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Safe use of pesticides

Third Report of the WHO Expert Committee
on Vector Biology and Control

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Geneva, 3-9 October 1978

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SAFE USE OF PESTICIDES

Third Report of the WHO Expert Committee on Vector Biology and Control

The WHO Expert Committee on Vector Biology and Control met in Geneva from 3 to 9 October 1978 to study recent developments in the toxicology of pesticides used for vector control, to advise on their safe use, and to consider other aspects of the safe use of pesticides both in public health and in agriculture. The meeting was opened on behalf of the Director-General by Dr T. Lipes, Director, Division of Malaria and Other Parasitic Diseases.

1. INTRODUCTION

Although progress has been made in genetic and other means of controlling disease vectors and agricultural pests, the use of chemical pesticides remains indispensable at present.

There has in fact been a very rapid increase in the use of pesticides in most developing countries, so that in many instances the safety services find themselves overwhelmed. Laws governing the importation, registration, and handling of pesticides may be lacking, and, even where they exist, many governments lack the technical and administrative capacity to implement them. Communications between officials in health ministries and officials in agricultural ministries are often inadequate. Those who actually apply pesticides in the field may have little notion of the dangers of the product they are handling, and there is an urgent need to ensure that information on safety reaches individual farmers and others who use pesticides. The large number of cases of poisoning reported from certain countries indicates clearly that the technology of pesticides has outstripped the social and legislative development needed for their proper control.

Antimalaria programmes are the main consumers of insecticides in public health. The development of vector resistance to certain common insecticides has been one of the causes of a resurgence of malaria in many countries, and WHO makes every possible effort to ensure that Member States can obtain alternative insecticides that are both effective and safe. High mammalian toxicity can render an otherwise cheap and effective compound unacceptable for indoor application. In saving lives

by controlling a vector-borne disease with insecticide, the health of the spraymen and occupants of sprayed houses must not be jeopardized.

Even a pesticide with a previously good safety record can cause poisoning among spraymen if the available formulation is of poor quality. About 2500 cases of such poisoning occurred in Pakistan in 1976 among malaria spraymen using malathion, and five of them proved fatal. In 1977 the Expert Committee established new specifications for malathion and its formulated products (1), the use of which should prevent further incidents of this kind. Moreover, poisoning by other pesticides might be forestalled by studying them closely in the light of the Pakistan incident to determine any possible impurities that could constitute a danger. A number of new experimental results and field observations on pesticides (including those in course of development) are now available and may be used in the evaluation of safety.

The Expert Committee strongly supported WHO's close collaboration with ILO, FAO, and UNEP with regard to the safe handling of pesticides, and it also emphasized the importance of cooperation between these agencies in providing education and training and in carrying out field surveys in developing countries.

2. NEEDS OF DEVELOPING COUNTRIES REGARDING SAFE USE OF PESTICIDES

The Committee recognized the need for an increasing use of pesticides for the control of vector-borne disease and for the expansion of food production. This increase may raise environmental and safety problems, and the benefit-risk evaluation of the use of a pesticide will vary from country to country.

Although considerable amounts of pesticides are at present being imported from industrialized countries, it is to be expected that more developing countries will in future prepare their own formulations and even manufacture their own pesticides. It will then be the responsibility of those governments to ensure good manufacturing practice and quality control and to ensure at the same time proper use of the product. To meet this responsibility, the authorities must have chemical, analytical, and toxicological facilities and the ability to monitor exposure to pesticides. Collaboration can be established with developed countries, but in the long run it will be essential for countries to achieve self-sufficiency. Coordination is needed between the government departments dealing with health, agriculture, and occupational hygiene so that all aspects related to pesticides used in public health and agriculture can be nationally covered in a single set of requirements.

The first priority is the establishment of an interdepartmental control agency for the registration of all pesticides, the evaluation of the need for them in particular areas, and the control of their use. It should also act as an advisory body for all concerned with the use of pesticides. As the agency develops, it should be able to carry out periodic re-evaluation of existing compounds in the light of new knowledge and practical experience in the field.

Legislation will be required to define the powers and responsibilities of the agency. Once in being, the agency will have to develop its own technical services for safety evaluation and pesticide analysis and establish close cooperation with local universities in order to make use of the available expertise in chemistry, pharmacology, biochemistry, pathology, toxicology, and hygiene.

