust ventilation, and for the provision of clean working-clothes and proper washing-facilities for the operatives.

Some of the manufacturers both of parathion and of some of the newer chlorinated-hydrocarbon insecticides have gone to much trouble to see that they sell their products only to those formulators who are equipped to handle them safely. They will actually refuse to sell to a formulator who is unwilling to carry out their recommendations for the provision of adequate safety measures for their workers. Some producers issue manuals of instruction for formulators in which the risks and dangers are described and information is given as to how these may be circumvented. In some cases, exact specifications for the type of equipment that should be used for carrying out the operation may be included. In all cases of doubt or difficulty, the formulator should be encouraged to seek advice from the primary producer about possible hazards in the handling of the active ingredient.

Despite all these efforts the hazards of formulating remain very real. Investigations in two small plants handling parathion showed that while the plant handling liquid concentrates appeared to be safe, an undue exposure of workers took place in another company handling a powder-and-dust preparation. Operatives at one stage in the latter plant exhibited a dangerous lowering of their blood cholinesterase and had to be taken off work. An investigation carried out in 1951 by the USPHS laboratory, Savannah, Ga., showed a general reduction in the blood cholinesterase levels of workers in a dust-formulating plant handling parathion for a few months. The levels gradually returned to normal after seasonal produc-
tion ceased. There were no cases of poisoning in this plant, but a potential danger obviously existed.

Although the safe manufacture of substances more toxic and hazardous than parathion would be possible, it seems that many of the formulating companies would not be in a position to handle them safely. With their limited size, capital, and turnover a majority would be unable to afford the installation of special equipment. On the whole, however, the conditions in these formulating plants should be amenable to control and improvement. Where a country has any legislation on factory inspection its provisions will almost certainly cover this kind of installation. The workers are in a limited environment and their activities are therefore the more readily controlled and supervised. It should be recognized, however, that many of the modern pesticides cannot be safely handled in plants which are adequate for the handling of less-toxic materials and that the process of formulation is a stage in chemical manufacture not suitable for techniques more appropriate to the kitchen. It is recommended that factory inspectors be made aware of the dangers associated with the manufacture and formulation of pesticides so that they may be able to provide appropriate advice and supervision. In France, the hazards of handling parathion have been recognized and poisoning included in the schedule of compensatable diseases.

SUMMARY

Dangers in the production of pesticides arise mainly during formulation. This process is carried out by a large number of firms, many of which are small and lack good equipment. The hazards involved are amenable to control by ordinary measures of industrial hygiene.

3. HAZARDS AND THEIR CONTROL DURING APPLICATION

3.1 General Considerations

An attempt will be made in this section to describe the various hazards that arise during the handling of pesticides in the field and to discuss at each stage what measures have actually been taken to control or reduce these hazards.

As several references will be made to legislation in the State of California, USA, an explanation is perhaps needed. There would seem to be little doubt that legislation for the control of agriculture is as advanced in California as anywhere else in the world. The State has a population of about 12,000,000, and 225 different crops are grown under a great variety of conditions, including artificial irrigation, which is practised in a large area. Agriculture has always been the main industry of the State,
and the present legislation is based on Acts dating from 1901. Each county
in the State has an Agricultural Commissioner with a staff under him
which varies in size according to the amount of agricultural work carried
out in the county. The Commissioners are responsible for a general surve-
llence of all the agricultural activities in the county and their main
role is that of adviser to the farmers. To their many activities in connexion
with cultivation, crops, harvesting, and livestock inspection, responsibility
for the control of the use of "economic poisons" was only a relatively
small addition. In the same way, the control of the sale and registration
of pesticides is only a small part of the activities of the State Department
of Agriculture. For the budgetary purposes of the Bureau of Chemistry,
for example, four-fifths of its income are considered to be needed for
fertilizer control and only one-fifth for the control of pesticides. These
facts should be borne in mind when considering the part played by these
materials in ordinary agricultural practices.

The regulations and practices in operation in California are cited
as an illustration of the type of regulation that has been made, and are
not necessarily an endorsement of the value or general applicability outside
California of any particular regulation or practice. It must be emphasized
that this highly developed control over these economic poisons has been
achieved in a country where all agricultural activities are under close
governmental surveillance.

3.1.1 Handling of concentrated preparations

In almost all procedures except dusting, the first step in handling a
pesticide is the dilution of the material received from the formulator into
a form suitable for application to the crop, livestock, or dwelling. It is
at this stage that the agricultural worker first comes into contact with the
material and at this stage that the greatest risk of poisoning exists.

It is necessary therefore to ensure that the right preparation is used
in the correct manner for the appropriate condition. This is the basis of
control by the registration and labelling of economic poisons. The registra-
tion of pesticides was introduced in some countries in order to protect
the farmer from the purchase of worthless and ineffective pest-control
materials. The existence of such legislation has been turned to good
account by making use of the labelling provisions so as to include adequate
warnings of dangers and how they may be avoided, and instructions for
proper antidote and first-aid treatment in case of accidents. Compulsory
registration of pesticides is in force in Canada and the USA both for
Federal control for inter-State commerce and in the majority of the indi-
vidual States. Many European countries also have a similar system,
while in others official approval is given to preparations which will in fact
(if used correctly) do what the labels claim they will.
3.1.2 Registration and labelling

Registration essentially implies approval of the label. This must state the contents with full details of the active ingredients, but the actual formulation is disclosed in confidence only to the registering authority. The label or accompanying leaflet must state the uses for which the preparation is effective and how it should be applied. It must be suitably labelled if it contains a poison. In this respect practices differ considerably in various countries. The United States Department of Agriculture has four categories:

(1) **Highly toxic**: to be labelled with skull and cross-bones, “Poison” in red lettering, and a statement of the appropriate antidote.

(2) **Toxic**, but not more than about one-tenth of the toxicity of (1): to carry the verbal warnings but not the skull and cross-bones or the word “poison”.

(3) Substances considered to present some hazard: labels must bear cautionary warnings.

(4) Substances considered to be free from danger.

In some European countries, poisonous materials are classified in accordance with general rules covering the sale of all kinds of poisonous materials, and the label must comply with the requirements of the appropriate body.

Several international regulations have dealt with an international system of labelling (the International Convention concerning the Transport of Goods by Rail, which entered into force in 1938; the International Convention regulating the transport of liquid fuel on inland waterways, which was signed in 1939; the Intergovernmental Maritime Consultative Organization regulation on transport by sea, 1948; the United Nations Economic Commission for Europe regulations on transport by road, 1950). At its third session, in September 1952, the ILO Chemical Industries Committee adopted five symbols for the labelling of toxic and dangerous substances, deciding, however, that each country should be free to determine whether or not to use and how to use such symbols in the labelling system adopted for internal trade. The international system adopted merely included one label for toxic substances. The problem of grading toxicity in an internationally-adopted labelling system thus still remains to be solved.

The WHO Expert Committee on Insecticides has included in its recommendations on specifications for insecticides details for the proper labelling of the material.

When a new material has been developed as a pesticide, a decision has to be made about the category of poison into which it should be placed. It seems to be a universal and satisfactory practice for this decision to be made by some interdepartmental committee with representatives, for example, from agriculture, industrial hygiene, and toxicology. In this way the authorities have made use of the laws demanding compulsory
registration to see that the user is given adequate warning of the danger in handling the material he has purchased. Nevertheless, the main purpose of the registration is to ensure that the material sold will be effective as an agricultural product in the way claimed on the label. In practice it has been found that, in about one-half or two-thirds of the applications for registration, discussions take place with the manufacturer before a final label is approved.

This practice of registration has proved very popular with all reputable manufacturers because the farmer is no longer in a position to waste his money on cheap but ineffective preparations, and only the genuine preparations are competing with each other for his custom. The Federal Government of the USA has registered over 35,000 products; in the State of California, 9,454 were registered in 1950. In Canada, about 2,000 products have been registered. In Belgium and Italy, the lists of approved products contain about 750 and 350 names respectively. There are certainly no signs of a monopoly having developed in this field.

It should be noted that no government exercises any control over the labelling of any pesticide produced for export only, and it is left to the firm to produce labels that conform to the requirements (if any) of the importing countries. A need for some international control is suggested by this situation.

Needless to say, even the most exact legal control over labelling will not prevent accidents arising from mislabelling. Thus, a batch of parathion mislabelled as a preparation of BHC was used to spray cattle, with dramatic results. Fortunately there were no human casualties in this incident. Another point that requires emphasis is the need for using a non-fading ink for printing labels. Many of these products stand out of doors, and some printing inks fade in a few days in bright light.

3.1.3 New preparations

When a new pesticide is being developed it may be applied experimentally on crops before it is registered in order that the information required by the registering authority may be acquired. Assuming that it eventually meets these requirements, the product will be registered and will then immediately become generally available. There seems to be considerable anxiety about the inflexibility of the law in such a case, and consideration should be given to some sort of provisional registration to allow a limited use of a new material by responsible people. In this way a product may find a gradually increasing use if experience continues to show that it can be safely handled. This point is discussed again in section 5.4 (page 45).

The vast number of preparations that are registered reflect both the commercial competition in this field and also the many formulations that are apparently found to be necessary for the successful application of the relatively few active ingredients to the crops.
3.1.4 *Types of preparations used*

Water-dispersible powders are very extensively used and this is probably the most popular form in which parathion is sold in North America. Because of the well-known difficulties in controlling powders and dusts, the British manufacturers agreed not to market parathion in a powder form in the United Kingdom, though such preparations were made to meet export demands. For the same reason, German manufacturers do not make water-dispersible powders containing parathion. Entomological opinion seems to demand that a free hand be given in formulations on the grounds that water-dispersible preparations may sometimes be safe where a similar concentration as an emulsion might have, for example, a prohibitive degree of phyto-toxicity.

As it seems unlikely that any authority will prohibit the use of powdered forms of the more-toxic insecticides, much more consideration should be given to their safe handling. The early accidents with parathion in the USA were frequently associated with the handling of powders, and the chief hazard arises when the water-dispersible powder, containing perhaps as much as 25% parathion, is being added to the water before dispersal. One regulation in California makes it an offence to package such powders in containers holding more than 5 pounds (2.3 kg). This ensures that the whole of a package will be used during any single operation and avoids the use of scoops and the handling of open, partly-used bags. Some consideration might be given to the design of suitable openings in the tanks of mechanical sprayers to allow the powder to be added without the simultaneous production of a dust cloud that can blow over the operator. Consideration has been given to the use of smaller quantities of more-heavily impregnated powders, which would contain so much of the liquid, active, principle that they would be sticky and not easily dispersible. However, when such a preparation is added to water, some of the insoluble liquid separates from the powder base and is not properly dispersed within the solution.

In some countries, pastes have been made for DDT concentrates. A properly made paste would seem to be the ideal form in which to handle a poisonous preparation in the field. The dust hazard of powders is avoided and also the risk of spillage and of soaking of skin and clothes associated with the use of concentrated solutions. It will, however, be necessary for the paste to have special properties of easy dispersibility in water. Much of the advantage of using a paste would be lost if dispersion required a lot of vigorous agitation.

Liquid concentrates of all highly toxic materials should be put in small containers that can be readily lifted by one man. The manipulation of strong solutions should be carried out in containers with proper handles and with good spouts for accurate delivery. One way of emptying fluid
from a 5- or 10-gallon (22.5- or 45-litre) drum is to hold the container with two to three fingers in the bung hole at the top. This would be a dangerous practice with containers holding parathion emulsions.

SUMMARY

An effective first step in the control of toxic pesticides is the compulsory registration and labelling of the preparations. Powders, liquids, and pastes may be used as concentrate; each presents difficulties in handling.

3.2 Medical Care for Users

While most of the emphasis must rightly be placed on the prevention of hazards, steps should be taken to see that proper facilities for treatment are available to the agricultural worker who may be poisoned. It is not reasonable to expect every medical practitioner in rural areas to be aware of the new chemicals being used on the farms in his area or to know of any toxic properties they may possess. It should be part of the duty of any agricultural service which knows of the use of any new and toxic pesticide to make certain that the practitioners and small hospitals in the area are given a full account of the signs and symptoms of poisoning and of any effective treatment. It is probably better to pass on the information to the doctors through one of their own professional organizations or through the public-health authorities. Another important step is that all contract sprayers (see section 3.7, page 26) should see that any of their employees working with toxic chemicals in areas far from his home should be supplied with the names and addresses of doctors and hospitals in the areas in which he works. Many cases of parathion poisoning have developed serious symptoms only after work has finished, and there is a distinct chance that any connexion between their illness and an occupational hazard will have been overlooked.

SUMMARY

It is necessary to ensure that facilities for the medical treatment of workers in the field are available.

3.3 Application by Hand or by Simple Manually-Operated Equipment

3.3.1 Conditions of use

The only widespread practice involving dispersal of pesticides by hand is in locust and grasshopper control. Baiting has been carried out on a large scale by simple hand-distribution of bran baits. A bait containing 0.065% BHC has been widely used for several years without producing
any obvious reaction among those handling the material. Smaller numbers
of men have prepared the bait by diluting strong BHC solution with bran,
but again no ill-effects have been observed. Aldrin has been used for
grasshopper control in North America and it is considered that the bait
itself will be safe to handle. It is planned to use aldrin extensively in the
Middle East in this way. That the bait is toxic is suggested by the warning
that it should not be left on the ground in heaps where livestock, e.g.,
cattle, may reach it. This warning is based on actual experience where
cattle were lost as a result of eating the exposed heaps of bait.

Hand sprays have been most widely used for house spraying in malaria
control. DDT, BHC, chlordane, and some dieldrin (5 tons—5,000 kg)
have been handled in this way in Italy and no ill-effects on the operatives
have been recorded. The ideal spray is one which ensures that the greater
part of the material released from the machine strikes and remains on the
wall. In actual practice, there may be considerable primary and secondary
airborne clouds of the sprayed material and the workers may be soaked at
the end of a day’s work of house spraying. In Italy and Greece alone, about
4,000 men have been employed for three to four months every year for
seven years spraying DDT in this way, and no noticeable ill-effects have
been produced. An inquiry made among leaders of malaria-control pro-
grammes in Ceylon, India, and South America all brought the same answer
that no trouble had been experienced during the years DDT and BHC had
been handled. (See also section 5.1, page 43.) At present the problem
is whether it would be safe to use dieldrin in this manner.

In Germany, parathion has been used to spray the interior of buildings
to get rid of bed-bugs, etc., without any accidents occurring among the
applicators. In a few instances hospital wards were sprayed with the patients
still in them. Nevertheless, operations of this kind if carried out day after
day would almost certainly entail a prohibitive risk for the worker.

3.3.2 Protection of operators

In considering all operations involving the manual application of
insecticide solutions, it should be remembered that hard physical work is
involved and that for the most part the work is done during warm or hot
weather. The climate of all malarious countries is hot during the season
when spraying is done and, with the exception of winter washes for fruit-
trees, most agricultural applications of pesticides are made during the
growing (warm) season. For this reason it is quite unpractical to suggest
that the operators of this type of equipment be clad in fully protective
clothing and be made to wear respirators or even goggles. Either the
operation will become impossible or, more likely, it will be performed
without the use of these precautionary measures.
3.3.3 Introduction of new preparations

In the light of existing knowledge, there seems no reason why the precautions at present observed in the application of DDT and BHC should be tightened up, as great experience has already been gained in the safe use of these compounds in this way. When it is proposed to introduce a new compound which, judged by animal experiment, is more toxic than DDT but considerably less so than parathion, there would seem to be the following possibilities with regard to its application: The material can be applied in the same way as DDT, although its introduction should be cautious and a careful medical surveillance should be kept on the exposed workers, and—as an added safeguard—more emphasis should be placed on simple, positive, hygiene measures such as facilities for washing and for changes of clothing. If experience under these conditions indicates that a hazard to health is incurred, then it will become necessary to consider other ways of treating closed spaces such as houses and buildings. If the material has properties which make it vastly superior to any of the insecticides that may be applied safely by hand, new techniques will have to be employed.

