SAFE USE OF PESTICIDES

Twentieth Report of the
WHO Expert Committee on Insecticides
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CORRIGENDUM

Page 31, fourth paragraph, third line

delete 5000 mg/m³
insert 5000 μg/m³
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WHO EXPERT COMMITTEE ON INSECTICIDES

* Geneva, 10–16 October 1972

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SAFE USE OF PESTICIDES

Twentieth Report of the
WHO Expert Committee on Insecticides

The WHO Expert Committee on Insecticides met in Geneva from 10 to 16 October 1972. Dr T. Lopes, Director, Division of Malaria Eradication, opened the meeting on behalf of the Director-General.

GENERAL INTRODUCTION

The application of residual insecticides, predominantly DDT, in vector control has been the most important factor making possible the eradication of malaria from large parts of the world in the last 25 years. Prior to the introduction of these compounds, effective control of malaria was feasible only in limited areas of sufficient population concentration and economic importance to justify vector control through engineering or repetitive antimosquito measures.

Anxiety about pollution of the environment and the adverse view taken of DDT as one of the pollutants have come at a time when this insecticide is still needed to control certain insect-borne diseases, particularly malaria. The problem has given rise to much controversy and even emotion. On the one hand, DDT has been indicted as a danger to certain forms of wildlife and as a potential hazard to people; and, on the other hand, recent events in India and Ceylon have shown how serious the recurdence of malaria can be where DDT is locally unavailable or is not applied at the appropriate time. Action taken since 1969 by certain developed countries to place severe restrictions on the use of DDT has been a matter of concern to governments of a number of developing countries who need the compound for antimalaria operations.

It has therefore become important to review objectively the issues at stake. Any risks involved in continuing the use of DDT in certain public health programmes need to be evaluated as fully as possible, and every opportunity must be taken to reduce unnecessary input of DDT into the environment. In doing this it is necessary to bear in mind that operations against vector-borne diseases, particularly malaria, must be continued by some method that is within the financial means and the logistic ability of countries in the tropics.

It was also emphasized that a number of other vector-borne diseases will have to be brought under control before agro-economic development in some tropical countries is possible. Examples of such diseases are oncho-
cerciasis and trypanosomiasis. Adequate control of vectors at present is only possible through the use of pesticides. It is important that the compounds to be used for this purpose receive the closest scrutiny, since bodies of water may need to be treated.

Important as it is, the use of pesticides for the control of malaria is only a part of the whole problem presented by the use of pesticides in public health and agriculture. Future trends in the use of specific groups of pesticides cannot be estimated accurately. The contribution of DDT to the total production of insecticides has declined markedly. In 1967, production in the USA, which is believed to be about half the world production, was 47,000 metric tons, which is 27% below the previous year’s production and 40% below the peak figures of 1960-63. It can be assumed that the decline has continued, although at a slower pace owing to the continued need for DDT in public health programmes and certain agricultural uses. Since there has been no fall in the total production of insecticides, it can be inferred that DDT has been replaced to a considerable extent by other compounds, some of which present greater hazards in manufacture, transportation, storage, and use.

The public has been made to feel concern about the use of pesticides, and this is unlikely to disappear. However, it has sometimes been due to misinterpretation or improper extrapolation of scientific data, which has even led some administrations to impose restrictions on the use of certain pesticides that cannot be justified on the basis of present scientific knowledge. In particular, in assessing hazards to animals and to man, the need to take into account the dosage-response relationship (see Part 1, section 1.2, p. 9) has frequently been ignored.

The WHO Programme for the Evaluation and Testing of New Insecticides has been playing an important role in meeting new problems of vector control and, more recently, in minimizing environmental problems. The programme has been in operation for 12 years and more than 1600 compounds have been evaluated. Three of these are now in operational use for the control and eradication of malaria. A few others are in use for controlling the vectors of other diseases. Compounds may be discarded because they are ineffective, commercially unavailable, or for other causes, but by far the most common reason for discarding compounds has been their toxicity. The Committee was impressed by the very thorough and conservative approach to safety evaluation that has characterized the WHO programme, which has now been expanded to include molluscicides, rodenticides, and alternative methods of control.

At previous meetings, the WHO Expert Committee on Insecticides had been concerned solely with the safe use of pesticides in vector control, but its scope has now been widened to include safety aspects of the use of pesticides in agriculture. The Committee endorsed the importance that the Organization attaches to this subject and emphasized the need to view
pesticide safety as a whole. In addition to relatively toxic pesticides that may be used in public health to replace compounds that are less toxic but more persistent in the environment, the Committee also considered the effects of a number of pesticides that are more hazardous than those used in public health. Where hazards may exist, they have been defined and assessed to the best of the Committee's ability, in order to guide the Organization on the future development of its programme. In this connexion, the Committee gave special attention to training, medical services, and other protective measures.

It seemed important to the Committee that the international organizations work together, particularly in education and training, in those countries where the use of pesticides for economic reasons has outstripped the present capacity of the authorities to cover the safety aspects adequately. Even in the developed countries there is a need for education of the public and the responsible authorities in the basic principles of toxicology in order to dispel excessive concern over hypothetical but unproven effects of pesticides and to ensure a more realistic appreciation of hazards.

The need for training in the distribution and control of pesticides is well illustrated by recent outbreaks of alkyl mercury poisoning. Mercury compounds have been used for seed dressing for a long time. Before 1930, inorganic mercury compounds were used but during the 1930s they were replaced by organomercurials. Despite several publications indicating their unusual, persistent toxic effects in man, alkyl (methyl and ethyl) mercury compounds were introduced commercially as fungicides shortly after 1940. They dominated the market in some countries during the 1950s, while in many other countries alkoxyalkyl and phenyl mercury compounds were the main fungicides used.

It has been known for a long time that the alkyl mercury compounds differ from phenyl, alkoxyalkyl, or inorganic compounds in their toxicological behaviour in the organism. The alkyl mercury compounds accumulate in the nervous system giving rise to irreversible damage, and they are excreted slowly. In the long view, it may be unwise to use any mercury compounds and certain other heavy metal compounds as pesticides. On the other hand, it is obvious that the risk to man and animals would be greatly reduced if the alkyl (ethyl and methyl) mercury compounds still in use as seed dressing were replaced by less toxic compounds (e.g., phenyl and alkoxyalkyl mercury compounds).

The Committee therefore recommends that the hazards from the use of mercurial compounds in agriculture be kept under constant review by FAO and WHO. It is also important that emergency teams should be available at short notice to go into the field wherever outbreaks of poisoning do occur (see page 46).
PART 1. INSECTICIDES IN PUBLIC HEALTH

1. DDT

The predominant use of DDT in public health is still for malaria eradication. More than 1000 million people are now living in areas that have been freed from the endemic form of the disease. However, it is becoming increasingly clear that to maintain this achievement and to permit the extension of protection to the many millions of persons still exposed to infection will require the continued availability of DDT. The withdrawal of this compound from public health use at this time could give rise to immense problems and expose large populations to outbreaks of endemic and epidemic malaria.

1.1 Tumorigenicity in mice

The Committee was informed of the results of experiments set up by the IARC following a report that mice subjected to prolonged exposure to DDT showed an increasing incidence of tumours at various sites in succeeding generations. Experiments initiated by the IARC at two centres have failed to confirm the occurrence of tumours at multiple sites or increasing incidence in succeeding generations. However, the IARC work has revealed parenchymal liver cell tumours in the treated animals, and some of these were malignant. At the highest dietary level (250 mg/kg of feed for the lifetime of the mouse) the incidence was increased in both sexes, and there was a significant shortening of the life-span. At the lowest level (2 mg of DDT per kg of feed, or about 0.3 mg/kg body weight per day for the lifetime of the mouse), which on a body weight basis represented a daily intake of DDT similar to the highest known human occupational exposure (see pages 9-11), one centre found a significant increase of liver tumours in the males only; at the other centre no increase in liver tumours in either sex occurred.

The Committee supported the proposal of the IARC Working Group\(^2\) that comprehensive metabolic studies should be carried out with modern

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\(^1\) In conformity with the present trend to use SI units for all measurements and with the recommendations of various international bodies, all concentrations in this report are expressed in mg/kg or mg/litre, rather than in ppm. It should be noted that, since 1 ppm = 1 mg/kg or 1 mg/litre, the figures remain the same.

methods on a variety of species, including man. Results of carcinogenicity studies already in progress on other species should be awaited.

The Committee took into account the fact that the first publication stating that DDT might have a "tumorigenic tendency" in rats appeared as long ago as 1947 and that no adverse effect has been observed in a small group of heavily exposed men who have been followed for 20 years.

Having taken full note of the views expressed on behalf of the IARC Working Group, the Committee did not regard this new evidence in mice as providing them with an adequate basis for recommending the withdrawal of DDT where its continued use for disease control and for protecting food and crops could be life-saving. This decision is based on the view that in these circumstances any possible risk to man, as indicated by the above-mentioned animal studies, is outweighed by the benefits arising from properly controlled use of DDT.

1.2 Storage and excretion

It is generally recognized that a dosage-response relationship exists for every effect of any chemical, whether it be employed as a drug or for some other purpose, or whether it is absorbed incidentally from the environment. Although this relationship may be demonstrated easily in animal experiments, it is often difficult in practice to measure the quantity of a chemical absorbed by persons exposed to it occupationally or accidentally. However, effects that can be measured are the storage and excretion of the compound itself or of its metabolites. Measurement of one of these parameters can be used to determine absorbed dosage in a particular instance, provided it is possible to construct a standard curve. Such a curve has been constructed for DDT by plotting (a) the concentrations of the compound in the body fat of people in the general population at different times against their intakes as determined by measurement of DDT in the total diet at the same times and (b) the concentrations of the compound in the body fat of volunteers against the dosages administered to them until a steady state of storage was achieved. The curve is shown in the accompanying figure.

It may be seen that the curve for DDT is bent near the origin, indicating that there is considerable change in the ratio between dosage and storage within the low-dosage area. As the dosage increases, storage increases, but at a progressively declining rate. The fit of the observed points to a smooth curve leaves little doubt that this relationship is real. The curve for DDT shows that the ratio between dosage and storage is approximately constant above a dosage level of 2.2 mg per man per day.

A moderate increase in activity of the microsomal enzymes of the liver has been demonstrated\(^1\) in men subject to occupational exposure to a mixture

of pesticides and in other men exposed to DDT only.\textsuperscript{1} It is likely, but not proved, that this may influence the shape of the dosage-storage curve.

In a person subject to occupational exposure the dosage can be estimated by measuring his storage level and reading off the dosage level from the figure directly below the point at which the curve intercepts the observed storage value. Obviously, the estimate will be more accurate when applied to the average storage for a group than when applied to a single measurement of storage.

From this curve for the storage of DDT and a similar curve for the excretion of DDA it was estimated that workers in one factory absorbed about 35 mg per man per day, or about as much as the highest dosage studied in volunteers and used in construction of the graph, while those in another factory absorbed between 17.5 mg and 18 mg per man per day. This was true even though the factories involved were moderately dusty so that the workers clearly would have acquired a tremendous dose if they had absorbed all the DDT they encountered.

A curve worked out for persons who are essentially at storage equilibrium cannot always be used for interpreting the dosage of persons subject to a single exposure or only a few exposures. This is particularly true for storage in fat and excretion in urine. It is less true for blood levels (see page 49).