The wider use of pesticides for crop protection, even in the remotest rural areas, has resulted in increased hazards for the local population and more poisoning cases. There is a real need for the development of preventive measures and diagnostic tests and for treatment facilities. Training in the diagnosis, treatment, and prevention of pesticide poisoning should be provided for physicians at both undergraduate and post-graduate levels.

It is generally accepted that little technical information reaches the farmer and even less is utilized. This situation could be improved by the use of extension workers to undertake the training of farmers in the choice of pesticides, storage, application techniques, the use of protective measures, and the safe disposal of containers. Information on advances in the treatment of victims of pesticide poisoning should reach health authorities and hospitals in areas where pesticides are extensively used.

The Committee emphasized that there is no substitute for local education and training in the safe and effective use of pesticides, and it urged governments to give this matter high priority.

The international agencies should support such activities by providing consultants and by continuing to publish information on pesticides. The FAO/WHO data sheets on pesticides and other information circulars on the safe use of pesticides have been found to be of great use to developing countries. Their distribution should be widened. A useful publication on this subject has recently been issued by ILO (2).

The extraction of information from these publications and its incorporation into material suitable for rural communities is a responsibility of the national authorities. Important though this work is, it should not be regarded as a substitute for personal contact between extension workers and users.

3. FACTORS INFLUENCING THE TOXICITY OF PESTICIDES

3.1 General

The most important single factor influencing the hazard from pesticides is dosage. There is no compound so safe that it cannot be dangerous and even fatal if sufficiently misused. Indeed, highly toxic compounds are excluded from use in vector control precisely because of the impracticability of reducing human exposure to them. Almost all safety measures are aimed at reducing the dosage absorbed by the operators or by those who might inadvertently come into contact with the toxic material. Dosage, whether due to single or repeated exposure, is the basic toxicological factor involved in all occupational and accidental exposure. Such exposure may result not only from actual use of the pesticide but from poor storage, bad labelling, failure to recognize that the material is a poison, and use of pesticide containers for food and drink. Illiteracy and low educational standards may also be important factors contributing to overexposure.

The next most important factor is the form in which the compound is used, because the materials used in formulations may contribute to its toxicity. Other factors to be considered include the occurrence of unexpected impurities (see section 3.2) and the effect of one pesticide on the toxicity of another.

The route of exposure is also important. Almost everyone understands that the ingestion of pesticides is dangerous, and workers are generally aware of the danger of inhalation. However, most members of the public and even some workers are unaware that dangerous amounts of pesticides may be absorbed through the skin.

The danger increases with temperature. In hot weather absorption through the skin is more rapid, volatilization of the pesticide is also more rapid, and the equilibrium concentration of a given compound in the air is higher. Therefore, both skin and respiratory exposure may be increased.

Animal studies show that toxicity may vary from one individual to another and that it may differ with strain, sex, and age. In man, however, these factors seldom cause marked differences in susceptibility to a poison. The greater susceptibility of children to parathion is one of the exceptions to this rule. In most instances, apparent differences in hazard associated with race, sex, and age are really due to differences in exposure (and therefore dosage) and not to differences in susceptibility. So far, there has been no example of human pesticide poisoning resulting from

a genetic abnormality. People with abnormal plasma cholinesterase (an inherited defect) are not unusually susceptible to organophosphorus or carbamate insecticides, although, as is well known, they are unusually susceptible to suxamethonium chloride.

Animal experiments have revealed other factors that may influence toxicity. They include nutrition, endocrinological status and other physiological factors, disease, relative humidity, pressure and altitude, light, ionizing radiation, and circadian rhythm. The importance of these factors is almost always overshadowed by dosage, but health authorities should be alert for their possible effects in man.

When considering the various factors that contribute to toxicity, their relative importance should always be borne in mind. Every effort should be made to use pesticides of lower toxicity, but it is clear that the most important way of reducing the danger of both occupational and accidental poisoning is limitation of exposure.

3.2 Impurities in pesticides

Although it has been known for over 25 years that small amounts of impurities in organophosphorus compounds can exert a profound influence on their biological activity, there have been few examples of illness in man resulting from the spraying of impure pesticides. The poisoning incident in Pakistan (1, 3) has brought into focus the hazards associated with impurities that can increase the toxicity of a pesticide formulation. The phenomenon of potentiation of the toxicity of malathion by inhibition of carboxylesterase was demonstrated in experimental animals as early as 1957, but the episode in Pakistan was the first example of its occurrence in man.