3.3.4 Work in orchards

In agricultural work, particularly in orchards, hand application of spray materials is usually effected from a fixed or mobile power unit supplying the solution under pressure to the sprays or lances. Proper training should be enough to teach the operators how to avoid the sprays made by themselves or their colleagues and this presents no particular problem in open fields. The possible hazards in orchards have been given more serious consideration, especially since parathion has been used so extensively for all types of tree-fruit crops.

Working in an orchard presents many obvious difficulties. The problem of covering the whole of the tree means that the spray must be directed in all directions around the tree regardless of the wind direction. The conclusions reached in an investigation of the spraying of lead arsenate 15 years ago are worth quoting: "Even the most careful worker in doing a thorough spraying cannot avoid direct contact with and inhalation of spray and dust". The sheltered and relatively still atmosphere in the centre of a large orchard suggested another danger, namely, that from the vapour released from the deposited spray materials. Investigations were made to assess this hazard. It was found that virtually no parathion vapour could be detected in the atmosphere within the orchard even an hour after spraying.

The hazards in orchards have been further assessed by air samples taken in the orchard during ground-level spraying and during dusting from aircraft, and from the workers' breathing-zone during mixing and hand application. The most significant observation was that the atmosphere in the breathing zones of those who mixed the various preparations for use
was five to ten times more heavily contaminated than the air in the orchard during ground or aircraft spraying. Similar findings were recorded 15 years earlier in the same area when lead arsenate was being used. In work elsewhere, the air breathed by hand sprayers in orchards was found to contain 2-15 μg of parathion per litre. The blood cholinesterase level of these hand sprayers showed a small but significant depression during the spraying season. Although vapour hazards with parathion may be disregarded, this might not be true if a more volatile member of this group of insecticides were to be used. Canadian observations indicate that the hazard will probably arise from inhaled or ingested airborne particles. Work in orchards, especially among the bigger types of citrus tree, involves risks of gross contamination from sprays, especially with an operator working on a tower to cover the tops of the trees. There is also the contamination from drips from treated trees. However, despite these risks and the wide use of parathion in orchards, there have been very few serious accidents from the spraying operation itself.

3.3.5 Serious accidents

Serious accidents have occurred in Brazil and Egypt during the application of organo-phosphorus insecticides to cotton crops. Some details of one incident are available, and it appears that the parathion powder was applied to the crop by spreading it on a sheet of sacking which the workers then shook over the crop. It is not surprising that with such gross exposure the unfortunate victims were found dead in the field.

As a problem in occupational-health protection, it must be appreciated that the educational level of field workers applying pesticides may be low. It may be possible to avoid hazards by relatively simple precautions, but the instructions for taking these precautions must be given in a way that the most illiterate worker will understand. Health and agricultural authorities must constantly satisfy themselves that such precautions are in fact being taken.

SUMMARY

Many operations involving the use of hand sprayers in houses lead to the extensive soaking of clothing with insecticide. DDT and BHC have been applied relatively safely for years under these conditions, but caution is needed in the introduction of the more toxic insecticides. The latter have already been applied in orchards, where the greatest risks are run by those persons mixing the solution. Protective equipment can be used if conditions of work are made suitable, but its use is often unpractical.

3.4 Application by Mechanically-Operated Ground Equipment

3.4.1 General considerations

Mechanically-operated ground equipment is widely used for the application of pesticides to field crops and special motorized equipment has
also been used for application to trees. With proper planning of the
operation, the driver of the vehicle can be protected fairly adequately.
His protection can be and in some cases has been made virtually complete
by the design of gas-tight cabins artificially ventilated by air drawn through
charcoal filters. Even with such equipment it has been necessary to design
the machine in such a way that the vehicle cannot be started until the door
is closed; otherwise the operator may prefer to leave it open!

In all mechanical spraying for crop protection the emphasis tends to
be upon as wide a distribution of the material as possible, and this means
the production of a fine spray. While increasing the efficiency of the opera-
tion it also increases the hazard by ensuring a wider distribution of the toxic
material in the form of finer particles that settle more slowly and are more
readily respirable. At the same time the hazard from the ingestion of
particles small enough to enter the upper respiratory tract but too large
to penetrate to the lungs should not be disregarded.

3.4.2 Use of DNC

In Great Britain and some other European countries there have been
a number of deaths among men applying DNC emulsions as a weed-killer
in wheat fields from tractor-driven sprays. These fatal accidents have
always occurred during hot weather and have often followed long hours
of work, but, while these are undoubtedly aggravating factors, the way in
which these men become poisoned is not well understood.

In central Africa, on the other hand, in an even warmer environment,
stronger solutions of DNC in oil have been applied over large areas for the
control of locusts without causing accidents to the workers. It is possible
that the oily solution used is safer to handle because it does not dry out
on the machinery and raise a secondary dust-cloud, as can happen with the
watery emulsions used for weed control. From all countries that have
used DNC for weed control there have been reports of accidents.

3.4.3 Seed dressings

Mechanical means are also commonly used for applying fungicides to
seed-grain as a dressing before it is bagged. All the dressings containing
mercury are toxic and liable to cause irritation of the skin or respiratory
tract. The machines usually operate inside buildings, and proper exhaust
ventilation should be provided over the operating zone. More considera-
tion might be given to the use of seed dressings in liquid form for virtually
no hazard would be involved in applying them.

3.4.4 Risks of traumatic injury

According to one authority, in California in 1948 there were 55 accidents
per 100,000 agricultural workers but only 18 per 100,000 factory workers.
This indicates that agriculture is a relatively hazardous operation. It has been said that more accidents arise directly from handling the machines that apply the pesticides than from poisoning by the pesticides themselves. This is not said with the intention of inducing any sense of complacency about these toxic hazards, but it does suggest that, in attempting further to reduce toxic hazards, care should be taken that the risk of accidents from mechanical causes is not thereby increased. To save life from one cause of death and increase the threat from a wholly different cause is not good preventive medicine. Consideration should be given to whether the use of goggles, respirators, gloves, heavy boots, and protective clothing are compatible with the safe management of heavy and complex mechanical equipment.

**SUMMARY**

Complete protection is possible for the driver of mechanically-operated sprayers if this is considered desirable. The risks of mechanical injury may be increased unless discretion is exercised in adopting personal protective equipment. The hazards from DNC are discussed.

### 3.5 Aerial Application

The aerial method of application of pesticides is one of increasing popularity. In California alone, in 1951, 2,900,000 acres (1,200,000 ha) were treated by aerial application. The reasons are not difficult to appreciate. For grasshopper control, it took two men with a ground sprayer one day to cover 100 acres (40 ha), whereas the same treatment can be applied over 1,000 acres (400 ha) by two men in 12 minutes in an aircraft. It is obvious, therefore, that more attention should be paid to the proper protection of pilots applying poisonous chemicals from aircraft.

#### 3.5.1 Reports of accidents in the USA

According to the Civil Aeronautics Administration (CAA) of the USA, 1,383 agricultural flying accidents occurred in the period 1948-51. An analysis showed that in only 11 of these cases could the cause of the accident be definitely attributed to the effect of a chemical or other noxious agent. At the same time the difficulty the CAA has in attributing an accident to the effect of a poison is emphasized. The CAA believes that lesser degrees of toxic action “may be partly or wholly responsible for a much greater number of agricultural flying accidents”. Its figures may well be an underestimate. Thus, of the 11 accidents only two were attributed to the effects of the organo-phosphorus insecticides, yet a single clinical report describes two aircraft crashes and one case of miosis in a pilot among the accidents reported in California alone for the years 1948 and 1949.
3.5.2 Causes of accidents

A surprising number of incidents are reported in which the pilot becomes covered in dust or spray during the operation; this suggests the need for a properly designed aircraft. At present, progress is being made towards this end by a collaborative effort between the United States Department of Agriculture, the CAA, and an aircraft construction company. Current practice consists in fitting the equipment to standard types of aircraft; this may mean long pipelines running at various places over the aircraft. The aircraft are often used on temporary landing-strips and very rough ground, which may account for stresses and strains that break pipelines. While the need for protective clothing, respirators, and goggles would seem very desirable, the type of flying required is such as to demand the fullest possible freedom of movement and the largest possible field of vision to prevent the accident-rate from rising even higher.

In view of the obvious popularity and extreme value of the aerial application of pesticides, it would seem that no amount of effort should be spared in designing a machine which could be safely flown, and used for applying even the most toxic material, without exposing the pilot to any hazard at all from defects in the machinery.

Many of the problems of the safe handling of toxic pesticides would be greatly reduced if aerial application were used. The hazards would then be confined to those persons handling this material for loading into the airplane. Here much the same considerations apply as were discussed in section 3.1.1 (page 15). It is to be hoped that full attention has been given in the design of the aircraft to the question of safe loading with liquid or dry pesticide materials.

SUMMARY

Aircraft have been extensively used to apply pesticides, but there have been a number of accidents due to the pilots becoming affected by the pesticides. Special care should be devoted to the design of an aircraft suitable for the work.

3.6 Care and Maintenance of Equipment

Special consideration should be given to the care, cleaning, and maintenance of machinery used in the application of toxic pesticides. The need for cleaning after use should be self-evident if the same machine is to be used for applying a pesticide to one crop after it has been used to apply a hormone weed-killer to another. A chance finding of a heavy deposit of arsenic on brassica offered for sale in a Californian market was traced to the fact that calcium arsenate had been run through a mixing-machine
which had then been used for rotenone without adequate cleaning. The brassica had received the contaminated rotenone.

With regard to this caution, the point to be borne in mind is that the men trained as engineers and mechanics who will be employed in overhauling and maintaining complex spraying equipment will normally have no experience whatever in handling poisonous materials, and it will be necessary to see that they are presented only with cleaned equipment to work on.

**SUMMARY**

Special steps must be taken to clean machines used for toxic pesticides and to see that persons doing this are made aware of the hazards.

### 3.7 Custom or Contract Spraying

#### 3.7.1 Type of service

For the application of a pest-control material, the farmer may purchase his own material and apply it with his own machines using his ordinary labour force for the work. In other cases a group of farmers and growers will co-operate to share equipment and assist each other during the season when applications are made. A third method is for the farmer to employ a professional operator to treat his crops. The firm he employs is usually referred to as a custom- or contract-spraying firm. With the ever-increasing complexity of materials and operations for applying them, it seems likely that this type of operator will increase and that it will be worth while to give some consideration to the implications of his development.

The extent to which contract spraying is practised varies greatly in different countries in comparable stages of agricultural development. It is almost non-existent in some, while in others 80% of the pesticides used in agriculture are applied by contract sprayers. The contract sprayer will employ a group of men who will eventually become experts at their particular tasks; this means that there are excellent opportunities for selection, education, and special training for the work they have to perform. From the agricultural point of view, this will have the obvious advantage that the job they do will presumably be well done. At the same time, the men can be trained to protect themselves from the hazards and can learn to handle dangerous materials safely. Furthermore, the contract sprayer should be able to afford the best type of equipment for the work. He will also be able to arrange for the constant medical supervision of his men as they will be exposed to hazards for the greater part of the year.

#### 3.7.2 Special risks of sprayers of parathion

The disadvantages of the contract-spraying system from the point of view of the danger from poisoning are that the men will be exposed to
agricultural chemicals continuously whereas the farmer’s employee will be exposed only intermittently. The degree to which any particular employee in a contract-spraying firm is exposed will depend to some extent on the firm for which he works. Some firms may apply all types of material to a variety of crops; other firms may work most of the time with one material. The latter practice has recently been carried to some extreme in southern California. Originally the sprayers applied parathion to citrus groves twice a year over two short seasons, and each firm employed a large number of men over a short period. Now it has been found that, except for one to two months in the year, parathion may be applied at any time. The groves are still treated twice a year but this can be done at almost any time of the year. Therefore, instead of employing 100 men to apply parathion for two periods of several weeks each year, a firm will employ about 10 men who work continuously the year round applying parathion to citrus trees. This is a recent development, and it is to be hoped that no untoward results will come of this persistent exposure. A number of laboratories in California have developed the technique for blood cholinesterase determinations, but many of these laboratories are really chemical laboratories not normally engaged in clinical biochemical work. One group of contractors have raised their fees to the cultivators in order to include the cost of regular blood cholinesterase determinations for their employees. At present what is essentially a medical diagnostic test is being conducted and interpreted without the direct participation of a medical man. There is certainly no generally agreed limit to which the blood cholinesterase level must fall before a man is removed from work. The situation is one that would appear to demand some medical participation at an early date, in order that as much information as possible may be derived from the experiences of these operators.

Observations were made on the blood cholinesterase levels of workers in citrus groves who had been applying parathion for weeks at a time; no serious depression of the normal level was observed. In another investigation in California, 11 men from a spray gang of 12 were found to have low blood cholinesterase levels after working continuously for five months. This was noted after six of them had become ill during hot weather.

Recent observations on orchard workers have shown that the incidence of mild symptoms of poisoning—headache, nausea, and fatigue—rises during the spraying season although in many of these cases there is no significant reduction of the blood cholinesterase levels. These observations suggest very strongly the need for making proper clinical examinations of exposed men instead of relying on the findings of blood cholinesterase determinations. An incidence of such mild intoxications shows that working conditions are not completely satisfactory and indicates a need for constant observation of the men if serious accidents are to be avoided. It also indicates
the difficulty in defining safe or dangerous levels of blood cholinesterase in exposed workers.

SUMMARY

The application of pesticides by firms of contract sprayers involves special risks to the men exposed continuously to them. On the other hand, there are better opportunities for observing and protecting these men.

3.8 Control of Agricultural Pesticide Application in California

The system of control of agricultural pesticide application that has been evolved in the State of California has evoked much interest in other parts of the world and is perhaps worth describing in detail.

3.8.1 Licensing of applicants

Contract pest-control operators must obtain a licence from the State. Before this is granted, a representative of the firm is questioned in order to find out whether he is aware of the difficulties and dangers to man, crops, and domestic animals of the operations he proposes to undertake. If he is not aware of these problems he is given suitable references and told to come back as soon as he has studied the matter. The firm may then be given a licence to operate in one or more of the following fields: home-garden application, weed control, citrus fruit, cotton crops, vegetable crops, etc. Normally the licence is extended to cover more categories as the firm gains the necessary experience and acquires suitable equipment. All pilots applying economic poisons by aircraft must also be licensed. There are 1,000 licensed firms in the State and 400 registered pilots, and it is estimated that they apply about 50% of the pesticides used in the State.