Although the general pattern of relationships between dosage and storage is similar for different compounds and different species, the quantitative relationships differ to such an extent that only curves for the same compound and species are of any use in estimating dosage.

For persons exposed in approximately the same way (for example, relatively constantly over a long period), the knowledge summarized by a curve relating storage or excretion to dosage has considerable diagnostic value. A degree of storage or excretion well within the range previously found to be tolerated is unlikely to cause illness. In a person with such values but exhibiting signs of poisoning, further search should be made for the cause of sickness. By the same token, if there is any record of poisoning associated with measured levels of storage or excretion, then a diagnosis of poisoning becomes more likely as values observed in a particular patient approach the threshold of danger.

In stating these generalities based on the study of many compounds, the Committee was aware that the highest concentrations of DDT that have been observed in body fat and blood are consistent with good health. Had it been possible to make such measurements some years ago, there is no doubt that substantially higher levels in blood, and perhaps in body fat, would have been found in persons who had ingested enough DDT to make them ill.

1.3 Levels in human populations

The Committee noted the numerous publications from many parts of the world giving data on the levels of DDT and its main metabolites in human fat. They considered that enough general surveys of this type have been made to confirm the wide distribution of DDT in human populations. The Committee believed that there was no point in seeking to obtain more data of this kind, for there is no medical reason for insisting that attempts be made to reduce these levels speedily.

The Committee hoped that any future surveys of DDT levels in people would be part of a programme to correlate such data with other factors. Because the levels found in the general population of different countries are so low, there is little hope of being able to link body burdens of DDT with the incidence of disease. The possibility of attempting such studies in heavily exposed groups is discussed elsewhere (see pages 12-15). There might, however, be value in setting up some long-term studies to determine the changes in the levels of DDT in populations of countries that have adopted
a policy of restricting or even totally eliminating the use of DDT and substituting less persistent materials. The Committee recommended that WHO should offer its help, at least as a coordinator, to any countries proposing to undertake such studies.

It is highly desirable that there should be agreement on the methods and techniques to be used in the future for all work of this kind so that valid comparisons can be made between the studies done in different places. The Committee considered that WHO and FAO could play a very important role in getting agreement on the techniques of measurement to be used (see pages 49-50) and above all in making the arrangements for the interlaboratory comparisons that are essential for achieving uniformity and accuracy in the data obtained.

1.4 Morbidity studies

Several previous expert committees have recommended that a study should be carried out on the effect of long-term exposure to DDT.

The only comprehensive reports available on the health effects of prolonged occupational exposure to DDT alone relate to groups of formulators in the USA. The exposure level was demonstrated to be 35 mg per man per day some years ago and around 18 mg per man per day more recently, and the men have been in the same work for periods of 10–20 years. When the intake was 18 mg per man per day, the mean fat storage levels were 30 times the average for the general population, indicating a dosage 450 times that of the general population. The reason for the difference in the ratio for storage and the ratio for dosage is the greater efficiency of excretion of this compound at higher dosage levels.

No specific complaints or medical findings that could be attributed to the effects of DDT were found on clinical examination. Furthermore, the general health record of these men showed a pattern of ordinary ailments that was indistinguishable from that experienced by men comparable in every other way except for an absence of exposure to DDT. No cases of cancer have been observed in these men, but as the group is small it was obviously reasonable to try to find larger groups for long-term study.

Two studies have been organized: one in Brazil is being undertaken by the Biological Institute of São Paulo with WHO assistance, and the other in India is being conducted by WHO in collaboration with the Indian Council of Medical Research.

(a) Survey in Brazil

This study at present includes the periodic clinical examination of 202 spraymen of the malaria eradication campaign who have been exposed to DDT for 6 or more years, of 77 spraymen who were exposed to DDT for 13 years from 1947 to 1959, and of 78 men who live in houses sprayed indoors with DDT every 6 months. The control group consists of 406 men
whose age distribution and socioeconomic level are similar to those of the exposed groups.

Over a 3-year period, a survey of illnesses requiring medical care in the 6 months preceding each periodic medical examination has not demonstrated any differences between the exposed groups and the control groups.

In the first clinical examination carried out in 1971, minor differences between exposed and non-exposed groups were observed in some neurological tests, but this result was not confirmed by the second examination in the same year. Preliminary studies on a relatively small number of serum analyses indicate a level in spraymen approximately 3 times that of the controls. More samples from both groups are being collected and analysed.

The periodic clinical examination of men living in houses sprayed indoors with DDT every 6 months and of controls who live in unsprayed houses did not show any difference between these groups. Serum DDT levels were also comparable.

Thus, no clinical differences between the exposed groups and the control groups have been revealed by the periodic clinical examination.

(b) Survey in India

As part of the feasibility study, 44 blood specimens were collected from men who had sprayed DDT indoors for 5 or more years, and from 27 controls. The results are summarized in Table 1.

<table>
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<th>Location</th>
<th>Exposed men</th>
<th>Controls</th>
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<tr>
<td></td>
<td>No. of blood analyses</td>
<td>Mean level of total DDT (mg/litre)</td>
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<td>(a) India</td>
<td></td>
<td></td>
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<tr>
<td>Preliminary survey a</td>
<td>44</td>
<td>0.761</td>
</tr>
<tr>
<td>Main survey</td>
<td>100</td>
<td>1.272</td>
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<tr>
<td>(c) USA</td>
<td>Formulators b</td>
<td>20</td>
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a Results on whole blood specimens; all other results on serum specimens.

By the end of the 1971 spraying season, examinations had been carried out on 104 similarly exposed men and 103 controls in Gujarat State.
No differences were found in cardiovascular indices but in neurological tests, knee reflexes were brisker in the exposed group, slight tremor was more often present, and performance in a timed Romberg test was poorer. No sensory changes were found, nor were there any significant differences in other reflexes, vibration sense, or coordination. No differences were found in weight, haemoglobin values, blood sugar, or urinalysis. The positive results led to the selection of 20 men for re-examination by a neurologist. From these follow-up examinations it was concluded that the differences found at the first examination were not real or else that the tests had returned to normal within the few months between the two examinations. In any case, the signs were not dosage-related, since they showed no correlation with serum levels of DDT.

The body loads of DDT found in exposed spraymen and shown in Table 1 are as high as those described among formulators in developed countries. No effects of this exposure have been discovered in the surveys so far carried out, even in spraymen who have had more than 15 years of exposure.

(c) General comments

In both the Brazilian and the Indian studies, long-term surveillance is envisaged and both are being carried out according to comparable protocols. Attempts at finding other countries in which to carry out similar surveys have not yet been successful. It seems clear that it will be very difficult to identify further groups that have been occupationally exposed only to DDT for periods in excess of 5 years. There are other difficulties in carrying out long-term studies. It has to be accepted that certification of the cause of death is subject to error in any country and this is even more so in rural areas in developing countries, where certification may not be available at all.

The only type of long term surveillance of highly exposed groups that is likely to be possible is a total mortality study, perhaps with a breakdown into violent and non-violent causes of death. For this, large groups would be required or smaller groups would have to be followed for very long periods. To investigate a specific cause of death, such as cancer, much larger groups would be needed, even in circumstances where the diagnosis could be relied upon. However, the possibility of identifying large groups exposed only to DDT for long periods seems remote, even on a multi-country basis. The use of DDT in malaria control is decreasing, mainly because some countries are achieving eradication and entering the consolidation phase, and to a slight extent because of the development by vectors of resistance to DDT. Furthermore, there is a considerable turnover of spraying staff in many programmes from year to year.

Despite the difficulties of carrying out long-term studies the Committee recommends that WHO continue to search for suitable groups of formulators and spraymen on a multi-country basis and, if feasible, attempt to extend
the groups already under study. The Committee also recommends that
the two studies described above should be continued with further periodic
examinations of the men already identified, whether or not they remain
exposed.

2. WHO PROGRAMME FOR THE EVALUATION AND
TESTING OF NEW INSECTICIDES

This programme was outlined in the Committee's sixteenth report\(^1\)
and a full account has been published more recently.\(^2\) The Committee
were informed that work in the programme continues satisfactorily. WHO
has established a number of research units in the field, which are well
equipped to perform all aspects of field trials including the safety evaluation
of new insecticides when applied against a wide variety of vectors using
an increasing diversity of techniques. While the original purpose of the
scheme was to develop insecticides that are safe to use where insect resis-
tance to DDT had made the use of this compound impractical, growing
concern with persistence of pesticides and their possible adverse effects on
other than target species has meant that more attention is being paid to
biodegradability. Although the main purpose of the work remains the
development of satisfactory alternatives to DDT for indoor application as
residual sprays for use in the malaria eradication campaign, there is growing
emphasis on compounds for use in the control of onchocerciasis, trypanoso-
miasis, filariasis, and other diseases.

During the past 5 years there has been a continuous decline in the
number of new compounds submitted to the scheme, so that only 38 were
received in 1971 as compared to 50–60 annually during 1967–1970 and
150–200 annually during 1962–1966. Steps have been taken to hasten the
progress through the scheme of compounds that show promise for anophe-
line control by making the first observations on safety in a somewhat
enlarged Stage IV, extending the trials at Stage V, and amalgamating the
work of Stages VI and VII (these stages are described in the two publica-
tions referred to above). Thus compounds evaluated under the scheme may
become available more rapidly for general field use.

The Committee noted that the programme is now concerned with the
safety not only of chemical insecticides, but also of molluscicides, rodent-
icides and other means of vector control. The safety aspects of some of
these materials are dealt with elsewhere in the report (pages 32-41).

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2.1 Insecticides for residual indoor application

The Committee noted that, following the recommendation made in its twelfth report, malathion (OMS-1) has continued in operational use in some areas.

2.1.1 Stage VI and VII trials

The further work on propoxur (OMS-33) and fenitrothion (OMS-43) recommended in the sixteenth report of the Committee has been carried out, and the aims of these and any other trials at Stages VI and VII are reiterated in the following paragraph.

Experience has shown that a large-scale operational evaluation of each new insecticide is necessary to determine whether any difficulties are likely to be encountered if it is used routinely for vector control. In this type of trial, the houses of 10,000–25,000 persons living in an area of 100–300 km² are sprayed under usual field conditions. A trial of this magnitude requires 20–30 sprayermen divided into 4–6 teams spraying for at least 6 weeks. Concurrently with observations related to the chemical properties of commercially produced formulations and their entomological effectiveness, the trial permits the collection of further toxicological information when the candidate insecticide is applied under true operational field conditions over a prolonged period of time. Thus the protocol for toxicological studies included the following points:

(i) Assessment of possible cumulative effects in spraymen by clinical examination and by a reliable field method for measuring the degree of exposure.

(ii) Establishing that the safety measures recommended in Stage V to be observed for the safety of operators, inhabitants, and domestic animals are feasible and adequate.

(iii) Assessment of any possible adverse effect of the pesticide if the precautions taken in its application are relaxed (a) intentionally, (b) due to adverse climatic conditions or (c) due to poor working discipline.

(iv) Evaluation of the adequacy and usefulness of the field method as a routine check for determining the degree of exposure.

(v) Information on the practicability, feasibility, and usefulness of any recommended procedure when undertaken under operational field trial conditions.