An investigation carried out by WHO and collaborating laboratories showed that the major toxic component was isomalathion. At its last meeting the Expert Committee considered the results of these studies and established new specifications for malathion and its formulated products (1). They specify the use of a gas-liquid chromatographic method for analysing the malathion content and impose strict limits on the amount of isomalathion that may be formed in malathion water-dispersible powder after an accelerated storage test.

The present Committee reviewed the subject of contaminants in pesticide formulations, including cases where toxic impurities had caused injury to men and animals. Impurities are sometimes introduced during manufacture or formed during storage as a result of interaction of the active ingredient with "inert" carriers or diluents. In other cases

toxic products are formed as a result of improper handling of the formulations. The Committee noted that the patents covering malathion had now expired and that the patents covering many other pesticides used in public health were due to expire in the near future. It was therefore to be expected that these pesticides would before long be produced by companies less experienced in their manufacture. In these circumstances, more products containing toxic impurities may reach the market. For malathion this can now be avoided if purchasing agencies insist on its conforming with the WHO specification (1). Vigilance is required for other pesticides because there is no assurance that adequate quality will be achieved in manufacture or that other unexpected reactions between a pesticide and its "inert" diluents will not occur in the future.

The elucidation of the malathion poisoning in Pakistan demonstrated the ability of WHO and its collaborating laboratories, with the cooperation of the chemical industry, to solve a problem of this nature. Research into the causes of the incident showed that even good commercial malathion is 4-5 times more toxic than highly purified malathion and that other impurities are present besides isomalathion. The research has thus revealed the potentialities for improvement, which may also apply to other pesticides.

If a pesticide is to be acceptable for vector control it should satisfy the following toxicological criteria.

(1) The concentration of pesticide required for insect control should not be hazardous to the operators. To allow for variation in the performance of spray operators and for difficult field conditions, a relatively high safety factor is required.

(2) Any effects of absorption of sprayed material during one day's work (e.g., inhibition of acetylcholinesterase) should be toxicologically insignificant at the beginning of the next day's operation.

Many of the currently used organophosphorus insecticides are dimethyl derivatives, which produce an unstable inhibited human acetylcholinesterase (dimethylphosphorylated enzyme) with a half-life of 51 min so that the interval between the end of one day's spraying and the beginning of the next (i.e., about 20 half-lives) should ensure the reactivation of all inhibited enzyme. However, dialkyl phosphorylated and phosphonylated cholinesterases change with time by losing one of the alkyl groups attached to the phosphorus atom (the "aging" phenomenon). The resultant inhibited enzyme cannot be reactivated by normal therapeutic measures. The half-life for this "aging" reaction for dimethylphosphorylated human acetylcholinesterase is 230 min, and it may

thus be predicted that 50% inhibition on one day will yield on the next 41% of the original active enzyme and 9% of the aged enzyme. The rates of analogous reactions for the carboxylesterase involved in the potentiation of toxicity of malathion and other pesticides are not known. The rates for both reactions (reactivation and "aging") for both enzymes (acetylcholinesterase and carboxylesterase) after inhibition by impurities in organophosphorus pesticides are also unknown.

Phosphorothionate pesticides are metabolized by the liver and other tissues to the inhibitory phosphates. The activity of the enzyme systems responsible for these conversions is modified by a variety of lipophilic chemicals, but there is no evidence that impurities or other substances in pesticide formulations will lead to significantly increased toxicity.

Besides isomalathion, commercial malathion also contains trimethyl phosphorothioates, which not only potentiate the toxicity of malathion but also possess unusual toxicological properties themselves. They are unexpectedly toxic to experimental animals, and delayed deaths are seen. Although these substances are not the major cause of increased toxicity of malathion water-dispersible powder, as observed in Pakistan, they are possible contaminants of other phosphorothioates, and their significance should be evaluated.

To minimize the possibility of other poisoning incidents and to gain a better perspective of the potential for improving the safety of pesticides, the Committee made the following recommendations.

(1) Additional research should be conducted on the toxicity of formulated pesticides after subjecting them to accelerated storage or long-term tropical storage conditions.

(2) The toxicity of pure organophosphorus compounds should be determined for comparison with the commercial materials.