Having procured a State licence, the firm must then register with the County Agricultural Commissioner (see section 3.1, page 14) in every county in which he proposes to operate. The firm may then apply pesticides for farmers in the county without further control except when they wish to employ (a) injurious herbicides or (b) injurious materials. The "injurious herbicides" include the hormone-type of weed-killer when used in certain designated areas of intensive cultivation. The "injurious materials" include, at the time of writing: powders containing arsenic applied by power machinery, TEPP, parathion, EPN, schradan, Systox, and dieldrin. New materials are added as they are developed and their use is extended.

3.8.2 Application permits

Before materials in the above-mentioned categories can be used, the contract-spraying firm (or the farmer, if he is to apply the material himself)
must obtain a permit from the County Agricultural Commissioner; before this is granted, the Commissioner must be notified exactly where and when it is proposed to operate. If the Commissioner is assured that no harm to neighbouring crops or livestock will result, permission is granted. This strict form of control was originally developed to protect susceptible crops from the drift of hormone weed-killer sprays and to stop the poisoning of livestock by the drift of arsenic dusts, intended for orchards, on to neighbouring pastures. The permit system allows the County Commissioner to be satisfied that no such incident will take place. The new toxic insecticides have been added to the list of injurious substances so that their application may be limited to the area intended for spraying. After application of parathion at or above the rate of one pound per acre (approximately 1 kg per ha), all such areas must be clearly demarcated with a warning notice telling people to stay out for two weeks from the date of spraying (stated on the notice).

One further important condition is that these materials shall not be applied when the wind velocity exceeds 5-10 miles (8-16 km) an hour. To some persons this may well seem a particularly irksome condition. It is indeed probably applicable only to a country where it does not rain from March to November, and where the climatic conditions are remarkably stable. In practice it means that these materials are usually applied very early in the morning.

The farmer is under the same obligation as the contract sprayer to obtain a permit, and it is usual for the salesman to warn him of the need to do this whenever he sells him a material which falls into one of these special categories.

3.8.3 Penalties

When the State Department of Agriculture hears of an infringement of these regulations, it usually calls a hearing to take evidence. If it considers the operator has been at fault, it will suspend the firm's licence to operate for a period. At a busy season suspension for a week may be the equivalent of a heavy fine. Legal proceedings are taken against the farmer if he has broken the regulations.

SUMMARY

In the State of California, USA, there is an elaborate licensing-and-permit system controlling the application of toxic pesticides.

4. HAZARDS TO THIRD PARTIES

In this section, the hazards to those not directly concerned with the handling of pesticides will be discussed. The greater part of the discussion will be devoted to the position of the consumer of products containing traces of pesticides.
4.1 Hazards to Travellers, Neighbours, and Trespassers

That pesticides and chemicals applied in the same way can travel well beyond the areas for which they were intended was well shown by the use of the highly active hormone weed-killers. The damage they can do to sensitive crops is readily detected, and special restrictions had to be put on the methods of application. The same restrictions were applied in the State of California to the organo-phosphorus group of insecticides. There have been reports of cases of injury to humans from the application of these toxic materials.

4.1.1 Complaints from residents

In 1951, a small group of people in one State of the USA complained that they had been poisoned by drift or dust from insecticides. An investigation was unable to establish that there had, in fact, been any possibility of exposure in this particular case. The blood cholinesterase levels of a few of the alleged victims were normal. In another State, about 20 patients in one community were reported to be suffering from the effects of parathion poisoning. The community was in the orchard area and there had been a high seasonal application of parathion dust at 3% instead of the correct 2% concentration. Several cases of illness were reported and some patients were in hospital several days. More serious was the attribution of two deaths—a child and an elderly man—to poisoning by parathion.

A paper discussing the action of atmospheric contaminants on allergic respiratory diseases quotes a statement from a doctor claiming that insecticides sprayed from aircraft on orchards have not only aggravated the troubles of asthmatic patients, but have even been shown in some few cases to have caused asthma.

Although concrete evidence is lacking that illness or death in these cases was due to the absorption of parathion, there can be little doubt that a potential hazard does exist. The application of sprays and dusts should not result in the contamination of people and domestic property with material intended for the protection of vegetable crops.

4.1.2 DDT in human fat

In the same area, DDT is also widely used on the orchards, among which many of the houses and communities are situated. It was felt that the people in such communities might have a heavier casual exposure to DDT than those in urban communities, but there have been no complaints associating any illness with DDT poisoning.

The United States Public Health Service examined the fat taken at elective surgical operations from members of these communities and also from a group in Savannah, Ga., composed mostly of sailors. In groups of
over 30 from each place, DDT was found in the fat of the majority, but there was no difference in the mean level of each group. Furthermore, no correlation was found, among individuals in the rural area, between their apparent exposure to DDT and their fat levels of DDT. Needless to say, it is impossible to measure the exposure these people may have had and its degree can be assessed only from their own statements. Once again these observations are in keeping with those made 15 years ago when it was found that the level of lead and arsenic in the blood and urine was no different among the inhabitants of rural communities (other than orchardists) than among residents of an urban community.

Another community which is spreading into surrounding citrus groves has raised the question of banning the aerial spraying of the trees with pesticides. This has been discussed, but there is as yet no evidence that anyone has suffered any injury or serious inconvenience from the prevailing practices.

4.1.3 Risks to wayfarers

Trespassers, picnickers, and casual strollers may possibly suffer ill-effects from entering recently treated orchards or fields. The studies referred to in section 3.3.4 (page 21) show that there is no vapour hazard; injury would only arise, therefore, if the people came into much direct contact with the treated foliage. In California, all areas treated with organophosphorus insecticides must be posted as dangerous to enter.

SUMMARY

Despite reports to the contrary, there have been no substantiated cases of poisoning among residents in areas where large quantities of pesticides are applied from the air. There is no evidence that residents in these areas have more DDT in their fat than those in urban areas.

4.2 Hazards During Harvesting and Handling of Treated Crops

One medical officer who had worked for the State Department of Public Health in California stated that it was his belief that there had been as many cases of poisoning from parathion among those harvesting or cultivating treated crops as there had been among those applying the insecticide to the crops. Unfortunately, figures do not exist to substantiate this statement.

Soon after the introduction of parathion, there was an incident in which over 20 men became ill within a few hours of starting to harvest pears that had been treated 12 days earlier. None was seriously ill and all recovered dramatically after receiving an injection of atropine. Analyses of the fruit and foliage revealed little residue, but in the region where it occurred the incident is accepted as an authentic case of poisoning. The
makers of parathion have always recommended that at least two weeks should elapse between the time of application and any handling of the treated crop. This is believed to be well within the safety limit as analyses of fruit-trees had shown that the greater part of the parathion had disappeared within 48 hours.

In 1951, another dramatic incident—reminiscent of the earlier one—occurred among a group of men working in a vineyard 33 days after it had been sprayed with parathion. Within a few hours 16 of the 24 men became very ill with symptoms of parathion poisoning, but they soon recovered after treatment in hospital. That poisoning by parathion was responsible was verified by the finding of reduced blood cholinesterase levels in some of the men. It is difficult to explain this incident unless it is accounted for by the rapid growth of the large upper leaves of the vine which thus spread over the lower leaves that had received parathion. The men were kneeling and thinning the foliage, and so would have been brought into intimate contact with any residues remaining on the leaves. In another case, two men became ill in a pear orchard, but in this case there was a thick ground-crop and, in addition, it is believed that the orchard had received more than the specified treatment. The contamination almost certainly came from the ground crop and not from the trees. From Canada, there is a recent report of three men who became ill and were taken to hospital with symptoms of parathion poisoning. They were culling peaches three days after the orchard had been sprayed with parathion. They recovered rapidly. There have been no reports of illness among workers in crops treated with other insecticides.

It is obvious that a potential hazard must exist if intimate contact is made with foliage recently treated with material as toxic as parathion. Furthermore, there may be conditions under which toxicity will persist for unusually long periods, as shown by the incident in the vineyard. No fatal cases of poisoning have yet occurred from contact in this way but any cases of illness in those working among recently treated crops should be viewed with suspicion. It is obvious that care must be taken where possible to ensure that applications of parathion are not made to crops just before they require cultivation or similar attention. This provision may be more difficult to enforce than one which forbids the use of the material within a given time before harvest. The latter restriction is based mainly on the consideration of residues that reach the consumer on the harvested crop.

There is probably no risk to those who handle harvested produce from treated crops except in so far as they may be liable to absorb small quantities in the same way as the actual consumer.

**SUMMARY**

There have been well-substantiated cases of poisoning among persons harvesting or handling crops treated with pesticides.
4.3 Hazards to Consumers of Food Containing Traces of Pesticides

4.3.1 Difficulties in assessing the hazards

An assessment of the hazards to consumers of food, etc., containing traces of pesticides is most difficult. It cannot be emphasized too strongly at the outset that there exists at the present time no evidence whatsoever that the ingestion of small quantities of those pesticides in common use have given rise to any symptoms or clinical syndrome of poisoning in man.

On the other hand, there is no one yet in a position to say with any confidence that the ingestion of small quantities of a material like DDT over the virtual life-span of a human being would be entirely harmless. Men worked for years in certain dye factories before it was realized that their exposure to specific compounds greatly increased their predisposition to cancer of the urinary tract. Workers in a nickel factory and in some chromate plants show a raised incidence of cancer of the respiratory tract, though the exact cause of this has not been discovered.

There is no shred of experimental evidence to suggest that DDT predisposes any experimental animal or man to malignant changes in the tissues, but the above-mentioned instances are given to illustrate the difficulty in being certain about anything related to the etiology of human disease.

4.3.2 Evidence that humans have absorbed DDT

That the ordinary population is ingesting DDT is clearly revealed in studies that have been made on human fat. In animals and (as seems probable) in man also, DDT shows a remarkable predilection for storage in fat, and in rats it is possible to find much higher concentrations in the tissue fat than are present in the diet consumed by the rat. When the figures for the DDT content of human fat are considered, it should be remembered that nothing is known about the source of this DDT. Although some may have been present in the food as purchased, there are many other possibilities because of the large number of domestic preparations used which contain DDT. In some cases a single gross exposure might have been responsible. Nothing is known about how the figures for the DDT content of fat in any individual of the general population will vary from month to month or from year to year.

When an attempt was made to assess the degree of probable exposure to DDT from the content in the fat, it proved impossible, with the exception of operators who had been exposed for the greater part of four or more years, to correlate the level found in the fat with the assessment of the probable degree of exposure. While errors in assessing ordinary exposure may well have been considerable, there remains the possibility that individuals dispose of ingested DDT in different ways. There is a sex difference.
in disposal in the rat, but little evidence of individual differences in a supposedly-uniform laboratory strain.

Assuming that there are differences in the ways an individual disposes of DDT, e.g., metabolism followed by excretion or storage, it is impossible to say which would be the most injurious. It has been suggested that the chronic toxicity of any one of these insecticides may be related to the predisposition it has for storage in fat. It may be equally important to consider the rate at which the stored compound will disappear from the fat.

There are certainly no adequate grounds for assuming that a member of the chlorinated-hydrocarbon group of insecticides is more likely to produce chronic toxic effects simply because it is readily stored in fat.

4.3.3 Risks facing the population

In the absence of any generally acceptable criteria for the measurement of chronic toxicity in small animals, the risk to health arising from the substitution of one type of insecticide for another when each leaves some residue must remain a matter of opinion. In view of this uncertainty, and since the problem is not one that is likely to be resolved in the near future, it is perhaps as well to consider other factors in relation to residue hazards.

The hypothetical risks discussed in the preceding paragraphs must be considered in relation to the practical advantages gained from the use of a pesticide. If large quantities of a staple item of diet are to be made available to an undernourished population, or if their health is to be secured by widespread insect-control, then the risks from eating contaminated food would seem to be well worth accepting. They can be accepted perhaps more readily when it is realized that agricultural practices may well change within a few years and that, even if they do not, the chemist will almost certainly produce one new material, if not several, during the lifetime of an individual. The likelihood of anyone ingesting traces of one particular chemical from early youth to even a premature old age is not very great. In more prosperous communities it is obviously more difficult to decide what risks should be run with the semi-luxury crops such as fruit and special vegetables. However, they are never a major item of anyone's diet, and if the staple articles of diet of this particular population are free from contamination (as indeed they are likely to be) then any risk must be correspondingly much less.

Much concern has been expressed about DDT in milk, and no measurable traces of DDT are allowed in milk produced in the USA. The cow is so efficient in absorbing and storing DDT and excreting it in milk fat that even the small quantities reaching its fodder from the spraying of barns and cow-houses were enough to lead to measurable quantities
appearing in the milk. Cows fed on sprayed forage containing 20 parts per million (p.p.m.) DDT will excrete milk containing 2 p.p.m. If that milk were to be made into butter, the DDT-content would rise to about 25 p.p.m. This ability to absorb and store DDT on the part of laboratory animals, domestic animals, and man has naturally focused a great deal of attention on this compound, but even so no connexion has yet been established between the ingestion of these small amounts of DDT and any human ailment.

An important cause of food loss is destruction by insects during storage. Insecticides such as DDT and BHC can be used effectively for the control of these pests in amounts that do not give rise to serious residue hazards in the final foodstuff; however, if a staple article of diet like bread is involved, then a careful control of residues is advisable.

4.3.4 Need to balance risks against advantages

The whole question of the possible toxic effects of chemical residues in food requires much further research and observation. Recent observations on the apparent effect of extremely small quantities of beryllium on a small proportion of the population exposed to them provide a warning. They also indicate again the need for careful observation on man rather than sole reliance on the results of animal experiments.

In the light of existing knowledge, the policy with regard to residues in food should be one of enlightened caution. The advantages of using the pesticide as represented by improvement in the nutrition of a population must be set against the hypothetical risks incurred. Definite rulings on these questions must await the slowly developing knowledge of how these chemicals act on the living body. Meanwhile, it is well to consider how residue hazards may be reduced by means of proper controls.

4.3.5 Control of residues by correct application

The first important factor in residue control lies in the correct application of the materials. Correct instructions for use should appear on the label, and these instructions must include provision for avoiding residues as far as possible by relating the time of application to the persistence of the pesticide and to the expected time of harvesting of the produce.

The next factor is the proper education of the cultivator so that he is made aware of the importance of avoiding residues as far as possible. For some crops, spraying programmes can be worked out so that the use of all insecticides leaving undesirable residues stops at specified times before harvest.

The organo-phosphorus insecticides do not normally present residue hazards, but if incorrectly used they can certainly make their presence
known. When parathion was first introduced into one country it was widely distributed among market-gardeners; however, an extensive outbreak of acute "gastro-enteritis" was eventually traced to the fact that vegetable and salad crops had been freely sprayed immediately before being gathered and sold in the local markets.

All the new "persistent" organic insecticides have some vapour pressure and will eventually disappear by volatilization in addition to ordinary weathering. In this they all differ from lead arsenate which is a truly persistent insecticide and can be removed only by mechanical dispersal.

Large residues are more likely to be caused by errors in timing the application of a pesticide than by errors in the amount applied. The new "persistent" insecticides disappear by volatilization at a constant rate. The amount lost in a given time will be proportional to the amount present, and the loss will be exponential in character. Thus, if two to four times the recommended dose is applied but the proper period is allowed to elapse before harvesting, the residue left may not be measurably larger than after a normal application. Many other factors, especially the weather in the case of outdoor crops, will affect the loss of pesticide. Naturally, crops harvested before this period will contain quantities proportional to the amounts applied.