Throughout this report pesticides are referred to by the names recommended by the International Organization for Standardization (ISO), where these exist, or by another nonproprietary name. Proprietary names are used only where no nonproprietary name has yet been assigned. For the convenience of readers who have been following the WHO testing programme, the OMS numbers used in this programme are given in parentheses after the first mention of the compounds.
**Propoxur (OMS-33)**

*Chemical name: o-isopropoxyphenyl methylcarbamate*

Large-scale operational field trials were carried out in El Salvador (1966–67, seven rounds of spraying), in Iran (1967), and Nigeria (1967). Altogether, over 30 metric tons of propoxur water-dispersible powder were used. Full descriptions of these trials have been published\(^1\) and a summary of the safety evaluations is given below. In no operation did a serious case of poisoning occur, but some complaints were encountered among both spraymen and residents in each operation except that in Nigeria. The first reactions to an over-exposure to propoxur (nausea, headache, excessive sweating, and general weakness) made the sprayman stop work. In every case a short rest away from further exposure led to a rapid improvement so that within half-an-hour to an hour work could be resumed and symptoms did not reappear. In El Salvador heat exhaustion when humidity was high, coupled with some dehydration and salt depletion—exaggerated by the excessive sweating induced by propoxur—probably contributed to some of the reactions seen among spraymen.

Safety measures used were limited to simple protective clothing and a good standard of personal hygiene. When personal hygiene was poor and dirty protective clothing was worn, the frequency of reactions rose.

Reactions to propoxur were reported by some residents of the sprayed houses in all trials except that in Nigeria. In Iran the complaints often occurred among those who had infringed the recommended precautions by entering the houses during or immediately after spraying or by sweeping the floors with an insufficient amount of water. In El Salvador small children crawling on floors that had not been swept after spraying sometimes showed reactions. The ill-effects were short-lived and did not result in residents refusing to have their houses resprayed in subsequent operations.

It should be recognized that the most common complaints of spraymen and villagers after exposure to propoxur (headache, nausea, vomiting, etc.) are common complaints that may be due to various causes; it is therefore likely that a group of spraymen or villagers not exposed to insecticides would mention a certain number of such complaints when questioned. No attempt was made to ascertain the extent of such a “background” of complaints among persons not exposed to propoxur.

The Committee noted that observations on the safety of propoxur when used as a residual insecticide have been carried out in several village trials (1962–66) and in operational field trials (1966–67) in three different parts of the world with a total of more than 4000 man-days of spraying. All these trials were conducted under medical supervision, and laboratory tests to determine cholinesterase inhibition and metabolites in urine were performed.

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In view of the very marked symptomless daily fluctuation in cholinesterase activity and the absence of a cumulative inhibitory effect during exposure over several weeks, routine blood cholinesterase examination is of little, if any, practical value in determining when spraymen should be withdrawn to prevent over-exposure. On the other hand, minor complaints, such as headache and nausea, cause the operator to stop work and thus prevent further exposure. He quickly recovers, particularly if he washes the contaminated skin.

Propoxur needs to be handled with somewhat stricter precautions than are generally taken for applying DDT. Detailed instruction sheets have been prepared to provide field personnel at all levels with the information necessary to ensure safe spraying of propoxur when used as a residual insecticide in houses in malaria eradication programmes and for the control of the vectors of Chagas' disease.

**Fenitrothion (OMS-43)**

*Chemical name: O,O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate*

In 1966 the WHO Expert Committee on Insecticides concluded that fenitrothion was an effective insecticide that could be used safely, but recommended that, once the problem of uniform formulation had been solved, this compound should be given further Stage VI trials.

An operational evaluation of fenitrothion has been completed by the WHO *Anopheles* Control Research Unit II near Kisumu, Kenya. Concurrent toxicological studies were carried out during 4 rounds of fenitrothion spraying undertaken at approximately 3-monthly intervals. Three different formulations of fenitrothion water-dispersible powder were tested, each of them being applied indoors as a residual spray with the aim of obtaining deposits on the wall containing 2 g of active ingredient per square metre. Bagging (see p. 20) was carried out by workers who were not engaged in spraying; there was no central mixing place but spraymen carried the pre-weighed insecticide into the field and prepared their own pump charges. A routine, twice-weekly, cholinesterase determination was carried out tintometrically in spraymen and packers.

The first 3 rounds of spraying lasted for approximately 6 five-day work weeks, and the fourth round lasted for 8 weeks. The spraymen's protective clothing consisted of overalls, broad-brimmed hats, tennis shoes, and gauze surgical masks. All protective clothing was washed daily, and soap was issued to each sprayman who was instructed to wash his hands and face after each pump charge and to take a shower at the end of the work-day.

Slight to moderate depression of cholinesterase activity determined tintometrically was observed in most of the spraymen towards the end of the spraying rounds; one sprayman was removed from the spraying sche-

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dule in the first round to allow cholinesterase recovery, and another was removed in both the second and third rounds of spraying. As a whole, in the fourth round of spraying inhibition of cholinesterase activity in spraymen was less pronounced; this is to be attributed mainly to stricter attention to safety precautions in spraying techniques and to improved supervision of workers. Except for one case of headache and slight dizziness associated with a 50% inhibition of cholinesterase, which took place on the final day of the fourth round of spraying, no other complaints attributable to the exposure to the insecticide were recorded during the total of about 2000 man-days of spraying.

No complaints whatsoever were received from the inhabitants, numbering about 20 000 people whose houses had been sprayed repeatedly.

A number of chickens were poisoned by drinking water contaminated with fenitrothion during the beginning of the first round of spraying. After special pits had been dug for disposal of pump washings, no further incidents were recorded. An important lesson to be learned from this is that arrangements for adequate disposal of pump washings should be made.

On the basis of these results, the Committee concluded that fenitrothion could be used safely as a residual spray in houses, provided that precautionary measures similar to those described above are followed. In view of the slight to moderate depression of cholinesterase activity found in most spraymen towards the end of each spraying round, cholinesterase determination should be carried out once a week whenever the spraying operation lasts for longer than 4 successive weeks or for any 6 weeks within a two-month period.

The Committee therefore supports the use of propoxur and fenitrothion operationally when the need for alternatives to DDT makes this necessary.

2.1.2 Stage V trials

Other compounds have been examined in the field on a village scale (Stage V trials) after appropriate studies in laboratory animals to determine the toxicity of each compound had indicated that no unjustifiable risk was being taken. It is often in this kind of trial that human exposure to a new compound takes place for the first time under field conditions. Thus, although village-scale trials are designed primarily for the entomological assessment of the effectiveness of new compounds, they also permit the collection of valuable toxicological information. The following objectives have been set up for such trials:

(1) Assessment of any adverse effect on spraymen and villagers by clinical examination and some laboratory tests. Information will be collected on signs and symptoms and duration of illness, if any, and the effect of therapy, if required.
(2) Assessment of the most important route of absorption and the main causes leading to over-exposure of spraymen and inhabitants.

(3) Determination of a safe technique of application, protective clothing required, and other precautions to be observed by operators.

(4) Determination of the precautions to be observed for protection of the inhabitants.

(5) Determination of the place of any laboratory procedure in controlling the degree of exposure and prevention of ill effects, with a view to deciding the need for a field method at later stages.

A medical toxicologist is always present during the spraying operations of a newly developed insecticide in Stage V trials. He carries out investigations according to the protocol specifically prepared for that trial. Whole blood cholinesterase activity is determined in operators by both spectrophotometric \(^1\) and titrometric \(^2\) methods; as a rule the latter test only was used for villagers. The inhabitants of the sprayed premises are also watched closely, and in a representative sample (30–40 people) blood cholinesterase activity is determined before and after their houses have been sprayed.

Water-dispersible powder formulations of insecticides (40–80%) have been used in all trials. These were dispensed into polyethylene bags by weighing the amount required to obtain a 5% suspension of the active ingredient when mixed with water. Bagging was carried out in the open or in a well ventilated room by 3 workers, who, as a rule, were not involved in actual spraying. They wore sou’westers, overalls, rubber gloves, respirators, and canvas ankle shoes. Bagging usually lasted for one day. The sprayman wore sou’westers, overalls (which were washed daily) and canvas ankle shoes; the mixer also wore rubber gloves. Soap and water were provided near the mixing point and each sprayman was instructed to wash his hands and face after each pump charge. The mixer washed his hands and face whenever he removed his rubber gloves. All the operators took a shower immediately after returning from the field. Spraying hours were normally between 8.00 h and 14.00 h. The number of pump charges sprayed was recorded for each sprayman. As a further precautionary measure, the spraying of some insecticides was introduced gradually and in empty houses, before the actual trial began. The villagers were warned to empty their houses of all belongings prior to spraying. The inhabitants and their domestic animals were kept well away from the houses while spraying was in progress.

Five organophosphorus compounds and 4 carbamate insecticides have been tested at the WHO *Anopheles* Control Research Unit I, Kaduna, Nigeria. The findings are reviewed below.


Dicaphon (OMS-214)

Chemical name: O-(2-chloro-4-nitrophenyl) O,O-dimethyl phosphorothioate.

This compound was reviewed in the sixteenth report of the WHO Expert Committee on Insecticides\(^1\) in connexion with an 8-day village-scale trial carried out in 1966. In 1968 a village trial was carried out near Kaduna in which dicaphon was sprayed for 3 days. No complaints attributable to the insecticide were recorded among the exposed operators or inhabitants. Slight depression of whole-blood cholinesterase activity was demonstrated by a spectrophotometric method in spraymen and negligible depression by the same method in villagers (mean value about 95%). In some spraymen a somewhat more pronounced depression was observed on the following morning. No inhibition could be demonstrated by the tintometric method in more than 50 parallel determinations carried out in spraymen.

While no complaints were received from the operators and exposed villagers when spraying with dicaphon was continued for 3 days, the possibility of a cumulative inhibitory effect on the spraymen's cholinesterase if the spraying operation had lasted for several weeks cannot be excluded. The above observations support the view expressed in the Committee's sixteenth report that dicaphon is a safe compound for use in larger scale trials, provided that cholinesterase determinations in spraymen are performed at the initial stages of such an operation and similar safety measures to those described for fenitrothion are observed.

Bux (OMS-227)

Chemical name: \(n\)-(1-methylbutyl)phenyl methylcarbamate and \(m\)-(1-ethylpropyl)phenyl methylcarbamate (3:1 mixture)

Four spraymen and one mixer were engaged in this trial. They sprayed 6-7 pump charges during the first day and 9-10 pump charges during the second day of spraying operations. No complaints were received during the first day of spraying in the field. One sprayman complained of "hunger cramps" in his stomach while a blood sample was being taken after work. The following morning the same sprayman and another one reported that they had vomited late in the afternoon on going home. They did not have any other discomfort. Cholinesterase determination showed a marked depression in activity (down to about 50% of normal) but by the following morning the cholinesterase activity had recovered in all the spraymen to 90% of the normal value. During the second day of spraying one sprayman vomited while at work after he had sprayed 9 pump charges. His pulse rate was 52 per minute, and he experienced some sweating, dizziness, and pupillary change. He recovered completely in a few hours. Two other

spraymen, although they felt well while coming back from the field and taking a shower, vomited afterwards but recovered rapidly. The cholinesterase determination in the spraymen showed a drop in activity similar to that after the first day of spraying. The following day all the spraymen felt well and their cholinesterase activity recovered markedly. None of the affected operators complained of headaches, a most frequent type of complaint encountered in cases of over-exposure to another carbamate insecticide (propoxur). Except for itching in two men, most of whose skin was covered with dust and earth, as they hardly wore any clothes, no other complaints were received from the inhabitants. Cholinesterase activity among residents did not show any marked depression when determined tinctometrically two days after their houses had been sprayed.