(3) Organophosphorus insecticides containing carboxyl ester moieties should be examined for the presence of impurities.

(4) The toxicology and enzymology of isomalathion and trimethyl and triethyl phosphorothioates should be studied in an attempt to develop an enzymic test for undesirable impurities in field samples of malathion and other insecticides. The new spectrophotometric field kit (see section 5.2) may be useful for this purpose.

(5) In view of the demonstration in man of the effect of one chemical on the toxicity of another, WHO should pay particular attention to other possible instances of enhanced toxicity of pesticides due to exposure to chemicals.

4. REVIEW OF NEW DATA ON PESTICIDES FOR PUBLIC HEALTH USE¹

Since the report on the safe use of pesticides produced in 1972 by the WHO Expert Committee on Insecticides (4) there have been few substantial changes in pesticide use in public health except for the emergence of the synthetic pyrethroids as a new class of insecticides and the use of insect growth regulators (insect development inhibitors). There has also been some emphasis on the development of new formulations, which may influence the hazards of handling the compounds. These include encapsulated, granular, and other types of slow-release formulations.

In recent years, industry has been increasingly reluctant to put resources into research on new insecticides and has largely redirected its efforts to herbicides and plant growth regulators. This is reflected in the reduced number of new insecticides available for evaluation and testing. Recent field research on specific compounds is reviewed below.

4.1 Insecticides for residual indoor application

The Committee reviewed the results of field trials organized by WHO since 1972. One carbamate insecticide, two organophosphorus compounds, and two pyrethroids have been tested at the WHO Vector Biology and Control Research Unit I, Kaduna, Nigeria, in Stage V (village scale) or extended Stage V trials. The latter involved several villages and more than one round of spraying. Four organophosphorus insecticides have also been tested at the Semarang Sub-Unit of the WHO Vector Biology and Control Research Unit II, Indonesia. These trials are of interest since they provided information on the safety of insecticides applied to house structures different from those in Nigeria.

Protective clothing and safety precautions for operators and inhabitants were similar in both the Kaduna and the Semarang trials and were essentially the same as those outlined on page 20 of the twentieth report of the Expert Committee on Insecticides (4). All spraymen, squad chiefs, and insecticide baggers were provided with cotton overalls, which were washed after each spraying day. Broad-brimmed hats were provided for spraymen. Canvas ankle-length shoes and cloth masks covering

¹ 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.

nose and mouth, changed twice daily, were used during bagging and spraying. Baggers and mixers also used impermeable gloves and wore a plastic apron. Washing of hands and face after spraying each pump-charge was mandatory. Showers were taken at the end of each day after returning to the field station. In the trials in Indonesia, umbrellas were provided for spraying staff on rainy days to keep their clothes as dry as possible in order to minimize the penetration of pesticide.

Whenever a compound was tested for the first time a medical toxicologist was present during the spraying operation.

4.1.1 *Organophosphorus compounds and carbamates*

Malathion

Two rounds of spraying with malathion 500 g/kg water-dispersible powder formulation, complying with the WHO specification, were carried out in 1977 in the Semarang area of Central Java, Indonesia. They were about 5 months apart and lasted for 4 weeks each. About 1200 kg of insecticide, applied at a target dosage of 2 g/m², were used for each round, with spraying on 5 days a week. The team consisted of 2 squad chiefs, 12 spraymen and 2 reserves. All were examined by a medical officer and were given training in safety precautions.

No complaints attributable to exposure to insecticide were received from operators or from people living in treated houses and no adverse effects on domestic animals were reported. Cholinesterase activity was determined by the tintometric method in all spraying personnel before each spraying round and weekly during the operation. No inhibition of cholinesterase was found during either spraying round.

Although the rounds lasted only 4 weeks each, the results showed that a good-quality malathion formulation can be used safely and without affecting spraymen's cholinesterase, provided adequate precautions are used during the spraying operation. It is most likely that the limitation of exposure (5 days a week and up to 5 hours a day) also played an important role by not allowing the potentially cumulative inhibition of cholinesterase to take place.