4.3.6 Control of residues by pure-food laws

In many countries there are some basic laws governing the purity of food, and by the strict letter of these laws it would be possible to ban a food containing any pesticide, or similar chemical, on the ground that the food contained a poisonous substance. Where it is impracticable to ensure that a food is free from any foreign material, permitted limits or tolerances are set up. Those for lead and arsenic are probably the oldest, and in England were based on outbreaks of mass poisoning early in the 20th century. Similar limits were applied to fruit treated with lead-arsenate sprays for pest control. A limit for fluorine was also set up.

In California, there is at present a State-permitted tolerance of 7 p.p.m. DDT. This is the only official legal limit for DDT. The United States Federal Security Agency has held extensive hearings with a view to defining permitted limits for some of the new pesticides, but so far no statutory limits have been laid down. Instead, the growers and others try to work to tentative limits which may be given or suggested in published papers or lectures by officials of the United States Food and Drug Administration.

In a similar way, tentative limits based on expert opinion are used in Great Britain. Such recommendations do not imply any legal limit, but express a consensus of expert opinion. In the light of prevailing
uncertainty about the hazards that may or may not be in the process of being incurred, it seems to be the only satisfactory way of dealing with the situation. There remains a reasonable flexibility behind which is the force of law to exclude any particular material from food if it ever appeared necessary to do this.

4.3.7 Control of residues by chemical analysis of food

However, with either tentative or legal limits there remains the need for a means of providing the evidence of contamination. For this purpose it is necessary to develop reliable methods of analysis, but this is proving to be extremely difficult as more and more chemicals of increasing complexity and little-known properties are released for use as pesticides.

The problems of residue analysis centre largely on the chlorinated-hydrocarbon group of insecticides. An excellent practical method for DDT analysis has existed for some years, hence the wealth of information about the behaviour of DDT. A simple workable method for BHC has now appeared, though until recently this had been an extremely difficult compound to estimate. Methods are in the process of development for aldrin, dieldrin, and chlordane. None yet exists for toxaphene.

All these methods are different, and it has been estimated that it takes a week to get one of them working and that the apparatus used may occupy a considerable part of the laboratory bench. To set up a number of laboratories, any one of which may be called upon to satisfy a request for an estimation of DDT today, aldrin tomorrow, and BHC next week, may involve considerable difficulty. It might be advantageous to make more use of the organic-chloride method. Admittedly this method is non-specific, but the errors are loaded on the side of safety. Thus, if no organic compound containing chlorine is present, there cannot possibly be any of the original insecticide left. If, however, some organic compound containing chlorine is present, it may or may not be the original compound, but for the purpose of computing the residue it will be taken as being the original material. If the method can be made applicable to all the existing chlorinated hydrocarbons, it would seem to be the one which should be adopted by all but the largest and best-equipped analytical laboratories.

Further refinements of analytical technique are certainly required as the need for more and more complex procedures grows. Techniques for extracting the pesticide from the material in which it occurs—fruit, cereal, milk, meat—need to be standardized. In one laboratory, much effort is being spent on the development of semi-automatic chemical manipulations which will reduce as far as possible human sources of error in these procedures.

It is quite useless trying to lay down legal or tentative limits for levels of pesticides in foods, or elsewhere, if methods do not exist for the determination of the compounds. Furthermore, no legal ruling is likely to
prove very effective in practice until the methods can be satisfactorily
carried out by analytical chemists running routine tests.

SUMMARY

There is a possible risk to health from the ingestion of small quantities
of pesticides in food, but there is no evidence that anyone has suffered
illness from this cause. Difficulties in assessing this hazard exist, but
control would be relatively simple provided that suitable methods of
analysis were available.

4.4 Accidental Poisoning (Non-Occupational)

A number of violent deaths have occurred from poisoning by the new
pesticides. Small children have drunk them from bottles left within their
reach, they have been administered to personal enemies, and they have
been used for suicidal purposes. On other occasions they have been quite
improperly used in the killing of insects, with fatal results. In this respect
these compounds differ in no way from any other poisonous material used
in or left about the home within the reach of all. The occurrence of such
accidents, tragic as they may well be, is no reason for banning the sale of
the compounds. Where their accessibility can be controlled by existing law
without interfering with their proper usage, this should be done.

SUMMARY

Non-occupational poisoning can follow the usual type of carelessness
but is no reason for restricting the proper use of pesticides, provided they
are accompanied by clear and explicit instructions for use.

4.5 Herbicides, Fungicides, and Molluscocides

DNC and the organic mercurial derivatives have been mentioned as
examples of dangerous herbicides and fungicides respectively (see page 23).
If mercurial fungicides become popular for treating food crops, as
opposed to seed, care will be needed to control the possible residue
hazard; the use of mercurial derivatives for prolonged periods will also
introduce the danger of chronic mercury poisoning, which is such a difficult
clinical entity to detect. The derivatives of dinitrophenol related to DNC
have similar toxic properties and must be handled with equal care. The
group of selective herbicides derived from phenoxyacetic acid appears to
be free from all toxic hazard and can be used with safety.

Copper sulfate is the most popular molluscicide and, like the copper
fungicides, presents no special toxic hazard; traces can be consumed with
safety. There are no new compounds in wide use yet as molluscocides.
Pentachlorphenol has been used for this purpose; it has been applied for many years as a timber dressing and, if ordinary care is taken to avoid gross skin-contact, should present no special toxic hazard.

4.6 Rodenticides and Rat Control

Several new compounds have been introduced as rodenticides in recent years.

Sodium fluoracetate has proved very effective because, in addition to its extreme toxicity, rats will readily accept it in food or water. Its action is swift and it is of special value in dealing with rats when an outbreak of plague occurs. With ordinary care it can be handled with perfect safety by the professional rat-catcher, but it must be treated as at least as dangerous as cyanide, which no one would normally leave within the reach of children or put into cups and bottles where it might be inadvertently consumed. Sodium fluoracetate is a weapon for the pest-control operator and not the individual user.

The new group of rodenticides containing coumarin derivatives represents a real advance. They are most effective when ingested in small quantities over several days. This means that so little need be added to the bait that the latter is not made unpalatable. A single accidental ingestion of contaminated bait would have no effect on man or domestic animals. If repeated ingestion were to take place, the symptoms and signs of poisoning would develop slowly and there is an effective antidote (vitamin K) available for treatment.

The use of bacterial rat-poisons would seem to provide a potential risk of human infection out of all proportion to their value as rodenticides. Their use is banned in many countries.

4.7 General Principles of Control of Hazards

The successful control of malaria by means of insecticides in some parts of the world has led to the development of control campaigns of ever-increasing size. Attention is now being paid to the control of the insect vectors of other diseases. Not only will DDT and BHC continue to be used on a large scale, but other insecticides are likely to find a place in vector-control programmes.

The demand for increased supplies of food suggests that a greater use of pesticides can be anticipated and that they will be required in countries which have hitherto had comparatively little experience in their use. Tragic incidents reported from several different countries indicate the dangers of a hasty introduction of the more poisonous varieties, such as parathion, under inadequate conditions of control. If a large and permanent require-
ment for a variety of pesticides is likely to arise in any country lacking experience in their use, the following factors demand consideration.

4.7.1 Control of manufacture

From the point of view of industrial safety, there would seem to be no reason why a great many of the pesticides should not be made in any country that can set up the necessary plant and arrange for the supply of raw materials. However, the safe manufacture of a material as toxic as parathion would call for the erection of a special plant, which could be safely run only by someone with experience in handling toxic chemicals in industry, and if adequate supervision, including periodical medical examination of the workers and notification of poisoning, were maintained.

Whether or not the active ingredients are manufactured locally, a need will almost certainly arise for formulating plants. The cost of transporting the inert fillers and diluents of formulated preparations from a distance would add unnecessarily to their cost if formulation could be done locally. In some, but not all, countries formulation is carried out by many firms, some of which are small and simply equipped. Small firms equipped for formulating DDT or BHC could certainly not handle the organo-phosphorus group of insecticides without a radical review of the safety of their equipment and methods. If such an industry were to be developed for the first time in a country, there would seem to be a good case for introducing strict supervision and a licensing system for the firms concerned. Advantage could be taken of such control to ensure that the materials were properly packaged in containers which complied with accepted rules for handling in the field.

4.7.2 Control of use

Insect-vector control programmes are normally under the charge of the health authorities so that medical advice and supervision will always be available to those persons handling the pesticides used in this work. Specifications for insecticides and equipment have been drawn up by WHO, and its recommendations will be continually revised as needs change.

When used in agriculture, pesticides at once pass from the immediate purview of health authorities; the latter should satisfy themselves, nevertheless, that the medical practitioners and the hospitals in rural areas in which these compounds are used are conversant with the diagnosis and treatment of poisoning by these pesticides. Every effort should be made to encourage the notification of any cases of suspected poisoning. Consideration might be given to the establishment of specifications for mechanical equipment used in the application of the more toxic insecticides.

Some system of registration of all pesticides seems desirable because through such a system it is possible to ensure that all preparations are
marketed with suitable and adequate instructions for their safe use. This control must be vested in some basic administrative organization connected with agriculture; the responsibility for enforcement can be allocated to any branch that has its agencies distributed in the field. It is inadvisable for any country developing its agricultural resources to do so without some field service to advise on such matters as seed, fertilizer, irrigation, harvesting, and general husbandry. Responsibility for enforcing any pesticide-control legislation should be vested in these agencies. A country not yet possessing some basic field organization of this kind is not yet in a position to handle modern pesticides safely. Their introduction into a country should not be left solely as a commercial transaction between salesman and farmer. Wherever licensing systems exist, they have been welcomed by all reputable manufacturers.

For the safe application of these materials by farmers it will be necessary to organize education and training. This might include courses of instruction and the publication of suitable articles in those sections of the agricultural press which are normally read by farmers. In many cases some instruction will be necessary in order to ensure that the material is used correctly from the agricultural point of view. No opportunity, therefore, should be lost of using the same occasion for giving advice on the safe use of the material, including emphasis on personal hygiene and protection as well as on the safe storage and disposal of containers. Instruction on these problems might form part of the curriculum in agricultural colleges and training institutions.

Where the need to use pesticides is urgent, a policy of taking a calculated risk must be adopted. The important factor is to have the use of any potentially dangerous material sufficiently under control so that, in the event of an unforeseen tragedy or threat to life and health, its use may be curtailed at short notice.

4.7.3 Control of application

The services of contract sprayers might well be of value for the application of pesticides in relatively underdeveloped countries. By ensuring that proper responsibility for their employees is adopted and that permanent staff rather than casual labour are used for the hazardous jobs, the chances of accidents will be much reduced. Care must be taken to see that only machinery properly designed for safe use is employed for distributing pesticides. There must be a general restriction of sales of all the more-toxic pesticides to individuals for house use. In countries where parasites abound on man and in his home, there is a temptation to use these agricultural preparations for domestic or even personal use. A number of fatal accidents have resulted from this.
4.7.4 *Control of residue*

The prevention of third-party risks will depend on labelling and other instructions for timing the application. Local factors may be important, as, for example, when a main crop is intercropped with domestic vegetables which might become grossly contaminated by a treatment perfectly in order for the main crop. The question of food and crop analysis for residues will not assume any importance until the agricultural and nutritional development has proceeded to an advanced stage. If, in timing the applications in relation to harvest, practices in use elsewhere are followed, there will be no fear of any disaster.

4.7.5 *Information on toxicity*

In all cases of doubt about toxic hazards, those with no experience in the use of a new material should consult the manufacturer of the main active ingredients. There is a well-established tradition which is widespread in the chemical industry that information and advice on toxic hazards is freely given whenever it is sought. Where a country relies on imports for its supplies of pesticides it should have no difficulty in obtaining full information on the properties and correct use of any new insecticide from official sources in any country where a similar preparation has been registered. No new material will be accepted for registration until every reasonable step has been taken to investigate its toxic properties and, if these exist, to make satisfactory recommendations for its safe use.

**SUMMARY**

The general principles of pesticide control are discussed in relation to the introduction of these materials for the first time into a country; this section is essentially a summary of the main recommendations contained in the preceding sections.

5. **SUGGESTIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH**

Advances in knowledge of the physiology and biochemical behaviour of pests and their hosts will undoubtedly lead eventually to different methods for the control of pests. There is certainly much scope for the development of more-selective pesticides, and as they become more and more selective, the probability that they will be harmful to man diminishes. Meanwhile, it seems reasonable to assume that man will have to become accustomed to living and working in varying degrees of contact with a number of different chemicals such as those used today as pesticides.
5.1 Further Study of Workers Exposed to Pesticides

There is an urgent need for a closer study of man himself under conditions of exposure to pesticides. As Simmons & Hayes have said with regard to such studies: "Careful attention should be given to the principles of epidemiology. In general those persons with the greatest exposure to a compound will show the greatest effects—if effects are to be shown." Nothing derived from a study of animals exposed to these materials would lead anyone to think anything to the contrary.

In manufacturing plants and in various parts of the world today, there are groups of men who have experienced considerable exposure to DDT and BHC for seven years or more. Sometimes the exposure is continuous; in other cases exposure has been for three to six months in the year. In many parts of the world the spraying operators employed in malaria teams are agricultural workers who are temporarily engaged in this work, but in some places, such as Venezuela, spraying crews are permanent and exposed to insecticides throughout almost the whole year. Smaller groups have been exposed for shorter periods to methoxychlor, toxaphene, chlordane, aldrin, and dieldrin. If exposure to these materials does present a hazard, now is the time to start investigating and laying the lines for information in the future. A simple assurance that the men in these occupations have shown no ill-effects is not always adequate evidence of the truth of that assertion. It is necessary to make a careful inquiry and to compare the health of these men with others who differ only in their non-exposure to these materials.

These compounds might exert their toxic effects by producing specific symptoms and signs of poisoning. On the other hand, their effects might be exerted in a more subtle way. It was not for very many years after its introduction into therapeutics that an association was established between the ingestion of amidopyrine and the incidence of agranulocytosis. An investigation of groups of men exposed to insecticides should include, therefore, a survey to see whether or not they have shown any exaggerated predisposition to other diseases. This type of investigation would seem well worth carrying out on as wide a scale as possible. Elaborate clinical or biochemical studies are not necessary at this stage; what is needed is an adequate record-system with means of finding out and recording illness in the population in question. If some kind of survey of these workers can be established, the opportunity might be taken on every possible occasion, for example, accident or elective surgery, to remove fat samples for analysis of insecticide content. Similar types of survey might be started among the employees of contract sprayers exposed to other pesticides, such as the organo-phosphorus insecticides and the herbicides.

There is always the fear that exposure to chemicals may predispose a person to cancer. Any undue incidence of this disease in such a population would certainly pass unnoticed unless a special inquiry were to be made.
5.2 Information on Accidents

At the present time in the countries where the more toxic pesticides are widely used it is extremely difficult to obtain figures for casualties. This is natural enough when they are occurring in widely scattered rural areas. Some incidents are reported many times: for example, a single death from parathion is described in four separate publications, the last of which appeared three years after the accident. Many others are never reported at all, and all kinds of rumours are rife. Notification systems are of little value unless the incidents are followed up, as otherwise mistakes in early diagnosis go uncorrected. No system is likely to cover every incident, but a need seems to exist for some international agency, such as WHO, to be made responsible for collecting information on these casualties and for following up stories. Such information is of value not only in assessing the total casualty-rate but in learning how these accidents occur and where further protection is needed.