Mammalian toxicity data on the original sample of this compound had indicated that in comparison with other carbamates it would be safe for indoor spraying. However, in view of reactions observed among the spraymen during the first two days of spraying, the trial was terminated and no entomological evaluation was made. It is worth noting that acute toxicity tests on rats with the batch used in 1970 showed it to be more toxic than the original sample.

In view of the reactions among the spraymen the Committee concluded that Bux should not be considered further for use as a residual insecticide for malaria control if standard house-spraying techniques are employed.

**Landrin** (OMS-597)

*Chemical name*: 3,4,5-trimethylphenyl methylcarbamate, 75%
2,3,5-trimethylphenyl methylcarbamate, 18%

Two trials have been carried out with this insecticide lasting for 4 and 2 days respectively. There were no complaints among the operators and residents although in one of the trials a water shortage prevented operators washing and bathing after work as frequently as planned. While moderate to pronounced inhibition of whole-blood cholinesterase was observed in some spraymen at the end of the day's work this was considerably less than that observed in the same spraymen when spraying propoxur, both a week before and a week after spraying Landrin. The Committee concluded that Landrin has proved safe enough to warrant extended field trials (Stage VI/VII), provided that similar precautionary measures to those for propoxur are taken.

**Mobam** (OMS-708)

*Chemical name*: benzothien-4-yl methylcarbamate

Spraying of Mobam was carried out during 1968 in three villages with a total of 463 houses and 405 other structures. Four spraymen and one
mixer were engaged. The spraymen wore sou'westers, daily washed overalls, and canvas shoes, and the mixer also wore rubber gloves.

In view of the previous year's observations on a sprayman and a mixer, both fully protected, who complained of headache soon after Mobam had been applied to a few experimental huts in the Stage IV trial, the village-scale trial was started by first spraying empty houses. On the first day two spraymen and the mixer worked for 2 hours only and 4 pump charges were sprayed per sprayman. On the second day the whole crew sprayed for 4 hours using 6 pump charges each. The spraying of inhabited houses lasted for 4 days and 6-10 pump charges were sprayed by each sprayman per day.

Three baggers, not involved in actual spraying, dispensed 100 kg of the insecticide into single pump charge amounts in polyethylene bags for 3½ hours. All three of them complained of skin irritation and two complained of headaches. During 8 man-days of work spraying empty houses and 20 man-days of village spraying, two complaints of headache, one of skin irritation and one of chest pain were received from the operators. All of these complaints were described as not severe and no changes could be observed on the affected skin areas. Cholinesterase activities were measured and it was shown that some absorption of the compound by the spraymen had occurred. No complaints were received from villagers living in the sprayed huts. The Committee agreed that Mobam has proved safe enough to warrant its being subjected to an extended field trial provided that precautionary measures similar to those used with propoxur are taken.

**OMS 1028**

*Chemical name*: o-cyclopropylphenyl methylcarbamate

In 1971 four spraymen and a mixer sprayed OMS-1028 in two villages near Kaduna. They sprayed 8-10 pump charges on the first day of the spray operation, 13-15 charges on the second day and 14-18 charges on the third day. The average number of working hours increased correspondingly, i.e., from 5.5 on the first day to 10 on the third day. No complaints were received either from the operators who were engaged for 3 days in the spraying operation (totalling 110 man-hours) or from villagers whose houses were sprayed. Slight to moderate inhibition of cholinesterase with rapid recovery was found among the spraymen and very slight, if any, inhibition among the exposed villagers.

The Committee concluded that OMS-1028 can be applied safely in larger trials (Stage VI/VII) provided that precautionary measures similar to those described in the introductory paragraphs are taken.

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1. The name "phencycloarb" has recently been proposed by ISO as a nonproprietary name for this compound.
Phenthoate (OMS-1075)

Chemical name: ethyl mercaptophenylacetate \(S-(O,O\text{-dimethyl phosphorodithioate})\)

In 1969 this insecticide was sprayed in a village near Kaduna. Clinical and biochemical observations carried out on five spraymen and one mixer engaged in a 3-day spray operation did not reveal any adverse effect attributable to exposure to phenthoate. Similarly, no effects could be detected among the villagers living in the sprayed houses.

The Committee concluded that the compound was safe enough to warrant its evaluation in Stage VI/VII trials.

Phoxim (OMS-1170)

Chemical name: phenylglyoxylonitrile oxime \(O,O\text{-diethyl phosphorothioate}\)

A village-scale trial of this compound was carried out at Kaduna in 1971. The water-dispersible powder formulation of phoxim smelt like cyanide when received. Test papers showed that hydrogen cyanide was present but at a low level. In order to assess this, an experimental hut was sprayed at 4 g/m² (instead of the normally applied target dose of 2 g/m²) and it was shown that no hydrogen cyanide was detectable by air sampling over a day and a night. It was only after this test that a decision to spray in the Stage V trials was made.

The insecticide was bagged by three workers, none of whom was engaged as a spray operator. They wore overalls, plastic helmets, rubber gloves, and dust respirators. The bagging was carried out in a well-ventilated room and the operators were placed upwind of the drum. While test papers put above the insecticide in a freshly opened drum became cyanide-positive within 10 minutes, those placed at several points in the room used for bagging were negative. Two of the three men complained of weakness after completion of the work. No clinical signs or other symptoms were recorded and they had recovered fully by the next day without any treatment.

Four spraymen wearing overalls, sou'westers, and canvas shoes, and one mixer who also wore rubber gloves sprayed a total of 93 pump charges over a period of 3 days. Two of them complained of pain in the face lasting for 1 hour after completion of daily work on the first and third days of spraying. There were no visible changes in facial skin at that time. The first and third days of spraying were sunnier than the second. Except for these complaints, which appeared within 1 hour of spraying, no complaints or any clinical findings attributable to the insecticide were recorded among the spraymen and villagers exposed to phoxim. Very slight depression of whole-blood cholinesterase was detected spectrophotometrically in some of the exposed spraymen and in some villagers (tintometrically).
The Committee discussed the above findings and considered that, although there is apparently no hazard from the use of phoxim as far as its anticholinesterase activity is concerned, further investigation of this compound at Stage V is required to assess its pain-producing effect and the possible risk from liberation of hydrogen cyanide.

**Chlorphoxim (OMS-1197)**

*Chemical name: α-chlorophenylglyoxylonitrile oxime O-ester with O,O-diethyl phosphorothioate*

A village trial with this insecticide was carried out in 1972. Three baggers, four spraymen, and one mixer were engaged. Bagging was performed in a well ventilated room and lasted for 4 hours. No hydrogen cyanide could be detected by the paper test method above freshly opened drums. Two out of three drums were used to prepare 169 bags. Spraying lasted for 5 consecutive days, during which 162 pump-charges were used to spray about 450 houses. No complaints were received and no adverse effects could be detected among exposed baggers, spraymen, or inhabitants during this trial. Whole-blood cholinesterase in spraymen showed no depression when measured spectrophotometrically and tintometrically, neither could any inhibition be detected tintometrically among the exposed residents.

Since there were no complaints among exposed operators and villagers and no clinical or biochemical findings of adverse effects, the Committee concluded that chlorphoxim should be safe enough to warrant its use in larger trials providing the precautionary measures described on p. 20 are observed. However, in view of the observation reported recently by the collaborating laboratory, that the toxicity of chlorphoxim water-dispersible powder formulation increases when it is exposed to sunlight, the stability of the compound during storage and handling prior to spraying should be investigated before it can be recommended for Stage VI/VII trial.

**Jodfenphos (OMS-1211)**

*Chemical name: O-(2,5-dichloro-4-iodophenyl) O,O-diethyl phosphorothioate*

Comprehensive studies on the safety of jodfenphos were performed during the 1969 trial in which five spraymen and one mixer with no previous spraying experience were engaged. In this trial, totalling 41 man-days of work in a village of 1819 inhabitants, no complaints attributable to exposure to the insecticide were recorded among the operators who sprayed jodfenphos for 8 days; neither were any complaints received from villagers living in sprayed villages. The tintometric method revealed no significant depression of blood cholinesterase activity among operators and exposed villagers. During trials conducted in 1970 the same precautionary measures were
taken and again no adverse effects were observed and no complaints were received from either spraymen or villagers.

On the basis of these results the Committee concluded that jodfenphos is safe for Stage VI/VII trials, provided that the precautions described above are employed.

2.2 Larvicides

2.2.1 Mosquitos

Insecticides for the control of mosquito larvae are applied to different types of water. The hazards to operators during any of these applications can be circumvented by simple attention to good hygienic practices. Consequently the mammalian toxicity of a larvicide need be taken into account only when the water that has been treated with an insecticide is liable to be drunk.

(a) For non-potable and grossly polluted water, fenithion (OMS-2) and Dursban \(^\text{1}\) (OMS-971) may be used safely.

(b) For outdoor water that is liable to be drunk, the more toxic larvicides mentioned above should not be used, but malathion, Abate (OMS-786), and OMS-1155 \(^\text{2}\) (the dimethyl homologue of Dursban) are not likely to present a hazard to the chance consumer if they are applied to the water as larvicides in the recommended manner.\(^\text{3}\)

(c) For domestic water containers, larvicides may be needed to prevent breeding over long periods, and their continued presence in high dilution is ensured by the addition of slow-release formulations. Because the mammalian toxicity of Abate has been extensively studied and these studies have included prolonged administration to volunteers,\(^\text{4}\) the Committee agreed that this larvicide is safe to use in drinking water at a target dose of 1 mg/litre (1 ppm).

Perifocal applications. These residual applications, which are used to eliminate *Aedes aegypti* by treating their breeding foci and the surfaces immediately surrounding them, need not involve any serious hazard to the spraymen provided good standards of hygiene are maintained. However, some operations will result in the contamination of potable water by the insecticide. Where such a possibility exists, the Committee recommends that the more toxic larvicides fenithion and Dursban should not be used.

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\(^1\) The name "chlorpyrifos" has been proposed by ISO for this compound, but is not yet accepted.

\(^2\) Several names for this compound are at present under consideration by ISO.


2.2.2 Blackfly

Very extensive application of larvicides is being planned in a big control programme against onchocerciasis in Africa. While DDT is still a very effective larvicide, its application to rivers is now regarded as undesirable because of its persistence. The Committee considered that methoxychlor (OMS-466), a biodegradable analogue of DDT with a lower mammalian toxicity and long history of safe use in agriculture, would be a safe substitute for DDT for application to rivers. The Committee also agreed that the less toxic organophosphorus compounds that are recommended above as mosquito larvicides for outdoor water, namely Abate and OMS-1155 (the dimethyl homologue of Dursban), as well as phoxim (OMS-1170) and chlorphoxim (OMS-1197) in the form of emulsifiable concentrates, would also be safe to use in onchocerciasis control.