Fenitrothion

A large-scale operational trial with fenitrothion 400 g/kg water-dispersible powder started in 1973 in an area near Kisumu, Kenya, bordering Lake Victoria. The spraying operation lasted 2 years and comprised 8 rounds of spraying. Each round lasted for 8 weeks and was

followed by 4 weeks of rest. Nine spraying squads, each consisting of 4 spraymen and a squad chief, sprayed 5 hours a day, 5 days a week. Although labour turnover was common, the nucleus of the spraying personnel remained unchanged for 2 years. Spraymen themselves prepared pump-charges and most of them applied more than 1000 kg of insecticide. Strict rules were applied throughout regarding the method of handling the insecticide, the wearing of protective clothing, and other precautionary measures.

During each round, pre-exposure and weekly determinations of whole blood cholinesterase activity were carried out for all operators by the tintometric method. Out of 35-40 spraymen, two or three had to be withdrawn from spraying during each round because of lowered cholinesterase activity. There was one unexplained case of illness, but there were no complaints attributable to exposure to the insecticide in a total of about 1500 man-days worked.

Because of the unique opportunity presented at the end of the two years' spraying operation, a special study was carried out on all spraying personnel and 44 matching control subjects. Clinical examination of spraying operators and control subjects did not reveal any significant difference between the two groups except in the pulse rate (61 per minute average in exposed men compared with 74 per minute in controls), which was attributed to physiological adaptation to the more intensive physical work performed by the operators compared to control subjects.

The following tests were performed on 31 operators who had been exposed for at least one year and on the same number of control subjects: haematocrit, haemoglobin concentration, erythrocyte number concentration, leukocyte number concentration and number fraction, serum bilirubin, SGPT and SGOT determinations, and measurement of serum alkaline phosphatase, total plasma protein and albumin, and urine protein and sediment including *Schistosoma haematobium* eggs. Statistically significant differences were found in leukocyte number concentration ($5889 \times 10^6/l$ in exposed men, $7026 \times 10^6/l$ in controls; $P < 0.02$), in the proportion of eosinophils (0.10 in exposed men, 0.07 in controls; $P < 0.05$) and in the activity of serum alkaline phosphatase (27 U in exposed men, 40 U in controls; $P < 0.001$).

A village-scale trial of fenitrothion was carried out in the Semarang area of Central Java in 1976, the insecticide being applied as an indoor residual spray at a target dosage of 2 g/m². The operation lasted 4 weeks, during which time 978 houses were sprayed with 1500 kg of 400 g/kg water-dispersible powder formulation. The population protected totalled 4469.

There were no complaints or clinical symptoms of organophosphorus toxicity among the spraymen or the inhabitants of the sprayed area. However, cholinesterase activity, determined by the tintometric method, was reduced in 4 out of 12 spraymen to 40–60% of the pre-exposure values after the third week of spraying.

The observations made during the two trials described above are in agreement with those made in other trial areas, which have already been reviewed by the Expert Committee on Insecticides (4, 5). The Committee stressed again the relatively low margin of safety of fenitrothion for spraymen applying it by conventional methods inside houses, and it also emphasized the need for cholinesterase monitoring, which permits spraymen to be withdrawn from further exposure before the occurrence of symptoms and signs of poisoning.

Chlorphoxim

When this organophosphorus insecticide was reviewed in 1972 the Expert Committee on Insecticides (4) noted that there had been no complaints or clinical or biochemical findings of adverse effects among exposed operators and villagers during a Stage V trial, but it nevertheless recommended that, in view of the reported observation that the toxicity of chlorphoxim water-dispersible powder increases when exposed to sunlight, the stability of the compound during storage and handling should be investigated before the carrying out of extended field trials.

Storage tests were accordingly carried out with chlorphoxim 500 g/kg water-dispersible powder formulations at the research unit in Kaduna, and the results showed that the formulation is reasonably stable. The content of active ingredient dropped from 51.0% to 49.5% after 10 months of storage under tropical conditions.

An extended Stage V trial was carried out during 1975 near Kaduna. Three rounds of spraying with chlorphoxim 500 g/kg water-dispersible powder were carried out at 3-month intervals, each round lasting for 8 working days. All rounds were carried out by the same personnel (5 spraymen and other helpers), who were under close supervision. Plasma and whole-blood cholinesterase activities were determined by the spectrophotometric method in all spraying personnel during all 3 rounds of spraying.

There were no complaints attributable to the insecticide from either the operators or the villagers during the trial period. No toxicologically significant inhibition of whole-blood cholinesterase activity was found, the mean reduction being about 10%. Plasma cholinesterase was found to be slightly more inhibited, and the level in some spraymen on the last day of spraying was approximately 75% of pre-exposure values.