5.3 Environmental Studies in Agricultural Work

There is also scope for further work on occupational health as applied to agricultural workers. A study of the environment in orchards has been made on several occasions. Dust hazards around seed-dressing machines and spray hazards on weed-spraying machinery have been investigated. More information of this type is needed so that it may be possible to assess any improvements in the design of machinery for applying toxic materials. With the possible use of more-toxic materials for house spraying in malaria control, a study of the inhalation hazard is urgently needed.

The design of efficient distributors of liquids and dusts has so far been mainly confined to improving the economy and efficiency of their distribution on plants, trees, or walls. Although the hazard to the operator should diminish in proportion to the efficiency of the application to the proper target, the possibility of the production of clouds of fine particles of respirable size should not be ignored. A loss in this form might be of such a small mass as to be ignored in calculating the efficiency of the machine. The part played by dried deposits on machines, or elsewhere, and the role of formulations in reducing hazards from inhalation and skin absorption, should be studied.

As mentioned earlier (page 15), the chief dangers in the field are associated with the handling of concentrated materials when diluting them for use. In both agriculture and malaria-control work some attention might be given to the production of simple field equipment which would provide safe mixing in bulk, and simple and safe methods of filling hand or machine sprayers with the diluted materials. The desirability of improving aircraft design has also been mentioned (page 25).
5.4 Experimental Studies on Toxic Properties

For the basic evaluation of toxic hazards of new chemicals, reliance must still be placed upon studies on experimental animals. Tests for acute toxicity can be carried out on a wide variety of animals and a reasonable conclusion as to the hazard to man can usually be drawn. The use of fowls to detect one of the side-effects of poisoning by certain organo-phosphorus insecticides illustrates the necessity for using a number of species in these tests.

Tests for chronic toxicity are not nearly so satisfactory. Current methods leave much to be desired from the purely statistical viewpoint alone. Whether it will be feasible to make much improvement in this type of test is perhaps open to doubt. What must not be lost sight of is the inadequacy of the present methods for the detection of small metabolic disturbances in experimental animals and the undesirability of drawing too many conclusions from observations on relatively small numbers of rats. Fed to most stock laboratory animals, triorthocresyl phosphate appears to be relatively harmless, yet man is extremely sensitive to its effects.

It must never be forgotten that the results of animal tests may be of little value in forecasting the effects of a substance on man. This makes it all the more desirable that, after registration for the first time, a new pesticide should only be introduced slowly for public use. There may in fact be a case for introducing it somewhat earlier so that observations on man can be made before the results of all the long-term animal experiments are available. There would seem to be less risk attached to such a practice than to that of allowing a more widespread use immediately animal tests seem to be satisfactory.

5.5 Studies on Mode of Action of Pesticides

There is a need for a much more fundamental study of how the pesticides at present in use act on the pest and upon mammals. The amount of enthusiasm shown for the search for new and better pesticides is perhaps disproportionately greater than that shown for the discovery of a little more information about the way those already available exert their effects.

Close attention must be given to the improvement of analytical methods for compounds now in use or proposed for use. Apart from its value to research workers, a reliable method is essential if legal limits to the amount of the material permissible in food are to be established. However, a method that can be used in a research laboratory may not be suitable for a routine analytical laboratory, and it is the need for simple, rapid methods that is so important.

One special development in pest control should perhaps be mentioned, namely, the development of what are called “systemic” insecticides. These materials are absorbed and translocated by the plant and they kill
insects feeding on the plant. No doubt systemic fungicides will also be developed. These materials have many obvious advantages. For example, mechanical application can be simplified because the plant will take up the material from its leaves or from the soil and redistribute it within itself.

What is needed is more knowledge of how these substances exert their effects. Do they remain unchanged in the plant or are they changed into something much more toxic for the insect? If the latter is the case, nothing is known about the properties of this hypothetical material. If these systemic pesticides are metabolized within the plant, do they disturb the normal ingredients of the plant? A few simple facts about the behaviour of these materials within the plant might do much to remove existing anxiety about their possible toxic properties to man or animals consuming produce treated by them. Their intrinsic toxicity to mammals seems to be similar to other members of the organo-phosphorus group of insecticides in use today.

**SUMMARY**

The need for further information on the hazards arising from the use of pesticides demands a closer study of those persons who are most heavily exposed to them during their work. Surveys over a number of years are needed. A better system for collecting information on accidents is desirable; this might be operated by an international agency such as WHO. Research is needed on the mode of action of toxic properties and on methods for the analysis of these materials.

**CONCLUSIONS**

Pesticides of all kinds are likely to be used on an increasing scale in the future for the control or eradication of diseases of man and his domestic animals, for the improvement of crop yields, and for the preservation of stored food products.

The problem associated with the handling of poisonous pesticides is not a new one but it has grown more serious because of the more widespread use of these materials and the great increase in the number of different chemicals employed for these purposes.

None of the materials in use today is so inherently poisonous that its safe use is impracticable. In those countries where new compounds are being developed, the control over their introduction is such that unduly dangerous materials are never likely to be permitted for general use. Indeed, so exacting are some of the requirements for preliminary testing becoming, that the expense of investigating promising material may discourage some private manufacturers from making the attempt. This is not to say that these preliminary tests should not be carried out but it may indicate the need for governmental assistance in conducting some of the more extensive tests if it is felt that the use of these materials is likely to be of economic importance.
Some of the materials in use today are capable of producing severe and fatal poisoning if handled carelessly in the factory or during application. Nevertheless, with experience, the number of accidents appears to have decreased despite increasing use of these materials. Really serious disasters have occurred when they were introduced for the first time into certain countries. It remains necessary, therefore, to ensure, by education and instruction, that these materials are used properly. Improved design of equipment based on a better understanding of the actual environmental hazard will be of value in protecting the field operator.

Other materials are unlikely to produce acute or fatal poisoning, but because of their stability and persistence may remain in food and be consumed in small quantities over many years by the general public. Much anxiety has been expressed on this score, and it is certainly desirable that food should not contain foreign chemicals lacking any nutritive or beneficial value to man. Nevertheless, there is no evidence whatsoever that the ingestion of these materials in this way has produced undesirable reactions.

It is perhaps too early to expect such reactions to have been observed. In order to be in a position to detect untoward reactions at the first opportunity, advantage should be taken of the existence of small groups of the population in manufacturing and processing plants and employed in field operations who come into much closer contact with these materials than the general public. Every effort should be made to keep health records of these groups for it is only data on man that will provide the necessary reassurance about the safety or otherwise of these new materials. The final answer will never come from animal experiments, though these must always be conducted to provide preliminary information.

Much has been written about the hazard from consuming food containing traces of pesticides, but there is no information about the extent to which this actually takes place. A good analytical service is essential for controlling the situation and gaining this information. The chief need here seems to be the development of methods of analysis suitable for this work on a wide scale.

Progress in the saving of life by prevention of accidents will be greatly assisted by a knowledge of how accidents have occurred. It is desirable that some international organization should take steps to secure this information. The success of any such effort will be dependent upon cooperation from each country where these materials are used. It must, however, be emphasized that the collection of this information in a form and to a degree of accuracy that will make it valuable is no small task. In many cases where incidents occur in widely scattered rural areas a personal investigation at the earliest opportunity must be made. If the dangers are considered to be serious then it would seem to be worth while to make such an attempt to gain the information needed for taking preventive action in the future.
Annex 1

THE TOXIC PROPERTIES OF SOME PESTICIDES

This annex represents an attempt to summarize existing information on the toxic properties of some of the newer pesticides. It must be read as a personal interpretation of facts and opinions expressed either in published literature or in more informal reports. The account is not intended for the research worker and it is not documented. However, a classified bibliography is given on page 75 to assist anyone wishing to start a study of this subject.

None of the materials to be considered fall into the class of general protoplasmic poisons. They all exert their effects after they have become in some way incorporated into the metabolic systems of the creatures that they intoxicate. Although some—for example, DDT—have been the object of considerable study, there is not yet any certainty about the way in which they exert their toxic effects. In the case of the organophosphorus insecticides, a considerable amount is known about the way they act in the mammalian body though less about their action on insects.

In a few cases the precise chemical structure of the pesticide is unknown. In other cases no good micro-analytical procedure yet exists. There have also been a number of discrepancies between the results obtained in different laboratories or between the results obtained in the same laboratory at different times. This can almost certainly be accounted for by the presence of impurities or differences in the constitution of the materials being tested. In some cases the impurities have a toxicity for mammals considerably greater than that of the main ingredient.

The compounds have been considered under a number of different headings.

1. The Chlorinated-Hydrocarbon Group of Insecticides

A general account will be given of the toxic properties of DDT, aldrin, dieldrin, chlordane, BHC, and toxaphene, with separate notes on each compound, together with a few notes on methoxychlor and DDD. Though possessing diverse chemical structures, these compounds have many toxic properties in common.

The most important chemical property that they share is insolubility in water, coupled with a free solubility in fats and in many of the common organic solvents. They are all comparatively stable compounds. Their insolubility in water precludes the use of aqueous solutions for oral or parenteral administration in determining lethal doses. They have been administered orally as powders, in tablets or capsules, as aqueous suspen-
sions or emulsions, or as solutions in mineral and vegetable oils. The speed and efficiency with which they are absorbed from the alimentary tract will depend to some extent upon the way in which they are administered. The lethal dose is smaller if the compound is given in vegetable rather than in mineral oil or as suspensions or dry powders. If different techniques have been used it may not always be possible to compare the results of one worker with those of another.

In some cases it has proved difficult to obtain a normal dose-response curve at the high dose levels. Difficulty in absorbing large quantities of insoluble material or of oil containing the material may account for this.

With some compounds, death with the characteristic signs of poisoning may not develop until 7-14 days after administration of a single oral dose to a small animal. The small intestine of a rat empties in 12 hours so that delay in absorption cannot account for such an observation. It suggests the likelihood of storage followed by slow release and cumulative poisoning.

In some cases it has been found possible to kill animals by giving small doses every day for 5-10 days, doses which in aggregate do not amount to more than half the dose needed to kill when given at one time. This may reflect a failure to absorb more than a fraction of the single dose; or it may mean that some cumulative effect persists after the compound has been removed which leaves the animal susceptible to a second dose.

There are differences in species susceptibility to some compounds but no consistent pattern of susceptibility of any one species to each member of the group. Susceptibility is probably not related to any constitutional differences in the ability with which different species can absorb fat. The existence of these differences emphasizes the difficulty of deciding on the basis of animal experiments what will be the poisonous dose for man.

In acute poisoning by any of these compounds, the first sign is an increase in activity due to irritability and a hypersensitivity to tactile and sometimes to auditory stimuli. Sometimes the animals become aggressive. With many of the compounds, fine and coarse muscular tremors then develop and may persist for hours. They are usually exaggerated when the animal exerts itself. Weakness and paralysis follow the period of hyperactivity, and convulsions universally occur in cases of severe poisoning. These convulsions are not necessarily fatal, and an animal may survive a considerable number of them.

Observations on the larger animals—cattle, sheep, etc.—suggest that they become blind during the excitable stage. Salivation and teeth grinding are common and animals capable of doing so—cats and dogs—habitually vomit. There is a complete anorexia and general apathy apart from the involuntary and convulsive movements. Anorexia is a striking feature in all cases of severe poisoning and may lead to considerable loss of weight. It is much more profound following poisoning by certain compounds, such as dieldrin.
Acute poisoning has been observed in man, although in many cases the features have been obscured by an uncertainty about the part played by the solvent simultaneously ingested. There have, however, been a number of cases where the solid material has been accidentally taken in food.

Vomiting and abdominal pain, associated with diarrhoea and developing within an hour or two of ingestion, have been universal features of such incidents, and in several cases where groups consumed DDT accidentally, the episode was characteristically that of acute “food poisoning”. Apart from the gastro-intestinal disturbances, dizziness, numbness, and tingling and hyperaesthesia of the extremities and face have been reported. Convulsions with recovery have been seen in patients poisoned by DDT, toxaphene, and aldrin. In well-authenticated cases of poisoning by ingestion there has been no persistence of the nervous signs and symptoms for the length of time recorded in some of the earlier reports of alleged poisoning by DDT. None has developed the syndrome portrayed by certain American physicians, and sometimes called “virus-X disease”, which has been attributed to DDT poisoning. Such alleged reactions from contact with DDT seem to be confined to persons having a very slight contact with the material. A similar condition occurring under somewhat similar circumstances has also been described among pet dogs. The thousands of field workers who have handled vast quantities of these compounds for several years in malaria-control work are apparently not susceptible to this type of intoxication.

Dermatitis has been brought on by contact with these materials but much of this was due to the solvents. A single case of periarteritis nodosa, another of agranulocytosis, and several cases of purpura have been ascribed to the results of contact with DDT, but these cases were not found among the most heavily exposed sections of the population. It would indeed be exceptional if there were no members of the population who were hypersensitive to any or all of these compounds. In view of their chemical nature it must be considered a matter of some surprise and satisfaction that so very few people appear to be hypersensitive to their effects.

Chronic poisoning can be produced in animals only by the continued administration of the compounds. No permanent injury to the nervous system has followed the persistence of tremors or of repeated convulsions over periods of weeks. Although liver necrosis is universally seen after large doses, there is no record of cirrhosis having developed in animals given repeated toxic doses of the compounds. In some cases a tolerance develops and animals poisoned to the extent of having convulsions may recover despite the continued administration of the compound by the oral or percutaneous route. Fed at low levels in the diet (10 p.p.m. or less) no compound produces untoward effects in rats, though cytological changes in some liver cells have been described. In more than one record of experiments of this kind, the animals at low levels of feeding have fared better
than the control animals as judged by weight gain and the number surviving for one to two years. Effects of chronic poisoning may be hard to observe. In some cases anorexia and loss of weight may be the first outward sign of poisoning; in other cases a convulsion may be the first sign.

Difficulties of chemical analysis have meant that little is known about the metabolism of any of these compounds with the exception of DDT. The best known metabolite of DDT is DDA (2,2-bis(p-chlorophenyl)acetic acid) and this is excreted in the urine. In man and in rabbits there is a rapid elimination of DDA within the first few days of giving a single dose of DDT, but in cats the excretion is very poor and in rats the conversion to DDA is very slow. The cat is more sensitive than the rabbit to DDT and the neurological signs of poisoning persist for longer. Whether this is related to the slower metabolism of DDT is uncertain.

All these compounds are stored in the body fat but the concentration in which they are stored in relation to the quantity ingested varies considerably from compound to compound. So, too, does the time for which they remain in the fat after ingestion ceases.

None of the compounds shows any tendency to accumulate in any vital organ. In no case where an investigation has been made has there been evidence of accumulation in the lipoid-rich brain-tissue. The kidney usually contains more than the liver. The site of action of these compounds is by no means clear.

In acute poisoning the main tissue injury judged by conventional histological standards is in the liver, but there is little evidence that death is due to an acute liver failure.

Tubular damage in the kidney is also frequently seen and albuminuria has been observed but there is no evidence of acute renal failure. In chronic poisoning, liver damage is seen if the poisoning has been severe but liver cirrhosis has never been recorded. This suggests that the damage seen at death was of recent origin. The liver does respond by a relative increase in weight in dogs and rats which have been fed quantities of these compounds even though no other striking change has been produced. There is some increase in the lipoid-content but otherwise the liver is apparently just larger.