2.3 Insecticides for human louse control

In the seventeenth report of the WHO Expert Committee on Insecticides, Annex 18 (Chemical Methods for the Control of Vectors and Pests of Public Health Importance) recommends the use of a 10% DDT dust as the treatment of choice where body lice are not resistant to this compound; where lice are resistant, the use of 1% malathion or 1% lindane dust is given as an alternative.

Since the seventeenth report was published, increasing restrictions have been placed on the use of DDT. Although such restrictions do not concern this particular use, the possibility exists that DDT may not be as readily available as previously for use against human lice. A more important problem is that resistance to DDT is common among lice.

There are reports that resistance of body lice to malathion has occurred at two widely separated points on the African continent — in Burundi and in Egypt. It is therefore imperative that alternative compounds be made available. Tests at the WHO International Reference Centre in Gainesville, Florida, USA, have demonstrated that satisfactory control of body lice can be obtained with powders containing 1% of Abate, 5% of carbaryl, and 1% of propoxur.

Mobam (OMS-708)

Chemical name: benzothien-4-yl methylcarbamate

Mobam was tested against DDT-resistant body lice in Korea on 100 volunteers. An average of 34 g of 5% Mobam in an inert powder was dusted once per man. No symptoms attributable to the treatment were reported by the attending physician, and no depression of erythrocyte or serum cholinesterase activity was found. Biochemical determinations failed to show significant differences between those dusted with Mobam and those
dusted with the inert powder. On the basis of these results, the Committee agreed that 5% Mobam is safe for the control of human lice.

**Abate** ¹ (OMS-786)

_Chemical name:_ $O,O,O',O'^{-}$-tetramethyl $O,O'$-thiodi-$p$-phenylene phosphorothioate

A 2% Abate powder was tested on an unspecified number of volunteers using the sleeve-test method; no ill effects were noted, and the cholinesterase levels were within normal range for the duration of the 7-week study. Control of body lice was excellent. The safety of Abate when administered to human subjects by the oral route has previously been reported.² The Committee agreed that 2% Abate is safe for use against human lice.

**Carbaryl** (OMS-29) and **propoxur** (OMS-33)

_Chemical names:_ 1-naphthyl methylcarbamate and $o$-isopropoxyphenyl methylcarbamate

These two compounds were tested by the sleeve-test method and no symptoms or blood cholinesterase changes were seen in the persons exposed. However, control of the lice was not as good as with the malathion standard.

### 3. ULTRA-LOW-VOLUME (ULV) APPLICATION

This technique involves the dispersal of fine liquid particles of pesticide concentrates containing 90% or more of active ingredients at application rates of 1 litre or less per hectare. There is growing evidence that the ULV application of organophosphorus insecticides will play an important role in the control of certain vector-borne diseases. The application may be made over open country or built-up areas by aircraft or in some cases by ground equipment, carried either by people or on trailers. Ground equipment may also be used for application inside houses, or sometimes through open windows or doors.

The hazards that might arise from this type of application are discussed below.

#### 3.1 Operator hazards

The high concentrations of pesticides used in these operations demand special care and training in dealing with spills and leaks from equipment,

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¹ The name "temephos" has been proposed by ISO for this compound but is not yet accepted.
though the absence of any need for mixing and dilution does reduce these hazards to some extent. The spraying equipment, which will contain the concentrated active ingredient, will need careful maintenance to ensure efficient performance, and again good training will be essential. Special attention must always be paid not only to the safety of aircraft pilots but also to ensuring that leaks and spills from poorly constructed equipment, which may not necessarily indicate danger of poisoning, do not distract the pilot from his exacting task.

High standards of maintenance of the engines driving the compressors of petrol-powered, knapsack sprayers must be ensured, since accidents caused by the ignition of spilled petrol constitute a well recognized hazard to users of such equipment.

3.2 Hazards to third parties

The nature of these operations is such that people are inevitably exposed to the falling particles outdoors or sometimes even inside rooms when an application is made from outside the house. The greatest mass of the material is dispersed as particles 20 μm or more in diameter, and, to avoid undue evaporation, the insecticides used must have a low volatility. Thus the amounts dispersed as small (< 5 μm), respirable particles or as vapour arising from the evaporation of these small droplets represents an insignificant exposure in view of the low toxicity of compounds appropriate for this kind of use.

From amounts of insecticide released to give a target application rate of, say, 500 g/hectare, it is possible to calculate that the amount falling on the whole adult body surface (1.7 m²) would not exceed 100 mg. In practice, only a small fraction of the body surface would be exposed to impacting droplets.

Inside a room the concentration of insecticide falls rapidly as the droplets settle, but even if the maximum concentration—around 5 ml of active ingredient in a 32 m³ room—were maintained for one minute the total amount of insecticide inhaled would be less than 5 mg.

The Committee considered that insecticides of a toxicity similar to, or less than, that of fenitrothion could be used in such applications, even if repeated regularly at intervals of 2–4 weeks, without exposing applicators and those in the sprayed areas to any toxic hazard from the insecticide.

However, the Committee recommended that studies of safety similar to those made in Stage V and Stage VI/VII trials of indoor residual insecticides be made on men applying ULV treatments and on those residents likely to be most heavily exposed. The Committee also recommended that ULV applications should not be made through windows or doors without first ascertaining that the room is unoccupied.
4. AIRCRAFT DISINSECTION

Synergized pyrethrins and pyrethroids

Until recently, aircraft disinsection sprays consisted largely of formulations containing DDT. Because of the increasing problems of insect resistance to this pesticide other insecticides have been considered. Among the more promising compounds are the mixtures of natural pyrethrins or synthetic pyrethroids with methylenedioxy synergists, such as piperonyl butoxide or Tropital. The pyrethrins and related compounds have a specific effect on nerve membranes and their physiological action is somewhat similar to that of DDT. The Committee took account of the low oral toxicity of the pyrethrin compounds and their analogues, but attention was drawn to their high toxicity when administered by the intravenous route. Little information appeared to be available on their toxicity by the inhalation route.

Recently pyrethroids of very low mammalian toxicity have been developed including resmethrin (OMS-1206) and bioresmethrin, which is its (+)-trans isomer. These compounds provide an adequate margin of safety when used in the prescribed manner for disinsection of aircraft. They are rapidly metabolized and detoxified so that no cumulative effects will be encountered.

The Committee also considered the methylenedioxy synergists, which act by inhibiting the mixed function oxidase enzymes that in insects are responsible for detoxifying the pyrethrins. Of these compounds, Tropital shows great promise.

The Committee agreed that there was no sound evidence to suggest that exposure to synergized pyrethrins or pyrethroids would present any toxic hazard to the passengers or crew of aircraft.

Dichlorvos (OMS-14)

Chemical name: 2,2-dichlorovinyl dimethyl phosphate

The safety of dichlorvos for disinsection of aircraft was considered in the sixteenth report of the WHO Expert Committee on Insecticides. Since publication of that report, other toxicological questions have been raised. Although it is realized that dichlorvos has several uses in public health and agriculture, consideration here is limited to its use for disinsection of aircraft.

1 piperonal bis[2-(2-butoxyethoxy)ethyl] acetal.
2 5-benzyl-3-(furyl)methyl (±)-cis-trans-2,2-dimethyl-3-(2-methylpropenyl)cyclopropene carboxylate.
Human exposure studies conducted since publication of the above-mentioned report have served only to reinforce the view then expressed that dichlorvos used under the prescribed conditions offers no hazard to either passengers or aircrew from the point of view of acute toxicity and has no effect on cholinesterase levels. One such study has shown that at exposure levels corresponding to a concentration \times time (ct) product up to 10 times that proposed for disinsection dichlorvos vapour exhibited no toxic effects on people at pressures corresponding to aircraft cabin pressures at operational altitudes. Other studies have shown that at concentrations 4 times those proposed for disinsection, a ct product in excess of 400 (mg/m²)-min is necessary to produce a detectable effect on plasma cholinesterase. Oral exposures at high dosage levels have shown that there will be no hazard from contamination of food exposed on aircraft during the disinsection process.

Recent chemical work has established that dichlorvos will methylate DNA \textit{in vitro} and the rate of methylation is comparable to that obtained with methyl methanesulfonate. Other work \textit{in vitro} with \textit{Escherichia coli} and HeLa cells has shown that the methylation of DNA by dichlorvos is much less than that produced by methyl methanesulfonate. Dichlorvos is converted rapidly in mammals to non-methylating products and removed by reaction with other biological material. The Committee therefore concluded that the amount of dichlorvos available for methylation of DNA in the body will be a small fraction of that to which humans are exposed.

Demonstration that a parent compound or a metabolite interacts with DNA \textit{in vitro} cannot be accepted as conclusive evidence of a mutagenic action. It should, however, indicate that biological testing be given high priority. Conventional 2-year feeding tests for carcinogenicity as well as recent \textit{in vivo} tests of teratogenicity, genetic studies in host-mediated assays (using the yeast \textit{Saccharomyces cerevisiae}), cytogenetic studies in mice and Chinese hamsters, and dominant lethal mutation tests in mice have proved negative. It is now generally accepted that data from submammalian species and from \textit{in vitro} mammalian systems have little direct relevance to man, particularly with reference to mutagenic and carcinogenic hazards. The Committee did not therefore consider such evidence to be relevant to the evaluation of the hazards to man of dichlorvos.

In order to simulate more closely the usual manner of exposure to dichlorvos vapour, a special carcinogenicity study in rats is in progress, with exposure by inhalation at 50, 500, and 5000 mg/m³ continuously for 2 years. After 15 months, no tumorigenic effects due to dichlorvos have been found, even though at the highest dose the cholinesterase of blood will be grossly inhibited.

The exposure (ct product) during an aircraft disinsection will not exceed 6 (mg/m³)-min whereas the exposure to the highest dose in the tests for carcinogenicity will, on completion of the study, be $5 \times 10^6$ (mg/m³)-min.
Taking into account the large differences in these exposures, the known capacity of the mammal to degrade dichlorvos to non-methylating products, and the negative results of tests in laboratory animals, the Committee concluded that the hazard resulting from exposure of passengers and crew will be negligible. In the light of the evidence now available the Committee supports the use of dichlorvos for the disinsection of aircraft in accordance with the prescribed procedures and dosage, provided that the inhalation carcinogenicity test proves negative.

5. ALTERNATIVE METHODS OF INSECT CONTROL

The Committee reviewed developments in the use of chemosterilants, of juvenile hormone mimics, and of biological control agents such as nematodes, fungi, protozoa, bacteria, and viruses. It noted the type of safety tests employed by Federal Government authorities in the USA to clear the use of Bacillus thuringiensis preparations and for temporary clearance of the Heliothis nuclear polyhedrosis virus.

It was pointed out that the natural origin of the alternatives to chemical insecticides does not necessarily mean that they are free of hazards to people, domestic animals and wildlife. As mentioned in the Committee's last report on this subject, any such material, whether living or dead, must be submitted to searching examination to exclude the possibility of toxicity to man and non-target organisms. Thus the Committee noted with approval the action taken by the Organization, in cooperation with FAO, to review the methodology of tests for safety of biological agents, particularly viruses, and to promote research on the subject. It also pointed out that the matter of the safety of such agents would require review by microbiologists as well as toxicologists.