Chlorphoxim 500 g/kg water-dispersible powder formulation was also tested in a Stage V trial in Indonesia in 1978. The spraying operation lasted 3 weeks. The same 16 spraymen were employed as in previous Stage V trials and the same precautionary measures were taken. Cholinesterase activity was determined weekly by the tintometric method in all spraying personnel. No complaints attributable to insecticide exposure were recorded, and no toxicologically significant reduction of cholinesterase was found.

The Committee noted that the results of these two trials are in agreement with previous observations. It recommended that chlorphoxim can be used safely as a residual spray indoors providing that the usual precautionary measures are taken.

Pirimiphos-methyl

This organophosphorus insecticide was evaluated in an extended Stage V trial near Kaduna in 1976. A 250 g/kg water-dispersible powder formulation was applied as a residual spray at a target dosage of 2 g/m² in 3 spraying rounds carried out at 3-month intervals. The same 6 spraymen, 2 baggers, 2 mixers, and 2 helpers were employed in all 3 rounds, and each round lasted 2½ weeks. A medical toxicologist carried out a physical examination of the personnel before spraying and kept them under medical supervision during the first round. Plasma and whole-blood cholinesterase activities were determined by the spectrophotometric method 3 times weekly for all personnel during the first and second rounds of spraying.

There were no complaints of illness attributable to pirimiphos-methyl from either the spray operators or the villagers, and there was no illness among domestic animals. The cholinesterase activity in the spray operators remained in the range of pre-exposure values throughout the first round of spraying. By the end of the second round, plasma cholinesterase activity was reduced to 70% of pre-exposure values in 3 out of 12 spray operators.

Pirimiphos-methyl was also tested in a Stage V trial in Indonesia in 1978. This operation took place 2 days after the spraying of chlorphoxim, and the same spraymen were employed. There were no complaints among the spraymen or villagers. During the total period of spray operations of 7½ weeks (3 weeks using chlorphoxim and 4½ weeks pirimiphos-methyl), none of the 23 spray personnel showed any toxicologically significant inhibition of cholinesterase, as determined by the tintometric method.

On the basis of these results the Committee concluded that pirimiphos-methyl can be used safely as a residual spray in houses, provided adequate precautionary measures are taken.

Landrin

This carbamate insecticide was reviewed in 1972 by the Expert Committee on Insecticides (4) after two Stage V trials had been carried out, one lasting 4 days and the other lasting 2 days. It was noted that while moderate to pronounced inhibition of whole-blood cholinesterase had been observed in some spraymen at the end of the day's work it was considerably less than that observed in the same spraymen after using propoxur. It concluded that Landrin had proved safe enough to warrant extended field trials.

An extended Stage V trial with Landrin was conducted in 1973-74 with 6 rounds of spraying at intervals of 3 months in a group of villages near Kaduna. Spraying operations were carried out by 6-8 spraymen and a team of mixers. About 1050 kg of Landrin 700 g/kg water-dispersible powder were used in the 6 rounds, applied at a target dosage of 2 g/m².

A close watch was kept on spraymen, mixers, and baggers, who wore protective clothing and observed normal safety practices.

Slight burning and irritation of the skin of the arms and face were reported by some of the baggers and spraymen. Only one sprayman developed persistent itching and skin rash and had to be withdrawn from the operation. Two spraymen vomited following slight nausea and giddiness. These symptoms, which normally last for only a short time after exposure to carbamates, disappeared after rest.

The Expert Committee noted that the observations of this extended Stage V trial confirm the earlier conclusion that Landrin can be used safely, provided precautionary measures similar to those used with propoxur are taken.

Conclusions. The field trials of water-dispersible powder formulations of organophosphorus and carbamate insecticides carried out since 1960 allow the following general conclusions to be drawn.

(1) Among organophosphorus compounds, fenitrothion (oral LD₅₀ for rats 500-700 mg active ingredient/kg) is at the limit of acceptable toxicity for conventional indoor application. Its relatively narrow safety margin calls for strict precautionary measures and regular cholinesterase monitoring of exposed people throughout the spraying operation.

(2) Organophosphorus compounds of toxicity similar to or lower than that of malathion (oral LD₅₀ for rats > 1000 mg/kg) are safe enough to be applied operationally without requiring routine cholinesterase monitoring, provided protective clothing is regularly cleaned and a high standard of personal hygiene is maintained.