Because of the predominance of nervous symptoms and the widely held belief that these compounds act upon the central nervous system, a careful search for histological changes in the brains of acutely and chronically poisoned animals has been made by a number of workers. No satisfactory evidence of cellular or tissue damage in the brain has been recorded.

No characteristic lesions have been described in other tissues, although a number of different workers have commented on the prevalence of vascular lesions in animals poisoned with chlordane.

Much attention has been paid to the reports that very small quantities of DDT can produce liver-cell changes in rats. There have in fact been very few detailed published accounts of these changes. At certain moderately
high levels of feeding, e.g., 50 p.p.m., there seems to be agreement that cellular changes can be seen and that their incidence diminishes as the dietary level is decreased. But at very low levels there seems to be no good evidence that the incidence of these cellular changes is significantly higher than in the control animals used in the experiments. No one has attempted to interpret the significance of these cellular changes. There is no evidence yet that they reflect cellular damage. It is probably wiser to consider the matter as of uncertain significance in assessing "toxic hazard" at low levels of feeding.

The physiological disturbances produced by these compounds have been the subject of very few successful investigations. In the insect, they appear to disturb nerve conduction and to cause repetitive firing from a single stimulus. In mammals, large doses of DDT may also cause what is called a "veratrine-like" response, that is, repetitive firing from a single stimulus. DDT shares this property with a number of other compounds including the herbicide dichlorophenoxyacetic acid. There are no gross defects in conduction across the myoneural junction of animals poisoned with DDT, and reports of histological changes in this organ can be disregarded.

Electro-encephalographic (EEG) studies of the brains of animals poisoned with DDT have shown an increased activity in both the cerebral and cerebellar cortex. In the rabbit, gamma-BHC produces an epileptiform discharge. These disturbances are suppressed by the barbiturates. A claim has been made that the characteristic disturbances of DDT poisoning do not take place if the cerebellum is removed. Other work shows that all the disturbances can be produced in cats with the whole brain destroyed. There would seem to be no really good evidence for disregarding the possibility that at least an important part of the action of these compounds takes place peripherally rather than in the brain and at the brain stem. The isomers of BHC produce different changes in the EEG pattern of rabbits, but they will all suppress the convulsions produced by the well-known analeptic pentetrazol (pentamethylene tetrazole). Nevertheless, they do this without in any way modifying the EEG changes produced by pentetrazol when administered in doses that would give rise to convulsions in normal rabbits. This again suggests a peripheral action.

The barbiturates will suppress the convulsions produced by some of these compounds in some species but not in every species after each insecticide. On the other hand, the newer anti-epileptic drugs, that is, Methadon and Tridione, do not have any effect on the convulsions produced by toxaphene in dogs.

Although these insecticides do produce some disturbance in cerebral or cerebellar activity, it is possibly the effect of this hyperactivity upon an unusually excitable peripheral nervous system that is responsible for the convulsions. The barbiturate drugs might act by damping down the stimuli from the higher centres.
The barbiturates are thus of value in suppressing convulsions and saving life in some species of animals poisoned by these materials; they will also control convulsions in men poisoned by these compounds.

Intravenous injections of calcium gluconate will save dogs and rats poisoned with DDT although there is no disturbance of the blood calcium levels. The disturbance produced in nervous activity in vitro by DDT can be arrested by raising the calcium level of the suspending medium to above that necessary for normal activity. There may be extremely local disturbances of calcium levels at nerve endings or nerve junctions that cause the convulsions, though it is not clear why calcium gluconate should affect them. Intravenous glucose is said to allay convulsions and tremors but reports of changes in the blood-sugar levels of poisoned animals are not consistent. The liver glycogen is depleted some say before the onset and others only as a result of the persistent tremors. A rise in blood potassium before the onset of convulsions has been reported, and barbiturates are said to lower it. If a rise in potassium is responsible for the convulsions then calcium might act by neutralizing its effects.

Little has been learnt from the study of changes in the peripheral blood of animals poisoned by these compounds.

As the site of action of these compounds is unknown, it is not surprising that their mode of action remains a complete mystery.

The metabolism of rats fed DDT at toxic levels in their diet is raised and so is the oxygen consumption of liver slices removed from these animals. The metabolism of brain slices remains apparently unaltered. Several workers have searched in vain for some evidence that DDT will upset enzyme systems working in vitro but no convincing evidence of such an effect has yet been produced. The poor solubility of these insecticides in water makes them unsuitable materials for this kind of study.

There remains a possibility that after their entry into the body they are converted into a more toxic metabolite which is responsible for the effects produced in the whole animal. Evidence from rats poisoned with DDT indicates that if such a compound is formed it must be active in very small concentrations. Nevertheless, if only 1% of the toxic dose of DDT were to be converted, the compound would need to have only about half the activity of TEPP. The methods of estimation are not accurate enough to detect such a small loss of DDT in the animal. The possibility that some change takes place in vivo is perhaps suggested by the very high toxicity to rats of milk from goats fed DDT. Unfortunately the DDT content of the milk was not given. Rats fed cows' milk containing only 44 p.p.m. DDT did not grow as well as controls fed on pure cows' milk. There is also a report that dogs fed the meat of sheep dying after repeated small doses of aldrin (less than 5 mg per kg) died from aldrin poisoning.

Some of the symptoms and signs of poisoning by these compounds resemble those produced by the organo-phosphorus insecticides—for
example, salivation, abdominal pain, nausea, vomiting, and diarrhea—
which suggests disturbances of the parasympathetic system supplying the
alimentary canal. Bronchial disturbances are not recorded and the tremors
are not the same as the fine muscular fasciculation of the animal poisoned
by TEPP.

Physostigmine (eserine) is said to aggravate poisoning by DDT and
BHC in insects and mammals. This suggests a possibility that cholinesterase
is inhibited by these insecticides. There has not yet been any evidence that
changes in tissue cholinesterase levels follow poisoning by these insecticides.
The compounds certainly have no activity in vitro against this enzyme.

Their action upon the gut with the resulting hyperactivity may explain
the anorexia which is a striking feature of poisoning by these compounds.
The fact that anorexia can be rapidly relieved in some cases by barbiturates
could be explained by the well-known sedative effect that these drugs
have upon the activity of the gut, although the action of these drugs on
the central nervous system may play an equally important part.

The preceding paragraphs are mainly speculation and they serve to
illustrate the prevailing ignorance of how these compounds disturb the
organism which they intoxicate and kill. Until more is known about this,
the actual hazards of exposure to this group of compounds must remain a
matter of opinion. A description of the special features, including notes on
the action on man, of the individual compounds (grouped chemically)
follows:

**Group 1: DDT, DDD (TDE), and methoxychlor**

**DDT.** The single lethal dose of DDT when given orally in vegetable oil
is about 200 mg per kg for most laboratory animals. Cats and mice are
slightly more susceptible than rats; dogs and rabbits are less susceptible.
Some of the larger animals—such as sheep—and birds are appreciably less
sensitive.

Hypersensitivity, persistent coarse tremors, weakness, convulsions, and
coma are the usual signs of poisoning, and either death occurs within the
first 36 hours or the animal recovers. Anorexia is also marked.

It takes a daily dose of 20-50 mg per kg, continued for several weeks, to
produce serious poisoning and death in rats and dogs. At levels of 400 p.p.m.
DDT in their diet, rats grow less than controls but there is no increase in
their mortality. At 150 p.p.m., the rats behave normally unless they are
starved; they may then draw on their fat deposit and be poisoned by the
DDT thereby released. At lower levels no ill-effects have been observed in
rats, though certain cytological changes in the liver cells are said to occur
more frequently than in normal animals at levels of 5 p.p.m. in the diet.

Fat storage readily takes place in rats fed as little as 1 p.p.m. in their
diet. Absorption through the skin of animals can take place from solutions
of DDT but not when the powder itself is applied.
Thousands of men have been exposed to DDT in malaria-control work for periods of several months each year for seven successive years. Despite the arduous nature of the work there has been no undue incidence of illness among these groups. There have been no reports of complaints resembling those attributed to the action of DDT in some of the earlier accounts, nor have there been any epidemics of “virus-X disease” among these workers.

Elsewhere authentic cases of poisoning have occurred, usually from the accidental ingestion of solid DDT, which seems to be found so often in kitchens among the more usual ingredients of bread and pastry. The usual features of poisoning are acute abdominal pain and vomiting. Dizziness and weakness are common and some cases have reported mild sensory disturbances of the limbs. In nearly every case the symptoms have disappeared in a few days, but in one incident weakness of the extremities persisted in a few victims for several weeks.

Many of the victims must have eaten comparatively little DDT. For example, some men were poisoned after eating pastry from a tart made with DDT instead of baking-powder. The individual consumption of DDT must have been quite small. There would seem little doubt that the report of the man who consumed pancakes made from DDT without ill-effect should be disregarded.

In several accidents the DDT has been dissolved in kerosene, and in these cases the solvent has probably been the principal cause of death. In a recent case a child of two had convulsions and went into a coma after taking DDT. It responded to barbiturates but was deaf and still having convulsions on the twelfth day. It had apparently recovered two months later.

With regard to the deliberate taking by mouth of DDT dissolved in oil, no symptoms were observed in a man who took a dose of 11 mg per kg, but another person who took a dose of 20 mg per kg noted hyperaesthesia of the mouth and face, dizziness, twitching of the limbs, and general malaise. There is no record of gastro-intestinal upsets in either of these cases. There has been a single report of widespread peripheral neuritis developing in a man who had rubbed DDT powder on to mattresses. The illness came on within 48 hours of the exposure and was of a serious and crippling nature but eventually resolved. No similar cases have been described.

All the evidence of this type of poisoning points to the probability that man is more rather than less sensitive to DDT than laboratory or domestic animals.

**DDD (TDE).** The single lethal dose of DDD (TDE) when given orally in vegetable oil is over 1 g per kg for rats; other animals seem equally insusceptible. The animals display none of the signs of nervous disturbances but die with severe liver necrosis.

In rats, prolonged feeding at high levels, for example, at 1,500 p.p.m., seems to be without effect. DDD is readily stored in the fat but disappears
much more rapidly than DDT after administration is stopped. Dogs, on the other hand, when given 50-80 mg per kg daily, developed a marked atrophy of the adrenal cortex. This is an apparently unique action of the compound and is seen only in the dog.

No accidental poisoning in man has been recorded.

_Methoxychlor_. Like DDD, methoxychlor does not produce signs of poisoning of the nervous system when given to mammals. Large doses produce severe liver necrosis only. At a level of 1% in their diet, the only effect upon rats was some reduction in their food intake. The insecticide is not stored in the fat. A dog withstood 1 g per kg daily for one month without showing any reaction.

No cases of human poisoning have been observed.

**Group 2: aldrin, dieldrin, and chlordane**

_Aldrin_. The single lethal dose of aldrin when given orally in vegetable oil is about 40 mg per kg for rats, and slightly more for dogs and rabbits. The majority of animals die within 24 hours but deaths up to eight days after a single dose have been observed.

The outstanding symptoms are hypersensitivity and convulsions. Persistent tremors are not seen. Anorexia is striking, and it may take the survivors of a near-lethal dose two to five weeks to regain their original weight.

Repeated daily doses of 2-5 mg per kg will kill dogs, sheep, and cattle within from a few days to a few weeks. At 0.6 mg per kg daily, some dogs lost weight; young dogs seemed to be more susceptible than fully grown ones. Fed to rats at levels of 25 p.p.m., aldrin produced liver enlargement and cytological changes in the liver cells. At 75 p.p.m. the animals failed to grow and at 300 p.p.m. they died. The rats were not affected at 5 p.p.m. The pathological changes produced by aldrin poisoning are confined to the liver.

There is some evidence that batches of aldrin prepared by different processes may also differ in their toxicity to animals. These differences may be explained by the contamination of aldrin by a much more toxic impurity when the insecticide is prepared by the older and now discarded method.

Aldrin applied as a solution in dimethyl phthalate is readily absorbed through the skin of the rabbit but much less readily through that of the rat. Repeated daily applications of 5 mg per kg to the skin of a rabbit will kill the animal in seven to ten days. However, doses smaller than this given daily to animals by the oral route will also kill them. There is no satisfactory evidence for the generalization that aldrin is more toxic when administered percutaneously than when given orally. The insecticide is stored in the fat.
Aldrin has been handled in large quantities in the field as oily solutions and emulsions for the control of locusts and grasshoppers. There have been no reports of serious accidents. Thirty-six men handled 10,000 gallons (45,500 litres) of 60% aldrin in grasshopper control over a period of four months in 1951. Ordinary care and the provision of washing facilities were the precautions taken. No illness was recorded. Three cases of illness of a mild, ill-defined nature had been attributed to aldrin by men using it for grasshopper control in a previous year.

Among factory workers there have been a number of cases of poisoning in men handling the powder. Several had convulsions but all recovered within a week. No evidence of chronic illness was found when a special investigation of the factory workers was made after three years of production.

A case of attempted suicide was calculated to have ingested a dose of 25 mg per kg; he had a convulsion within 20 minutes. The patient was kept under the influence of barbiturates and it was 12 days before he had fully recovered. EEG disturbances were recorded and they gradually cleared up.

_Dieldrin_. The average single lethal dose of dieldrin when given orally in oil is 50 mg per kg for rats. There are no reports of striking species differences in susceptibility.

The signs of poisoning are hypersensitivity, convulsions, and coma, associated with marked anorexia.

If repeated doses are given, the first sign of poisoning may be a convulsion or a very rapid loss of weight due to anorexia. Even if no further doses of dieldrin are given, the animal may continue to have convulsions and die. Fed at 5 p.p.m. to rats, dieldrin had no apparent effect. At 25 p.p.m., there was some interference with growth and histological changes occurred in the liver, but it was not until the level exceeded 75 p.p.m. that deaths occurred. Rats given repeated doses of dieldrin may develop convulsions and some will die, but the rest will recover in spite of the continued administration of the insecticide. In acute and subacute poisoning, histological changes have been observed mainly in the liver.

Dieldrin readily penetrates the skin of rats both in solutions and if applied as a dry powder. Little is recorded about the storage of dieldrin in the fat.

No cases of poisoning in man have yet been described. Dieldrin has been used on a limited scale in malaria control and in some places has apparently been handled with no greater care than DDT. An incident reported in America early in 1952 as being due to dieldrin poisoning turned out not to have been so on closer investigation.

_Chlordane_. The single lethal dose of chlordane when given orally in vegetable oil is 200-300 mg per kg for rats, rabbits, and dogs. The
animals exhibit hypersensitivity and tremors followed by convulsions and coma. However, in rats and rabbits the signs of poisoning followed by death may not appear for as long as two weeks after the administration of a single dose.

Sheep are reported to be very sensitive to chlordane, and symptoms of poisoning with subsequent recovery were reported after the administration of 70 mg per kg. Rats appear to be equally sensitive to DDT and chlordane given either in single doses or in repeated sublethal doses of as little as 10 mg per kg. On the other hand, long-term feeding tests indicate that chlordane is more toxic as judged by liver-cell damage. When given a daily dose of 10 mg per kg by mouth, rabbits died before they had received a total dose of more than two-thirds of the single lethal dose.

Unfortunately, commercial chlordane is an ill-defined chemical entity and no satisfactory method for its identification and estimation exists. One report states that two batches of chlordane gave quite different results when applied to sheep, and that the older was the more toxic batch.