Juvenile hormone mimics prevent insects from developing adult characteristics, ovaries, and eggs. So far, these compounds are free of resistance problems. Those being developed commercially are metabolically labile and of negligible toxicity to warm-blooded animals. Results of tests now being made of their possible teratogenicity or carcinogenicity are awaited.

With respect to chemosterilants, the Committee could not envisage at present how those that are alkylating agents or their analogues could be used with safety in the field, owing to the risk of contaminating the environment. However, their use to chemosterilize insects in laboratories producing sterile males could be made a safe operation. The Committee noted that the procedure followed at the WHO/ICMR Research Unit on the Genetics of Mosquitoes, New Delhi, in chemosterilizing Culex pipiens fatigans with thiopeta applied to the pupae did not result in the persistence of any

detectable amounts of this alkylating agent in the adult mosquitoes at the time of their liberation into the field. The use in the field of antimetabolites and miscellaneous compounds such as triphenyltin, is a possibility, but each compound should be judged on its own merits with respect to safety.
PART II. MOLLUSCICIDES IN PUBLIC HEALTH

Schistosomiasis as a major cause of disability is a growing threat in many parts of the world, including those around man-made lakes in tropical areas. At present it is generally conceded that the most practical means of controlling the spread of this disease involves the use of molluscicides to reduce the number of snail vectors in the affected areas. The eradication of the snail is not considered feasible, but chemical means are now available to reduce the snail population so that a measurable reduction in the incidence of new infections takes place. While the use of drugs and an improvement in general sanitation are important ancillary control measures, the main attack upon the spread of this disease is likely to depend upon the effective use of molluscicides for some years.

The Committee therefore discussed the probable safety of using the compounds now being developed and the type of information that would be needed by WHO before it could undertake trials involving the exposure of people to new molluscicides.

1. GENERAL CONSIDERATIONS

The old established molluscicides (copper sulfate and pentachlorophenol) are no longer used widely. The most effective molluscicides for use in aquatic habitats are niclosamide and N-tritylmorpholine. Yurim in (see p. 36), a less well studied compound, is preferable for use on soil against amphibious snails.

Certain organotin compounds, such as tributyltin and triphenyltin, are at an earlier stage of development. Because of the mammalian toxicity of the organotin compounds, there is increased interest in the development of slow-release formulations for molluscicides. These formulations may improve efficiency and reduce costs in some situations. This type of formulation ensures a greater safety in use, and it is possible to consider employing other compounds that would be unacceptably hazardous in conventional formulations. The Committee therefore recommended that WHO continue to support work on the development of such slow-release formulations.

1.1 Hazards to operators

Neither niclosamide nor N-tritylmorpholine has such an acute toxicity to mammals as to present a hazard when being applied to water. However,
the Committee stressed that it is important for men handling concentrates to be trained in the practice of good general and personal hygiene. Care has to be taken in the storage of supplies and the disposal of empty containers so that, if at any time in the future a new compound of greater toxicity is introduced, the good practices adopted will be such as to ensure the safety of the applicators.

1.2 Hazards to the general population

The effective concentration of molluscicides in treated water will not usually exceed 2–4 mg/litre and in some instances may be around 0.05 mg/litre. Applications are arranged so that the snails will be exposed to the higher concentrations for periods of 24 hours and to the lower concentrations for 4–5 days. Applications are not repeated more often than every 4–8 weeks, though such programmes will have to continue for many years if good control of the disease is to be achieved. It must be assumed that water treated with molluscicides might be used for drinking and for domestic purposes. Agricultural workers and others may be exposed to treated water during work and recreation. People living in the treated areas and drinking water every day might receive a maximum dose of 10 mg for one or several days, repeated not often than every 4 weeks. In practice, the dose is likely to be very much lower.

1.3 Hazards to other organisms

In addition to risks to man, hazards to other living organisms in the aquatic environment must be considered—particularly hazards to fish where they are an important source of food. Noting that WHO was supporting studies on biodegradability and on the possibility of pesticides being incorporated into food chains, the Committee recommended that such investigations should be made on any molluscide likely to be used extensively.

The Committee recognized that in evaluating the potential hazard of a candidate molluscide to man or the environment it would be necessary to balance the risk from having a molluscide residue in the water against that from the vector of the disease.

2. COMPOUNDS OF IMMEDIATE INTEREST

Niclosamide

Chemical name: 2',5-dichloro-4'-nitrosalicylanilide

This compound has a low toxicity to rats, the single oral lethal dose exceeding 5000 mg/kg. By intraperitoneal injection the LD<sub>50</sub> is 250 mg/kg. The compound is rapidly metabolized and excreted in the urine as the
amino derivative, and no cumulative effects have been observed in either rats or dogs given repeated doses over a period of one year.

The toxic effects are related to niclosamide's ability to uncouple oxidative phosphorylation. This mechanism of action is well known and is displayed by a number of compounds, including pentachlorophenol and 4,6-dinitro-o-cresol (DNOC). Niclosamide has a very low mammalian toxicity compared to other well known poisons with a similar mode of action.

The Committee considered that, on the basis of studies on experimental animals, there are no grounds for suspecting that the consumption of the very small amounts likely to be present in water after mollusciciding operations would present any hazard to people in treated areas.

**Frescon**

*Chemical name: N-tritylmorpholine*

This compound has a low single-dose oral toxicity to rats (LD₅₀ more than 1000 mg/kg) and also to mice and ducks. In 3-month feeding studies on rats no toxic effect except some impairment of growth was observed in animals on a diet containing 1000 mg/kg. No information is available on the mode of action of this compound in mammals, but no pathological lesions have been described after acute or repeated exposure. The Committee considered that it would be necessary to have more detailed information on the animal studies before a final opinion on its safety could be expressed. However, in view of the very low levels of any likely human exposure, the Committee agreed that in the meanwhile further use of this compound could proceed safely.

**Yurimin**

*Chemical name: 3,5-dibromo-4-hydroxy-4'-nitroazobenzene*

The only information on the toxicity of this compound available to the Committee was the acute oral LD₅₀ for mice, stated to be 170 mg/kg. The compound appears, therefore, to have a much higher acute toxicity to mammals than the two molluscicides considered above. It is therefore very desirable to obtain more information about the mammalian toxicity of Yurimin before embarking on any extensive trials.

**Organotin compounds**

Triphenyltin salts have been used safely for some years in agriculture for spraying crops such as potatoes. There is extensive information on their mammalian toxicity. By the oral route, the guineapig is very much more susceptible than other common laboratory animals, particularly to the cumulative effects of triphenyltin compounds. While the toxic effects
of these trisubstituted organotin compounds on isolated systems are fairly well understood, e.g., their capacity to inhibit oxidative phosphorylation, the cause of death in poisoned animals is not obvious. An effect on the immune mechanisms has been suggested in some instances.

Tributyltin salts have been used as antifouling agents and timber preservatives. Their acute toxicity is similar to that of triphenyltin salts and they produce the same biochemical disturbances. They have not been so extensively studied in conventional mammalian toxicity tests as the triphenyltin compounds, but their industrial application has not been associated with any reports of ill-effects on exposed workers.

The Committee was informed that, if used, these organotin compounds would probably be formulated in slow-release devices.

3. STUDIES OF NEW MOLLUSCICIDES

As exposure to molluscicides in water will be widespread and likely to occur at intervals over long periods, data on mammalian toxicity of any candidate molluscicide should be provided by the manufacturer before any field trials involving human exposure are carried out. The toxicological information to be supplied would be that normally required for the registration of a pesticide likely to leave a residue in human food. The Committee recommended that WHO should collect as much information as possible on the mode of action, metabolism and breakdown of a candidate molluscicide in order to enable an assessment to be made of its likely safety in use.

To facilitate any future decision about the likely safety in use of these compounds, the Committee suggested that it would be of great assistance to have accurate information on the levels actually found in water to which people would be exposed.
PART III. RODENTICIDES IN PUBLIC HEALTH

Following the introduction of the anticoagulant rodenticides in the early 1950s, there was a decline in the use of the "acute" rodenticides, i.e., those likely to cause the death of an individual rodent as a result of a single feeding. However, the rapid spread of resistance to the anticoagulant rodenticides among rats and mice has made it necessary in many areas to rely again upon the "acute" rodenticides. Such resistance has occurred in substantial areas in Denmark, Germany, Holland, the United Kingdom, and, more recently, the USA.

The Committee welcomed WHO's decision to introduce rodenticides into the existing scheme for evaluating new pesticides and urged that new compounds showing promise be tested under field conditions at the earliest opportunity.

Meanwhile, in view of reports of accidents from the use of some rodenticides, the Committee urged WHO and FAO to draw the attention of member governments to the fact that some rodenticides in current use were unacceptably hazardous and the use of safer substitutes should be encouraged. In this connexion, the Committee reviewed a number of "acute" rodenticides with respect to their toxicological hazard. At the same time, the Committee emphasized the safety of the anticoagulant rodenticides and urged that they be used when required in areas where rodents are not resistant to them.

The rodenticides described below are arranged in groups based mainly on hazard but in part on effectiveness:

1. "ACUTE" RODENTICIDES REQUIRING ORDINARY CARE

    Red squill

Red squill is not readily accepted by animals other than rodents. It will cause vomiting in many animals but, since rodents cannot vomit and thus eliminate the material, it can be effective against them. However, cases have been reported of poisoning of cattle, sheep, chickens and dogs. Red squill is extremely irritating to the skin, and it should be prepared using rubber gloves. There is no necessity for any other special precautions in regard to possible hazards to man. The Committee endorsed its use from the standpoint of safety.

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1 Barium carbonate is of such low efficacy against rodents that its public health hazards need not be considered.
Norbornide

*Chemical name:* 5-(α-hydroxy-α-2-pyridylbenzyl)-7-(α-2-pyridylbenzylidene)-5-norbornene-2,3-dicarboximide

Norbornide is characterized by a fairly high efficacy against rats and by extremely low toxicity to other mammals, e.g., the toxicity to rabbits (LD50) is around 1000 mg/kg and long-term toxicity studies in dogs produced no harmful effects at a dietary level of 1%. The Committee concluded that it was one of the safest rodenticides and endorsed its use.

Zinc phosphide

Zinc phosphide is a widely used and generally effective compound whose toxic hazards are far less than those of thallium. When moist, the chemical slowly releases phosphine gas, giving off a garlic-like odour which is repellant to man and domestic animals but which does not seem to reduce acceptance of the compound by rats and is even thought by some to be attractive to them. While highly toxic to domestic fowl, the safety record of this compound has been good. The Committee therefore endorsed its use.

2. “ACUTE” RODENTICIDES REQUIRING MAXIMAL PRECAUTIONS

Sodium fluoroacetate and fluoroacetamide

Sodium fluoroacetate and fluoroacetamide are extremely hazardous to all mammals and are nowhere recommended for general use; in virtually all countries only pest control operators are permitted to use them. In public health programmes, use of these compounds must be restricted to those areas, such as locked warehouses and sewers, to which access by unauthorized persons and useful animals can be prevented completely. The Committee recommended, however, that these compounds continue to be used, but only by trained pest control operators and under the conditions specified.