(3) Among carbamate insecticides, propoxur (oral LD₅₀ for rats 116 mg/kg) is at the limit of acceptable toxicity for conventional indoor application. In view of its relatively narrow safety margin strict adherence to recommended precautionary measures is required. No cholinesterase monitoring is indicated when carbamate insecticides are applied because the inhibited enzyme reactivates rapidly, causing marked symptomless daily fluctuation in cholinesterase activity, thus rendering the monitoring of little practical value. In addition, there is no aging of the inhibited enzyme.

(4) Carbamates of higher toxicity than propoxur may be considered for indoor residual application provided the concentration of the formulation, the spray concentration, and the target dosage are reduced proportionately.

(5) Limitation of exposure to 5 hours daily and 5 days weekly appears to be an additional factor of great importance in preventing any cumulative adverse effects of insecticides that have a narrow margin of safety.

4.1.2 *Pyrethroids*

Pyrethroids developed within the past five years are among the most active insecticides known. Most are related to pyrethrin I, the most potent of the six natural esters, from which their structures have been derived by successive modifications.

Two particular discoveries have stimulated the recent interest in pyrethroids—first, that compounds with structures modified for greater stability in light retain many of the advantages of the natural pyrethrins and earlier pyrethroids; second, that these same compounds are more active than established insecticides and are particularly effective against the larval stages of lepidoptera that attack a wide range of agricultural crops, including cotton. When the efficiency of the more stable pyrethroids was demonstrated they were recognized as sufficiently promising to attract industrial research, despite their chemical complexity.

Sixteen synthetic pyrethroids have so far been tested in the WHO programme. The compounds submitted recently are more stable to light

and less volatile than the compounds submitted previously. The high insecticidal activity of these compounds makes them potentially useful in public health. Their unit cost is high but their cost-effectiveness may be acceptable. This and the effects on non-target organisms will be critical to their acceptance for vector control. Relatively few data on the toxicity of pyrethroids have yet been published, but a number of unpublished reports have been made available to WHO.

Mammalian toxicity. The acute mammalian toxicity of some synthetic pyrethroids approaches that of highly toxic insecticides of other chemical groups. The data have mostly been obtained from experiments on rats and mice. Owing to the poor solubility of pyrethroids in water, various solvents have been used in toxicity testing, and these have sometimes produced markedly different results. For some pyrethroids toxicity has been tested on dogs, guinea-pigs, hamsters, birds, and fish.

Among the limited number of pyrethroids examined (the structures of which are shown in Annex 1) at least two types may be distinguished (6, 7). Class 1 compounds, including allethrin, biopermethrin, cismethrin, permethrin, and resmethrin, produce hyperreactivity. Rats are aggressive to each other and react to a sudden stimulus with uncontrolled bouts of general tremors; the final stages of poisoning consist of convulsive twitching, prostration, and death. It appears likely that these symptoms are peripheral in origin. Class 2 compounds, which include cypermethrin, decamethrin, Sumicidin,² and Sumitomo S-3206,³ produce excessive salivation and irregular jerking of the limbs, progressing to rolling convulsions (choreoathetosis) and occasionally to both tonic and clonic convulsions. Atropine may suppress salivation and reduce the severity of some of the signs of poisoning. The convulsions are almost certainly caused by a disturbance of the central nervous system.

The toxicity in dogs and cats is comparable with that found in rats. Preliminary experiments have not yet elucidated the possibility that toxicity is cumulative. After infusion of decamethrin into the jugular vein of rats at different rates (0.025 to 1.6 times the intravenous LD₅₀ per hour) no increase in the total dose tolerated was found at the slower rates of infusion. In other experiments a dose of 10 mg/kg/day of decamethrin was tolerated for 15 days and the daily symptoms of poisoning did not increase in intensity.

Neurological signs of changes in gait sometimes seen in rats after administration of high doses of a few pyrethroids have received some

² Also known as fenvalerate.

³ Also known as fenpropanate.

attention. When such animals are killed for neuropathological investigations and the nervous tissue carefully perfused with fixative, pyrethroid-dependent changes are seen only in the sciatic nerve. Moreover these changes (minimal demyelination and the occurrence of myelin ovoids) also occur in control rats, and their frequency is only slightly increased after doses of pyrethroids producing signs of poisoning. This aspect of the toxicity of pyrethroids must be kept under review.