Solutions and emulsions readily penetrate the skin of large and small animals. The insecticide is stored to some extent in the fat of animals being fed chlordane in their diet.

In addition to those lesions in the liver produced by all members of this group of insecticides, chlordane will also produce small haemorrhagic lesions; these are most commonly found in the lung.

There is one known fatality due to chlordane. It occurred in a formulating plant where a young woman spilt well over 100 ml of concentrate on her dress. She died within 40 minutes, before receiving any medical attention.

Chlordane has been widely used for fly control under conditions similar to those used in the application of DDT in the field. No reports of illness have been made to those responsible for these campaigns. It is also widely used in agriculture and to some extent in the home.

**Group 3: BHC and gamma-BHC**

BHC is normally produced as a mixture of four isomers, known as the alpha-, beta-, gamma-, and delta-isomers. Of these isomers only the gamma-isomer is an effective insecticide; it is normally present to the extent of about 12% in commercial BHC. The gamma-isomer is now prepared in a pure form.

The average single lethal dose of BHC when given orally is about 1,000 mg per kg, though symptoms of poisoning have been observed in dogs receiving only 350 mg per kg. For gamma-BHC, the dose is 100-200 mg per kg.

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b Gamma-BHC of very high purity (99% and above) is known as lindane.
Hypersensitivity, tremors, and convulsions are the outstanding signs of poisoning and dogs usually vomit. Anorexia is a characteristic sign. Death usually takes place within 36 hours of a single oral dose but may be delayed for several days.

Dogs have survived 50 mg of BHC per kg administered daily for six to eight weeks without apparent ill-effect and rats fed for two years on a diet containing 100 p.p.m. were unaffected. Emaciation, tremors, and convulsions are the signs of chronic poisoning and the usual liver lesions are seen. A widespread distribution of fine, fat droplets within the cells of many organs in acute and subacute poisoning has been described. The significance of these changes, which are said not to occur with DDT, is not yet understood.

The isomers of BHC possess distinctive biological properties. Gamma-BHC has an acute toxic effect on mammals which is much greater than that of any of the other isomers. On the other hand, the beta-isomer is stored much more readily in fat. Chronic toxic effects—death and failure to grow—are produced at much lower levels of feeding with the beta-isomer. Gamma-BHC can be fed to rats at 100 p.p.m. for two years without producing ill-effects.

Gamma-BHC in solutions or as emulsions will readily penetrate the skin of animals.

The physiological action of the isomers is interesting. The delta-isomer is purely a depressant of the central nervous system of rabbits, while gamma-BHC acts as an excitant. The alpha- and beta-isomers act first as excitants and then as depressants.

To some extent the convulsions produced by gamma-BHC may be suppressed or prevented by the delta-isomer, but its action in this respect is not nearly so efficient as that of phenobarbitone. Dogs saved from the effects of a lethal dose of gamma-BHC by treatment with barbiturates made a complete recovery and showed no evidence of permanent or recurrent effects of the gamma-BHC.

Another property shared by all the isomers of BHC is that after injection into rats or rabbits they will prevent the convulsions that would be produced in a normal animal by the appropriate dose of the analeptic pentetrazol. Furthermore, this effect will last for at least seven days after administration of a single dose of these isomers. The significance of these observations remains obscure.

Despite the preparation and use of thousands of tons (millions of kg) of BHC and gamma-BHC, no well-authenticated case of systemic poisoning in man has been described. One suspected case in a factory worker has been published. Dermatitis and skin sensitivity have been described in factory and field workers. Nevertheless, in some parts of the world BHC pastes are mixed by hand before dilution for use in malaria-control work.
Cases of poisoning have, however, been recorded among men and women given BHC by mouth as a vermifuge. A healthy adult had a convulsion after a single dose of 45 mg of BHC (less than 1 mg per kg!) in an emulsion and two others after 2-3 times this dose. On the other hand, many children and adults have received larger doses without ill-effect. A group of nine adult volunteers took repeated doses of several preparations of BHC containing different proportions of gamma-BHC. A daily dose of 40 mg for ten days was tolerated but a daily dose of 110 mg for six days produced diarrhoea.

These observations suggest that man is more susceptible to BHC than laboratory and domestic animals.

**Group 4: toxaphene**

The lethal dose of toxaphene when given orally in vegetable oil is about 100-200 mg per kg for rats and rabbits. Dogs, on the other hand, appear to be particularly sensitive and 20-40 mg per kg in vegetable oil may be fatal. Much larger doses may be given in mineral oil without killing the dogs. In large animals—sheep and goats—signs of poisoning may appear after a dose of 50 mg per kg, but a dose of 250 mg per kg is not necessarily fatal.

The symptoms of poisoning are hypersensitivity with weakness and unsteadiness leading to convulsions. Recovery may follow convulsions and is usually complete within 24 hours. Delayed deaths after oral administration of single doses have not been recorded.

Dogs have withstood repeated daily doses of 4 mg per kg for two to three months without obvious ill-effect, but when fed toxaphene at 50 p.p.m. in their diet they develop marked liver enlargement. Rats, on the other hand, can tolerate 1,500 p.p.m. in the diet without ill-effect.

Toxaphene is stored in the fat of dogs but not to any very great extent. It can be absorbed through the skin when applied in solutions or as emulsions. When it is applied by this route, the rabbit is more sensitive than the dog, probably because the compound is absorbed more readily by the rabbit’s skin.

Large quantities of toxaphene have been used for a variety of agricultural purposes but there appear to be records of only two incidents of possible poisoning. In the first, 18 men applying toxaphene in a tobacco field collapsed with symptoms of shock. None had any of the signs of poisoning by this type of insecticide and all made a rapid recovery. In the second incident, a man sprayed his own vegetables with toxaphene one morning and later in the day his wife picked, washed, and cooked some greens which seven people ate that evening. Three became ill and had convulsions but rapidly recovered. The others were unaffected. The greens were found to have about 5,000 p.p.m. (equal to 5 mg per kg) of
toxaphene on them. If each victim had consumed 250 g of greens he would have ingested a dose of approximately 20 mg per kg only.

2. The Organo-Phosphorus Insecticides

The organo-phosphorus insecticides are esters and amides of phosphoric and pyrophosphoric acid which, when introduced into the animal body, inhibit the enzymes that hydrolyse acetylcholine.

They may be divided into two groups: The first group will inhibit the enzymes in vitro, and, as a general rule, their activity as inhibitors is proportional to their toxicity to mammals. Susceptibility to aqueous hydrolysis also parallels their activity as inhibitors. The second group may have little or no activity as inhibitors of cholinesterase in vitro, but once inside the animal body they become changed into active inhibitors of uncertain chemical constitution. The original compound is much more stable to hydrolysis and some of the group are valuable insecticides. TEPP is the best-known member of the first group while parathion, Potosan, and schradan fall into the second category.

The signs and symptoms of acute poisoning by all the members of the organo-phosphorus group of insecticides are the same. The speed with which intoxication follows the introduction of the compound into the body depends upon which type is used. The signs of poisoning are those that would be expected from an excess of acetylcholine persisting at those nerve-endings where it normally functions evanescently as a transmitter. Salivation, abdominal pain, vomiting, and diarrhoea result from over-activity of the parasympathetic nerve supply to the alimentary tract; bronchial secretion and spasm reflect parasympathetic effects upon the bronchial tree. Fasciculations, irregular contractions, and weakness of voluntary muscles indicate excess of acetylcholine at the myoneural junctions.

At the present time it is uncertain what part inhibition of the cholinesterase in the central nervous system plays in producing the signs of severe poisoning. Some of the convulsions at any rate are asphyxial in origin. Death occurs from failure of respiration and this cannot yet with certainty be attributed to a peripheral or central failure of conduction of stimuli to the respiratory muscles. Observations in both man and animals have shown that a period of artificial respiration may save life and be followed by a renewal of normal respiratory activity. In some cases, however, an apparent recovery from the acute phase of poisoning may be followed by a later gradual collapse and death. The cause of this is not clearly understood.

Chronic poisoning can be produced in animals by feeding them on diets containing these compounds. Excessive secretions and hyperactivity of the gut, together with a general weakness associated with persistent muscular fasciculation, result in a general picture of sick, dirty animals.
This may persist for weeks at a time but on removal of the compound from the diet the animal makes a rapid and complete recovery. Rats killed after being fed for a year on a diet containing parathion in a concentration high enough to produce symptoms intermittently throughout the period had no histological evidence of damage to their tissues.

Unfortunately this apparently very satisfactory picture has been marred by the recent discovery that certain members of this group of compounds can produce in susceptible species serious structural changes in peripheral nerves and tracts of the spinal cord. Enough is not yet known about the characteristics of the many members of this group of inhibitors of cholinesterase to know what chemical or physical characteristics they must possess in order to be capable of producing these lesions.

Acute poisoning in man follows the expected pattern with all the symptoms that would arise from a hyperactivity of the parasympathetic nervous system. Exposure to TEPP may bring on symptoms almost immediately if it reaches the eyes or is inhaled, and in this way withdrawal from exposure takes place rapidly, either voluntarily or as the result of collapse of the victim. Exposure to parathion, on the other hand, unless large quantities are drunk, as in suicide attempts, leads to a more gradual development of symptoms; as a result, many of the victims of poisoning have first become seriously ill after they have left work. The explanation of this probably lies in the fact that parathion must first be converted into another compound before cholinesterase is inhibited, and it may take time before enough of the absorbed parathion has become metabolized in this way and has brought about a sufficient reduction of the level of cholinesterase to produce symptoms. As previously mentioned, some cases of parathion poisoning have apparently recovered from the acute phase of poisoning, but have later relapsed and died. This may be the result of the continuous metabolism of parathion, though a similar condition is seen in experimental animals poisoned with TEPP and revived by artificial respiration.

Chronic poisoning can be recognized in some of the case-histories where men have had intermittent nausea and headaches aggravated by each fresh exposure to the compound.

Long-lasting chronic effects have been recorded so far in only two victims of accidental poisoning with bis(monoisopropylamino)-fluorophosphine oxide. They followed immediately after recovery from acute poisoning and closely resembled the lesions of triorthocresyl phosphate poisoning. A single case of multiple neuritis of a similar type has been described in a man who had had repeated exposure to parathion in a glass-house. However, this man's condition did not appear until three months after his last exposure to parathion. No other cases have so far been reported from among the fairly numerous survivors of accidental poisoning by parathion.
The metabolism of the compounds having a direct inhibitory activity against cholinesterase is probably quite simple. They are rapidly hydrolysed both physically and enzymatically as soon as they reach the tissues. It is during the attempt to hydrolyse them that the cholinesterase enzymes are inhibited, and instead of the alkyl-phosphate groups immediately coming off the active centre of the enzyme they remain there and prevent the enzyme exerting its usual function of splitting acetylcholine.

The metabolism of the indirect inhibitors is not yet understood. In the case of schradan the conversion to an inhibitor takes place almost wholly in the liver, at least in the case of the rat. How much schradan is converted and the chemical nature of the inhibitor are unknown. From animal experiments it seems that schradan is metabolized rapidly, since chronic poisoning is not produced by a single dose. The metabolism of parathion is also not known but it seems very probable that at least some of the thiophosphate ester is turned into the phosphate ester (paraoxon) which is a very active inhibitor of cholinesterase. It is not known where the metabolism of parathion is carried out. Once converted into an inhibitor of cholinesterase, the behaviour of the esters is probably the same as that of TEPP, and the final result is the inactivation of some or all of these enzymes at various sites in the body. There is no evidence that these compounds exert any action other than that of inhibiting cholinesterase and, as a result, allowing certain specially sensitive areas in the different tissues of the body to be affected by an unusually high concentration of acetylcholine, which is itself produced by many normal physiological processes.

These inhibitors have frequently been called "irreversible" inhibitors because it was believed that the enzyme attacked by them was permanently destroyed and that recovery took place by the formation of new enzyme molecules. However, there is now much evidence to suggest that at least some of the restoration of tissue cholinesterase levels comes about as a result of a reversal by hydrolysis of the phosphorylated, inhibited enzyme. Furthermore, the rate of this reversal is dependent upon the nature of the alkyl groups attached to the phosphorus.

Scores of these compounds have been synthesized and undoubtedly many have been screened for their activity as insecticides and for their toxicity to mammals. At present too little is known, especially in the case of those compounds that have to be converted by the mammal before they become poisonous, about the factors which will determine their effectiveness as insecticides. Any that are found to be more toxic than parathion to mammals in an acute-toxicity test are apparently—temporarily at least—disregarded. On the other hand, compounds several times less toxic by this test may not be harmless, as experience with bis(mono-isopropylamino)-fluorophosphine oxide has shown. It is clear that very much more is known about the way in which these insecticides exert their
effects than in the case of the chlorinated-hydrocarbon group. When
generalized absorption of these compounds has taken place, the blood
cholinesterase level always falls to less than one-fifth of its normal activity
before symptoms are noticed. Methods of estimating the activity of
cholinesterase have been adapted for use in chemical laboratories and,
where circumstances require it, there is no reason why those exposed to
the effects of these insecticides cannot undergo regular blood examinations
and be withdrawn from exposure as soon as a significant lowering is detected.
Such surveys will also indicate what are the most hazardous of the opera-
tions connected with the use of these compounds.

When applied as contact insecticides, these compounds do not cause
any anxiety on account of residues. Most of them will disappear rapidly
by hydrolysis and any traces that are infected will be rapidly metabolized.
When used as systemic insecticides, uncertainty is increased by ignorance
of the effects these compounds may have on the plant; however, problems
of the toxicity of a particular insecticide will be similar to those of other
members of this group.

The compounds listed in the following tabulation have been developed
and, to a varying extent, used in the field as insecticides. The approximate,
average, single lethal dose when administered orally to male rats is given
for each compound.

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Average single lethal dose (per kg)</th>
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<tbody>
<tr>
<td>TEPP</td>
<td>2 mg</td>
</tr>
<tr>
<td>Paraoxon</td>
<td>2 mg</td>
</tr>
<tr>
<td>Dimefox</td>
<td>5 mg **</td>
</tr>
<tr>
<td>Schradan</td>
<td>10 mg **</td>
</tr>
<tr>
<td>Parathion</td>
<td>15 mg *</td>
</tr>
<tr>
<td>Systox</td>
<td>15 mg</td>
</tr>
<tr>
<td>Potosan</td>
<td>25 mg *</td>
</tr>
<tr>
<td>EPN</td>
<td>40 mg *</td>
</tr>
<tr>
<td>Malathion</td>
<td>&lt; 1,000 mg</td>
</tr>
</tbody>
</table>

* Female rats considerably more susceptible
** Female rats somewhat less susceptible

Only in the case of dimefox is the volatility of the active ingredient
great enough to present a hazard; this will much increase the dangers
of using the material under the conditions under which the others have
been successfully and relatively safely applied. Paraoxon would also
probably prove to be hazardous if widely used because it is much more
stable than TEPP and has a similar toxicity.

3. DNC and Related Dinitro Derivatives

The toxic properties of dinitrophenol were first experienced when it
was manufactured as an explosive in the first World War. Its action and
that of related compounds was reinvestigated about 20 years later when their stimulating effects upon metabolism were discovered and they were introduced into clinical medicine as "slimming" agents. A number of sudden deaths and the development of lens opacities among those taking them soon resulted in their being discarded as therapeutic weapons.