Strychnine

Strychnine is the principal alkaloid present in *Nux vomica*. Strychnine is still widely used as a vertebrate pesticide, mainly for the control of jack rabbits, coyotes, wolves, and even some pest birds. It is only moderately effective in rodent control but may be quite hazardous to human beings and domestic animals if poison bait is consumed unintentionally or, in the case of animals, through secondary poisoning. The Committee agreed that use of strychnine should be limited in exactly the same way as the use of sodium fluoroacetate and fluoroacetamide.
3. "ACUTE" RODENTICIDES TOO DANGEROUS FOR USE

Arsenic trioxide

Arsenic trioxide has been used for many centuries, although in recent years many countries have imposed restrictions on the sale of arsenical compounds. The rodenticide is very effective against rodents but is also dangerous to man, other mammals, and birds. For this reason the Committee did not recommend its use.

Phosphorus

White phosphorus is sold in many countries in a 1–2% paste formulation for use as a cockroach poison and a rodenticide. The pure chemical cannot be mixed with baits because of the fire hazard but must be mixed with materials containing liquids, such as molasses, water, or fat. Phosphorus used as a pesticide has led to poisonings, especially among children who have consumed the formulation. A dose of 15 mg may be severely toxic and one of 50 mg may be fatal. For these reasons and because there are more effective rodenticides, the Committee recommended that phosphorus should not be used.

Thallium sulfate

Thallium sulfate is highly toxic to all species of rodents. Its action is slow and, in the case of the Norway rat, death may not occur until 1½–6 days after consumption. It has proved highly effective for the control of animals such as jackals and pest birds. Unfortunately it is one of the most hazardous compounds to non-target species, including man. Useful animals may be killed if they eat other animals intentionally poisoned by thallium. The compound does not have an unpleasant taste or odour nor is it irritating to the skin. It is, however, readily absorbed through both the skin and gastrointestinal tract, and elimination occurs only very slowly. For these reasons the Committee recommended that thallium sulfate should not be used as a rodenticide.

1-Naphthylthiourea (ANTU)

A possible hazard to man arising from the use of ANTU is the induction of bladder tumours due to the presence of approximately 2% of 2-naphthylamine as an impurity. For this reason, the Committee recommended against its use.
Gophicide

*Chemical name: O,O-bis(p-chlorophenyl) acetimidoylphosphoramidothioate*

Gophicide is a recently developed organic phosphate rodenticide of high toxicity to rats and other mammals. It may be hazardous because of its ready absorption through the skin. Since its action is relatively slow, atropine can be used as an antidote in cases of accidental poisoning. However, recent toxicological studies have shown that this compound exhibits a delayed neurotoxic effect in hens, and for this reason the Committee recommended that it should not be used.
PART IV. HEALTH ASPECTS OF PESTICIDES NOT DIRECTLY ASSOCIATED WITH VECTOR CONTROL

The Committee recognized the important role that pesticides play in food production and agricultural economics, and it is clear that pesticides must continue to be used for these purposes. Some compounds, however, present serious toxic hazards in their transportation, storage, and use. It is therefore important that these hazards should be clearly defined so that effective preventive measures can be devised.

The Committee approved the programme that has been developed by WHO for this purpose and noted that close collaboration is being maintained with FAO and ILO.

During the meeting, a number of toxicological problems were mentioned that are important in agricultural practice but could not be discussed in depth for lack of time. The possibility has therefore to be envisaged that it may be necessary at some time in the future for WHO and FAO to convene a joint meeting to consider the toxicological problems that arise in agriculture.

1. ASSESSMENT OF MORBIDITY AND MORTALITY

The Committee considered the global incidence of accidental (as opposed to intentional) poisoning due to pesticides. While it is apparent that pesticides are responsible for only a small part of the whole problem of accidental poisoning due to chemicals, from the information available at present, it seems possible that the number of cases of accidental poisoning due to pesticides may be of the order of half a million a year.

The mortality rate is low (about 1%) in those countries where medical treatment and antidotes are readily available, but it may be higher in other countries. The Committee considered that an attempt should be made to obtain better data on accidental intoxication, and that the data obtained should be related to whether the poisoning was occupational or non-occupational, and to the quantity and types of compound involved. FAO might be able to provide figures on the use of pesticides. Such information would greatly assist any future meeting of experts to judge the lines along which preventive measures might be directed. Although there are undoubtedly difficulties in any system of notification, the Committee recommends
that each country should attempt to obtain accurate information on the occurrence of cases of poisoning by chemicals of all kinds. Information might be sought from appropriate governmental authorities such as those responsible for health and agriculture. The Committee recommends that WHO invite member states to submit annual reports of the data collected.

2. DATA SHEETS

In its sixteenth report, the Committee recommended that data sheets should be issued on insecticides used in public health programmes. The Committee was informed that, following discussions with FAO, it was now suggested that data sheets should be issued in conjunction with that organization. These sheets would be primarily designed to be of assistance to developing countries and in addition to general information and notes on use, would contain recommendations on control for regulatory authorities, the precautions to be taken in use, and medical treatment for cases of poisoning. The sheets would be reviewed by members of the WHO Expert Advisory Panel on Insecticides and by recognized authorities on individual compounds before issue and the industry would also have an opportunity to comment.

The Committee endorses the present extension of the earlier concept and recommends that WHO and FAO issue such sheets for the information of national authorities as soon as practicable.

3. CLASSIFICATION OF PESTICIDES

The Committee noted that a number of classifications of pesticides, based on their toxicity, are at present being used by national administrations and organizations regulating transport in international trade. WHO has received several requests from member countries and United Nations bodies for assistance in classification and the Committee advocated that one of the objectives of such a classification should be to distinguish between the more and the less hazardous forms of each pesticide. Furthermore, the Committee considered that the classification should be in such a form that it would apply not only to pesticides but also to other chemicals, that it should permit formulations to be classified according to the percentage of the active ingredient, and that the physical state of the formulation should be taken into account.

Although the oral LD₅₀ for the rat is not entirely reliable as a measure of toxicity, particularly where a wide species variation has been demonstrated

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in toxicity tests, its determination is a standard procedure in toxicology and, provided adequate allowance is made for dermal hazard where this exceeds the oral hazard, the Committee agreed that it could be used as a starting point for such a classification. In assessing the level of hazard, 3 or more stages should be used, based on a logarithmic progression. It is not possible to devise simple criteria that may be easily applied to every chemical or pesticide. Therefore, provision should be made for the classification of a compound to be modified if (a) it has an unusual or severe toxicological effect, (b) its effects are irreversible, (c) its inhalation hazard exceeds that of the oral or dermal hazard, or (d) it is known to be substantially more dangerous to people than animal tests would indicate.

On this basis, the Committee supports the development by WHO of a classification of pesticides according to the hazard they present. It recommends that any new classification should differ as little as possible from those now in use and then only for clearly justified cause. To this end the Committee recommends that (a) present classifications should be studied with regard to the extent of use, the length of time they have been in use, and their specific advantages and disadvantages; (b) selected classifications be tested to see how each would influence the regulation of specific formulations that historically have produced injury, including burns, trauma, or intoxication of workmen or third parties.

The Committee hopes that agreement on a tentative classification will be reached and that this tentative classification will be submitted to relevant national and international agencies for comment.

4. PROMOTION OF MEDICAL AND OTHER SERVICES TO DEAL WITH POISONING

The provision of medical and technical facilities for the treatment of pesticide intoxication should normally be integrated with existing arrangements for health care and public health. However, when large operations are mounted involving the considerable use of pesticides, it may be necessary for specific arrangements to be made for the surveillance and care of workers, and for the treatment of cases of poisoning. Although such arrangements may be set up by the body responsible for the operation, the health authority should always be closely involved.

The Committee considered that the following steps might be taken by developing countries for the promotion of medical and other services to deal with poisoning:

(1) It is important that governments set up a pesticide registration scheme to control the entry of pesticides into the country and their distribution. Such a scheme permits the supervision of labelling, a most
important contribution to safety. It also provides an indication of what medical and preventive measures are needed for further protection.

(2) Information on the effects and treatment of poisoning should be regularly included in the normal medical curriculum, and especially in specialized studies for physicians who supervise agricultural workers.

(3) Field methods for the diagnosis of pesticide poisoning, where these exist, should be made available to hospitals and medical practitioners in agricultural communities.

(4) Means of sampling and of transporting samples for analysis in a well equipped, regional laboratory should be investigated and promoted. Where a suitable laboratory does not exist in a country, arrangements should be made for analyses to be carried out on a regional basis, and the Committee recommends that WHO should continue to encourage the establishment of such regional arrangements.

Emergency aid teams in rural areas should, in addition to their standard training, be provided with some instruction in the treatment of early symptoms of pesticide poisoning and the resuscitative measures to be applied.

All people having to use or to be in contact with pesticides should be given appropriate instruction in the hazards and in the safety precautions to be observed, as well as in the treatment of the early symptoms of poisoning. Such instruction should be included in health education programmes, both for pesticide users and for the general population, and might be provided through existing social organizations.

The occurrence of acute cases of intoxication provides an opportunity for reminding appropriate authorities of the need for preventive measures such as safe working methods, protection of the worker, the use of safer products, and the minimal and realistic use of hazardous chemicals.

The Committee recommends that, where possible, specialized pesticide application teams should be formed. This facilitates adequate technical and health education, and increases the chance of preventing intoxication through the use of more adequate equipment by better informed operators.

The Committee was informed that ILO, in collaboration with WHO and FAO, is preparing a Code of Practice for the Safe Use of Pesticides. This will complement other publications being prepared by ILO on occupational health and safety in agricultural work.

The Committee emphasized that the continuing control of pesticides from a safety point of view should always be on a multidisciplinary basis. When a country requests assistance in establishing control procedures, it is suggested that a team of consultants specialized in toxicology, epidemiology, and chemistry be sent to that country.
5. PROVISION OF EMERGENCY AID IN OUTBREAKS OF POISONING

Of various major outbreaks of poisoning that have occurred during the last 20 years several were finally shown to be due to pesticides. Some were caused by accidental contamination of food during transportation or storage, while others were due to the consumption of treated seed grain. The Committee took the view that, although important progress in regulating the safe shipment of chemicals has been made recently by some national and international agencies concerned with transportation of dangerous goods, new outbreaks caused by pesticides or other chemicals may nevertheless occur.

The investigation of poisoning outbreaks is a multidisciplinary procedure and requires initially the services of (a) a toxicologist to assist local practitioners in the diagnosis and treatment of cases; (b) an epidemiologist to study the distribution of cases in order to identify as rapidly as possible the source of the outbreak, and (c) a chemist to identify and, if possible, quantify any pesticide or other chemical in samples taken from the patient himself or his immediate environment. It was noted that for many years WHO has had an effective plan to deal with outbreaks of epidemic disease and other emergencies. Aid has been given by the Organization in connexion with a wide range of acute problems, including poisoning by pesticides and other chemicals. The Committee noted with approval that WHO proposes to expand the list of suitably qualified and experienced experts in the three disciplines mentioned above.

It should be remembered that, while the first objective in any emergency aid operation is to treat the patients and to identify and eliminate the cause of the outbreak, much valuable information on the illness and its cause can be obtained. The Committee recommends that, whenever an outbreak of poisoning does occur, WHO should promote research in cooperation with the authorities of the country concerned and with the WHO collaborating laboratories.