They have been and are still widely used as insecticides and ovicides and as selective weed-killers. Human casualties have been experienced during manufacture and during their use as selective weed-killers.

By injection, a single lethal dose for most laboratory animals is about 25 mg per kg. By mouth, about twice that amount is needed. Symptoms of poisoning begin within a few minutes of injection and rapidly increase until the animal dies 10-60 minutes later. The characteristic sign is a progressive increase in the rate of respiration until the animal becomes acutely distressed; it then usually collapses and at this stage may die quietly. Small laboratory animals become completely stiff almost instantly owing to widespread muscle rigor.

Those that do not die gradually recover so that within 4-6 hours they again appear normal. Such near-lethal doses may be given to rats day after day for six weeks without producing any change in the reaction of the animal or any histological evidence of tissue injury. A cumulative effect is seen if small doses are given at much shorter intervals. There is no special syndrome of chronic poisoning in experimental animals except loss of weight. Rats have been given up to 100 p.p.m. DNC in their food for six months without any effect upon growth. At 500 p.p.m., growth is not as good as in control rats.

The toxicity of DNC to small laboratory animals is significantly increased if their environmental temperature is raised after giving the drug.

A number of cases of serious and fatal poisoning in man have been reported among factory workers and among those applying DNC emulsions as weed-killers. They all present a similar picture suggesting an acutely raised metabolic-rate. The skin is hot and sweating is profuse. Rapid pulse- and respiration-rates with attendant general distress and weakness characterize the late stages of poisoning. In the fatal cases, death has almost always taken place within 24 hours of the victim last being at work.

Early signs of poisoning do manifest themselves but they may be overlooked because of the nature of the environment in which the victim commonly finds himself. Controlled observations made when these drugs were being developed for clinical use showed that a feeling of warmth in the skin, with excessive sweating and an accompanying thirst, was the first sign of poisoning. The next sign was one of general debility and weariness. It is perhaps not surprising that such symptoms, when experienced by a man working a 12-hour day in warm weather spraying crops, are put down to the effects of physical exertion. As a consequence of this, the first intimation of poisoning may be the collapse of the man and the
recognition that he is severely poisoned. These fatalities have usually occurred during hot weather and after the victim has been applying DNC for several consecutive days. Inquiry may reveal that he has been sweating a lot, has had a severe persistent thirst, and has been sleeping badly, but these symptoms are not usually attributed to the effect of the material with which he is working. Some of the victims in recent years have collapsed after ignoring these warning symptoms, even though they had a leaflet describing them in their pocket.

Factory workers have usually been affected when handling DNC as a powdered preparation. In one factory, no trouble had been experienced as long as pastes were used. The history of the factory workers is much the same as that of the agricultural ones. A general feeling of weakness and great thirst have been ignored, and a rapid collapse has taken place at or soon after leaving work. The striking postmortem rigidity and its extremely rapid onset have been recorded by one observer of two fatal cases.

Both factory and agricultural workers have recorded losses of weight when handling these preparations.

The dinitrophenols have been extensively studied in recent years by biochemists. It appears that their action on all forms of living tissue is similar. They disturb the normal complex phosphorylating enzymes essential to so many vital processes and, at the same time, greatly accelerate the oxidative mechanisms. Animals probably die from a combination of the effects of both these actions. Excessive muscular activity is demanded to supply oxygen by respiration and to circulate the blood, while at the same time impairment of the phosphorylating processes makes muscular performance more difficult. The exact way in which the nitrated phenols exert this effect is unknown. There is no evidence that they have any specific effect on fat metabolism.

In vitro at least, many tissues, but particularly the liver, can rapidly reduce the dinitrophenols to mono-nitro mono-amino derivatives and these are devoid of toxic effects. It is not known to what extent the duration of symptoms in dinitrophenol poisoning depends on the continued presence of the compound and to what extent on the persistence of the effects its presence may have had upon metabolism. Claims to have isolated DNC from the tissues of fatal cases have been made. In some animals and in man, DNC can be detected in the blood for several days after the poisonous effects have worn off. To what extent in man this reflects an increased susceptibility to the compound is not known. In certain laboratory animals its presence does not indicate an increased sensitivity to the drug.

However, the measurement of DNC in the blood—which can be readily carried out even on small quantities—has been used in surveys of workers handling the material. The presence of DNC indicates that exposure has taken place, and a rising level indicates that exposure is
continuing. The significance of the various blood-levels observed must await the results of further observations.

The related compounds 2-sec. butyl, 4,6-dinitrophenol and 2-cyclohexyl 2,4-dinitrophenol have been used in weed control. They are not significantly less toxic to laboratory animals.

Cataract (lens opacity) has never been recorded in agricultural or industrial workers handling DNC, though it was found in about 1% of those taking DNC for slimming purposes. Experimentally, it has been possible to produce lens opacities in ducklings. Dinitrophenol, DNC, and 2-sec. butyl, 4,6-dinitrophenol all produce these opacities but 2-cyclohexyl 4,6-dinitrophenol does not.

4. Pentachlorphenol

Pentachlorphenol and its salts have been extensively used for many years as fungicides, especially for timber dressing. Its use is being considered as a herbicide and as a molluscocide.

The lethal dose for animals is about five times that of DNC, but the toxic effects are much the same and it is believed to interfere with metabolism in a similar way.

Serious intoxication in man from pentachlorphenol has not been recorded but it must be handled carefully in order to avoid contact with the skin as it readily produces dermatitis. Recently, a group of cases of transient sciatic neuralgia have been described among men who were shovelling the compound in a manufacturer’s plant.

5. Organic Mercurial Compounds

The commonest use for mercurial compounds in agriculture is as fungicides for dressing seed. A considerable number of compounds have been used and most of them have not given rise to ill-effects.

If handled, most of them irritate the skin and they may cause dermatitis. They are all inherently poisonous when absorbed and, as with the simpler mercury salts, in experimental animals the most striking damage is to the kidney.

There is one group of mercury compounds with a methyl radical attached to the mercury which seem to have a predisposition to attack the central nervous system, especially the sensory side. Permanent distressing injury and disabilities have resulted from poisoning by these compounds.

The manufacture of organic mercurial compounds containing the methyl radical was abandoned in Great Britain after a series of cases of poisoning had occurred in a factory in 1939. During the second World
War, methyl mercury hydroxide was used in Sweden and a number of severe cases of poisoning occurred during its manufacture and use.

More recently a less-volatile methyl mercury derivative has been widely used as a seed dressing in Sweden and other countries. There have been no reports of poisoning from its use, though there have been accidents arising from gross carelessness, such as the consumption of treated seed. The fact that no cases of poisoning by this particular preparation have occurred may be accounted for by the fact that it is a liquid. Mild cases of poisoning and skin irritation have occurred when other mercury-containing seed dressings have been handled, but these are all dusts or powders. Although special machines are built for applying these dressings, the control of dusts is notoriously difficult to achieve.

Mild, chronic, mercury poisoning is extremely difficult to detect clinically because emotional rather than physical signs predominate. However, there is little risk of such a condition developing in those persons applying seed dressings because application continues for only a very short season. If mercurial fungicides are developed for other processes and are handled for longer periods, a close watch will have to be kept for this somewhat elusive clinical condition.

Annex 2

CONTROL OF AGRICULTURAL PESTICIDES IN DIFFERENT COUNTRIES

The following brief statement describes the control of the use of insecticides in the various countries visited by the author:

Belgium

All pesticide preparations must be registered and their labels approved before they can be sold. A provisional registration may be granted subject to confirmation after tests by the Phytopharmacy Station (a Government body).

Poisons are labelled:

(1) Toxic, e.g., parathion  Red wording; “Poison” clearly written; skull and cross-bones insignia.

(2) Hazardous  Green wording; cautions about use.

(3) Others  Any other colour on label.

Contract sprayers apply about 80% of the pesticides; they are not registered or licensed.
The staff of the agricultural field service visit the Phytopharmacy Station once or twice a year for information on the use of new pesticides. *Residues in food*: no regulations exist.

**Canada**

All pesticide preparations must be registered and the labels approved. Registration is renewed annually. There is no control over materials not offered for sale or offered as part of a contract service.

Poisons are classified on the lines adopted by the United States Department of Agriculture. No special control is exercised except by labelling. Contract spraying is very little developed.

Agricultural advisers and growers associations co-operate actively in devising treatment programmes.

*Residues in food*: no regulations have been established but milk and bread must not contain insecticides.

**Denmark**

All pesticides must be registered by the Chemical Control Division of the Ministry of Agriculture. There is no control of labelling except informally. Certain uses are approved by the Pest Control Laboratories of the Ministry, and a statement to this effect may appear on the label.

Poisons are classified under rules of the Ministry of the Interior and of Housing and the onus remains on the seller to see that the poison is sold to someone for a legitimate use.

New legislation is planned.

Contract sprayers apply about 80% of the pesticides; they are not licensed.

The field staff of the Ministry of Agriculture work in close collaboration with the powerful farmers’ co-operatives on such questions as the uses of new materials.

*Residues in food*: no regulations exist.

**France**

All pesticides must be registered and their labels approved by the Ministry of Agriculture. They are often tested by the Ministry’s Station at Versailles.

Poisons are classified on the basis of the opinion of an interdepartmental committee, and special regulations may be made for their use and labelling.

Contract spraying is quite extensive; no licensing system exists.

There is a well-developed agricultural advisory service in the field which supplies farmers with information.
Residues in food: no regulations exist but the problem is being considered.

Germany

There is no registration of pesticides.
A few named substances, e.g., cyanides, are on the poison list but none of the new compounds is included.
New legislation is being drafted.
Contract spraying is not widely used.
There is an active advisory service in the field.
Residues in food: no legislation exists.

Greece

There is no registration of pesticides.
Special regulations were recently introduced to control the use of parathion after there had been accidents.
Contract spraying is not carried out.
There is an agricultural advisory service in the field acting like a fire department and ready to tackle a problem brought to its notice.
Residues in food: no legislation exists.

Italy

Pesticides must be registered by the Ministry of Agriculture. There are no categories for poisons.
Contract spraying is not developed.
An agricultural field service is active, especially in co-operation with the growers' co-operatives. Most small farmers do not use any pesticides.
Residues in food: no legislation exists.

Switzerland

There is no federal law on pesticides. An unofficial poison commission classifies new pesticides, but each Canton makes its own decisions; e.g., in some it is forbidden to use parathion.
Contract spraying is not developed.
Residues in food: no legislation exists.

United Kingdom of Great Britain and Northern Ireland

There is voluntary registration of certain pesticides. Certain procedures are officially approved and preparations which can be applied by these can carry an official approval mark.
Poisons are classified by a special Board, under the Home Office, which regulates the labelling and sale.
Contract spraying is fairly widely carried out.
There is a well-developed National Agricultural Advisory Service.

Residues in food: no legal tolerances exist but unofficial ones are operated for DDT and BHC.

USA

Federal

All pesticides must be registered and their labels approved. Registration must be renewed every five years. If a manufacturer has a preparation rejected he may appeal and the Department of Agriculture will register it "under protest".
Poisons are classified according to the size of a single lethal dose:
(1) Highly toxic "Poison" and skull and cross-bones on labels, and warning statements.
(2) Toxic Warning statements only.
(3) Hazardous Caution and statement of hazards.
(4) Considered safe
Contract spraying is irregularly developed but not widely carried out in most areas.
Advisory service: this is a State concern.

Residues in food: no legal limits on the newer pesticides exist, but informal limits are in effect. Milk must be free from pesticides.

State

Thirty-three States register pesticides.
Four States license contract sprayers.
California has legal tolerances for lead, arsenic, fluorine, and DDT.

Annex 3

GLOSSARY OF NAMES OF PESTICIDES USED IN THE TEXT

Aldrin *
1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethano-naphthalene

BHC *
mixed isomers of hexachlorocyclohexane (benzene hexachloride)
Chlordane *
  1,2,4,5,6,7,8,8-octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane

Chlorinated-hydrocarbon group of insecticides
  typical examples are marked * in this glossary

DDD *
  2,2,-bis(p-chlorophenyl)-1,1-dichloroethane (synonym : TDE)

DDT *
  2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane

Dieldrin *
  1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4,5,8-
  dimethanonaphthalene

Dimefox ***
  bis(dimethylamino)-fluorophosphine oxide

DNC
  4,6-dinitro-o-cresol (synonym : DNOC)

EPN **
  ethyl p-nitrophenyl-thionobenzene phosphonate

Gamma-BHC *
  gamma-isomer of hexachlorocyclohexane (synonym : lindane)

Malathion **
  S-(1,2-dicarbethoxyethyl)-o,o-dimethyl dithiophosphate

Methoxychlor *
  2,2-bis(p-methoxyphenyl)-1,1,1-trichloroethane

Mipaflox ***
  bis(monoisopropylamino)-fluorophosphine oxide (synonym : Isopestox)

Organo-phosphorus insecticides
  compounds marked ** in this glossary are examples

Paraoxon **
  o,o-diethyl p-nitrophenyl phosphate

Parathion **
  o,o-diethyl p-nitrophenyl thiophosphate

Phenoxyacetic acid derivatives
  substituted phenoxyacetic acid compounds used as selective herbicides

Potosan **
  4-methyl-7-hydroxy-coumarin diethyl thiophosphate
Schradan ***
    bis(dimethylamino) phosphonous anhydride (*synonym*: OMPA)

Systemic insecticides
    compounds marked *** in this glossary are examples

Systox ***
    a mixture of \( o,o \)-diethyl-\( s \)-ethyl mercaptoethanol thiophosphate and
    its isomers

TEPP **
    tetrathyl pyrophosphate

Toxaphene *
    chlorinated camphene

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Dr. Wayland J. Hayes, jr.  Senior Surgeon, Technical Development Branch, Com-
                           municable Disease Center (United States Public
                           Health Service), Savannah, Ga., USA

Dr. H. L. Haller  Assistant Chief, Bureau of Entomology and Plant
                 Quarantine, Agricultural Research Administration,
                 United States Department of Agriculture
<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Affiliation</th>
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<tr>
<td>Dr. E. F. Knipling</td>
<td>In Charge, Division of Insects Affecting Man and Animals, Bureau of Entomology and Plant Quarantine, Agricultural Research Administration, United States Department of Agriculture</td>
</tr>
<tr>
<td>Dr. A. J. Lehman</td>
<td>Chief, Division of Pharmacology, United States Federal Security Agency</td>
</tr>
<tr>
<td>Professor G. R. Cameron</td>
<td>University College Hospital, London</td>
</tr>
<tr>
<td>Dr. R. A. E. Galley</td>
<td>Colonial Products Research Council, Imperial Institute, London</td>
</tr>
<tr>
<td>Dr. F. A. Denz</td>
<td>Toxicology Research Unit, Medical Research Council, United Kingdom</td>
</tr>
<tr>
<td>Dr. E. J. Pampana</td>
<td>Chief, Malaria and Insect Control Section, WHO</td>
</tr>
<tr>
<td>Dr. M. I. Roemer</td>
<td>Social and Occupational Health Section, WHO</td>
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<tr>
<td>Dr. T. S. Sze</td>
<td>Social and Occupational Health Section, WHO</td>
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<tr>
<td>Mr. R. N. Clark</td>
<td>Division of Environmental Sanitation, WHO</td>
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