6. EDUCATION AND TRAINING IN PESTICIDE TOXICOLOGY

In many countries there is a considerable shortage of physicians and scientists competent in pesticide toxicology. The Committee considered it necessary, however, that every country should have a small cadre of experts trained in the disciplines concerned. Although a general discussion of this subject was beyond the scope of the Committee, it recommended that WHO should promote training in the field of pesticide toxicology and that WHO and FAO should organize joint seminars on the safe and effective use of pesticides in public health and agriculture.
7. USE OF PROTECTIVE CLOTHING WITH PARTICULAR
REFERENCE TO TROPICAL AREAS

Instruction in the use of protective clothing should be included in any
comprehensive programme of prevention, but the Committee emphasized
that protective clothing is a passive protection and should always be regarded
as a second line of defence. Emphasis should be placed first on safe working
methods and, where possible, on the use of compounds of low toxicity.

Protection from absorption of pesticides consists in avoiding inhalation,
ingestion, and contamination of the skin. For some pesticides skin absorp-
tion has been demonstrated to be a more important route of entry than
inhalation, 8 times as much pesticide being absorbed through the skin,
and in the tropics skin absorption may be influenced by sweating, increased
cutaneous blood flow, and inadequate protective clothing. Although indi-
vidual farmers and cultivators as a group apply the largest total quantity
of pesticides, the most important population group to be considered com-
prises those persons subject to a relatively heavy and prolonged occupa-
tional exposure when working as sprayers either in agriculture or in public
health programmes. In this vulnerable group, the safe handling of toxic
chemicals is a major problem.

The Committee was informed that ISO is considering standards for
materials giving protection against noxious substances, including pesticides,
and noted its work on the preparation of standards for air-permeable
protective clothing, which will afford partial protection.

It recognized that protection may be needed both against the active
ingredients and against the solvents. If it proves impossible to insist that
solvents be specified on the label, pesticide registration schemes should
restrict formulations to include only permitted solvents.

Protective clothing for use with toxic chemicals may not always be
available in the developing countries, mainly because of cost. It was there-
fore desirable that the protection offered by the cotton materials available
in the developing countries be further examined. The Committee recom-
mended that where possible government or privately trained demonstration
spraying teams be formed in communities in which there was heavy and
prolonged use of pesticides. Such teams would provide a service on request
to farmers and would organize demonstrations using recommended appli-
cances, correct techniques, and approved protective clothing. They might
also give advice and provide supervisory service to private farmers during
spraying operations.

The Committee recommended that WHO should maintain close coopera-
tion with member governments and extend all possible aid to them in
connexion with programmes of protection, including development of ade-
quate protective clothing. WHO should keep in touch with ISO regarding standards for protective clothing.

It should, however, be emphasized that very substantial protection against pesticide sprays is afforded by ordinary clothing and headdress. A set of working clothes that is changed at the end of the working day and is washed sufficiently frequently to prevent it from becoming grossly soiled with spray deposit will effectively reduce exposure during almost all pesticide applications.
PART V. PROGRESS IN DIAGNOSIS AND TREATMENT

1. METHODS FOR DETERMINING THE EXTENT OF EXPOSURE TO ORGANOPHOSPHORUS AND CARBAMATE INSECTICIDES

A number of field methods available for measuring cholinesterase activity were reviewed in the sixteenth report of the WHO Expert Committee on Insecticides\(^1\) and at the International Conference on Alternative Insecticides for Vector Control.\(^2\) Few developments have occurred since then.

The Committee recognized that although several methods of field measurement are available, none of these is entirely satisfactory and there is still a need for alternative and more satisfactory methods of determination for both types of cholinesterase (i.e., erythrocyte cholinesterase and plasma cholinesterase).

A proposal was made for the development of a multipurpose field kit that would permit the determination of exposure to anticholinesterase compounds and other pesticides. As a first step, a method based on the Ellman spectrophotometric method for cholinesterase determination is being considered. This may include a robust, battery-operated instrument, preweighed reagents, and disposable reaction vessels.

The Committee recommended that WHO promote research on the development and testing of such a field kit.

2. STANDARDIZATION OF METHODS FOR DETERMINING ABSORPTION OF ORGANOCHLORINE PESTICIDES

From the data on DDT referred to in Part I, sections 1.2 and 1.3 (pages 9 and 11) and from other data not considered in detail by the Committee, it is evident that a considerable amount of information is available on the concentrations of organochlorine insecticides in the tissues of people in a number of countries. Much less is known about the concentrations of these insecticides in solid tissues other than fat. However, the concentration of these compounds in the blood is of value in assessing the

intensity of occupational exposure to them and as an aid in the diagnosis of suspected intoxication. Since samples of blood are easier to obtain from living subjects than samples of fat, it is desirable to know the concentrations of these compounds in the blood of the general population (i.e., those not occupationally exposed) and the relationship between the concentrations of these compounds in blood and in adipose tissue.

A detailed review of recent developments in the analytical methods for the organochlorine insecticides is not considered necessary here, but there are certain aspects of these methods that warrant discussion. The analytical procedures used in the majority of the recent surveys of the concentrations of organochlorine insecticides in human tissues involve the following steps: extraction, clean-up, gas-liquid chromatography, and quantitative detection.

Few outstanding developments in clean-up procedures have been made recently. As the commonly used electron capture detector is not specific for organochlorine compounds, the validity of the concentrations reported is dependent upon the efficiency of separation of the gas-liquid chromatographic step in the analysis. Increasing appreciation of the deficiencies of gas chromatographic systems and the detection systems used in the last few years has prompted the investigation of various qualitative and quantitative confirmatory techniques. The best of these is the combination of gas chromatography with mass spectrometry, whereby positive identification of compounds can be achieved and quantification at extremely low levels is possible.

The Committee advocated increasing use of these new techniques and suggested that interlaboratory comparisons of blood sample determinations be undertaken.

3. THERAPY OF INSECTICIDAL POISONING

The therapy of poisoning by cholinesterase inhibitors was considered in detail in the sixteenth report of this Committee, and a summary of treatment was added as an annex to that report. The Committee was informed that this annex had been circulated widely to medical practitioners in some countries. There have since been no major advances in the therapy of poisoning, and the considerable experience gained has confirmed the recommendations made in the sixteenth report.

The Committee therefore recommended that the summary be reprinted as an annex to the present report. Minor changes have been made in the light of experience and a section has been added dealing with the therapy of organochlorine poisoning to make the summary more comprehensive.

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Annex

SUMMARY OF TREATMENT OF POISONING WITH INSECTICIDES (CARBAMATES, ORGANOPHOSPHORUS, AND ORGANOCHLORINE COMPOUNDS)

As with all other types of intoxication, treatment is based on measures of the following two kinds:

1. removal of non-absorbed material;
2. specific antidotes and symptomatic treatment, such as artificial ventilation.

These procedures must be instituted rapidly in order to prevent a fatal outcome. As a rule, neither type of treatment is sufficiently effective if used alone.

In intoxication by mouth, rapid gastric lavage is imperative. For removal of secretions and maintenance of a patent airway, place the patient in a prone position with head down and to one side, the mandible elevated and the tongue pulled forward. Clear the mouth and pharynx with finger or suction. Use an oropharyngeal or nasopharyngeal airway or endotracheal intubation if airway obstruction persists. If the body is soiled with the insecticide or if vomiting or hypersalivation has occurred, clothes must be removed and the skin washed with soap and water for at least 10 minutes. Contamination of the eyes is treated by washing of the conjunctiva.

Depots of compounds such as organophosphorus insecticides may be present in the skin or in the gut, from which a continued absorption may occur for days. The condition of exposed persons who have become free of symptoms may deteriorate when new toxic material reaches the circulation.

If a number of patients are found to be exhibiting symptoms of poisoning by an insecticide (or other chemical) without a history of exposure the possibility of the cause being gross contamination of an item of a food or of drinking water should be borne in mind.

Intoxication with carbamates

Since symptoms of intoxication with carbamates disappear comparatively rapidly, atropine treatment is often not necessary by the time the patient reaches the place where the antidote is at hand. In case of accidental poisoning or manifest symptoms, 1–2 mg of atropine sulfate (adult dose)
may be given intramuscularly or even intravenously and the dose repeated as necessary. Care should be taken to avoid overdosage in cases of carbamate poisoning, especially in children. Oximes should not be given in cases of poisoning with carbamates.

**Intoxication with organophosphorus compounds**

On signs of systemic absorption, both atropine and reactivators must be given parenterally.

Persons without signs of respiratory insufficiency but with manifest peripheral symptoms should be treated with 2–4 mg of atropine sulfate and 1–2 g of a soluble salt of pralidoxime or 250 mg of obidoxime chloride (adult doses) by slow intravenous injection. More atropine (with or without the reactivator) may be given depending upon the severity of the intoxication and the response to the first dose. After the administration of oximes, less atropine may be required.

Severely intoxicated, unconscious persons with respiratory difficulties and convulsions should be given atropine and a reactivator as above. In addition to this, the airways must be kept free and artificial ventilation applied if required. Mouth-to-mouth respiration is to be avoided when it is suspected that the patient has been intoxicated by mouth since vomited material may contain dangerous amounts of toxic substances. Atropine should not be given to a cyanotic patient until the cyanosis has been overcome, since this may lead to ventricular fibrillation.

In these cases of severe intoxication, 4–6 mg of atropine sulfate should be given initially, followed by repeated doses of 2 mg or as much as required to maintain full atropinization. The patient's condition, including respiration, convulsions, blood pressure, pulse frequency, and salivation should be carefully observed as a guide to further administration of atropine. Initially atropine may have to be given at 5- or 10-minute intervals. Cases are described in the literature in which several hundred mg have been given during the first 24 hours. Usually, however, it is not necessary to exceed 50 mg. Every 2-mg dose gives a short-lasting improvement of respiration and reduction in cyanosis and convulsions. Tachycardia may occur and a watch must be kept on salivary secretion in order to prevent over-atropinization. The pulse rate should not be allowed to exceed 120/min. There may also be a short-lasting improvement in miosis.

If possible, blood samples should be taken for cholinesterase determinations before and during the treatment. In parathion poisoning, reactivation of the enzyme activity of the red blood cells may be observed within one hour, but if the patient comes late to the treatment (after 36 hours) oxime therapy may be less effective.

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1. Automatic injectors loaded with a combination of atropine sulfate and obidoxime chloride are available. For pharmaceutical reasons, the combination of atropine and a pralidoxime salt is impractical.
Because most intoxications occur after exposure of the skin or after ingestion, any deterioration in the patient’s condition due to delayed absorption into the circulation must be carefully watched for. Reactivators are excreted fairly rapidly if kidney function is normal (in the case of pralidoxime 80% in 2–3 hours) and repeated doses of 1 g may be needed.

The intravenous injection of oximes should be made slowly, especially in small children.

**Intoxication with organochlorine compounds**

The organochlorine compounds most commonly causing poisoning are endrin, aldrin and dieldrin.

Treatment is aimed at controlling the symptoms, especially hyper-reactivity and in some instances convulsions. Artificial ventilation may be required. Anticonvulsant treatment with soluble barbiturates, diazepam, or paraldehyde should be given in sufficient dosage to calm the patient and prevent convulsions.

Blood analysis for organochlorine levels may be used to confirm the cause of poisoning, but this is at present a lengthy and highly specialized procedure. Treatment should never be deferred pending the result of a laboratory test.