Work is proceeding in several laboratories on the mechanism of action of the synthetic pyrethroids both *in vitro* on isolated nerve preparations and *in vivo* on the whole animal. Studies are being pursued on changes in neurotransmitters—in particular large changes in the concentrations of the secondary transmitter cyclic guanosine monophosphate (8)—as well as on the anatomical origin of the signs seen after the administration of different pyrethroids (6).

No definitive molecular basis for the mechanism of action of pyrethroids is available at present, but it is known that after the exposure of isolated nerve preparations to allethrin repetitive activity is seen, resulting from a single nerve impulse evoking a train of end-plate potentials (9). No effective treatment for poisoning can yet be recommended because some anticonvulsants seem to be active in some species but not in others.

Metabolism in experimental animals. The metabolism of synthetic pyrethroids has been studied in the rat with particular emphasis on permethrin and decamethrin, for which compounds the total metabolic pattern has been worked out (10, 11).

Pyrethroids with dihalovinyl substituents are metabolized in animals (and in the plants examined so far) by reactions that involve no modification of the dihalovinyl group. Other portions of the molecule, particularly the ester linkage and alcohol moiety, are more susceptible to attack.

On oral administration to male rats, decamethrin and various metabolites derived from its acid and alcohol moieties are almost completely eliminated from the body within 2–4 days. The acid moiety is excreted as the free acid and its glucuronide and glycine conjugates, and there is virtually no evidence of metabolites arising by hydroxylation of the geminal-methyl groups. Metabolites of the cyano group are eliminated more slowly; elimination from the skin and gastrointestinal tract is particularly slow owing, in the latter case, to temporary retention in the stomach of thiocyanate formed from released cyanide.

Microsomal enzyme systems from mouse and rat liver have been used to examine the effect of the dihalovinyl group on the metabolism of pyrethroids. The *cis*-isomers are not hydrolysed at a significant rate by

esterases, but they are oxidized at nearly the same rates as the corresponding *trans*-isomers. The toxicity of some pyrethroids administered intraperitoneally to mice is increased by inhibitors of esterases and mixed-function oxidases. If such synergists are to be used with dihalovinyl-containing pyrethroids, they must be selected with care and the mixture thoroughly tested to ascertain that it is not hazardous.

Detection and determination of metabolites. In a fully equipped modern analytical laboratory the detection and quantitation of the metabolites of synthetic pyrethroids present no problem. The techniques of gas chromatography and mass spectrometry are fully able to quantitate the metabolites derived from the acid or alcohol moiety of the molecule, sometimes after hydrolysis of conjugates.

In the case of decamethrin the formation of thiocyanate in experimental animals can be measured by means of the colorimeter or gas chromatograph after derivatization, and a dose/response relationship can be obtained. Unfortunately, this colorimetric procedure cannot be used to monitor human exposure to decamethrin because thiocyanate is a normally occurring metabolite in man (higher values being present in smokers than in non-smokers).

Gas phase analysis after hydrolysis of conjugates has been used in one field trial of pyrethroids. Urine samples were taken from operators employed in WHO field trials of permethrin and decamethrin as mosquito imagicides at Kaduna, Nigeria, in 1977 (see section below). The samples were transported frozen for analysis. It was demonstrated that, when spraymen were exposed to the equivalent of 6 kg of permethrin, the excretion of permethrin as the metabolite in the urine amounted to no more than 2 mg/day. This level of excretion was not related to the safety equipment worn by the operators.

Analytical difficulties made it impossible at that time to perform the same evaluation for decamethrin. There is a need for further analytical studies in man comparing decamethrin and permethrin and different routes of administration. So far, these two pyrethroids are the only ones to have reached Stage V trials.

Permethrin

A Stage V trial of permethrin 250 g/kg water-dispersible powder was carried out near Kaduna in 1977. The insecticide was applied as a residual spray indoors at a target dosage of 0.5 g/m². One bagger, 1 mixer, and 3 spraymen were employed in the spraying operation, which lasted only 2 days. The spraying personnel wore daily washed overalls, canvas shoes

or rubber boots, and hats. The mixer wore a cartridge-type respirator and rubber gloves and the bagger was similarly equipped, with an apron in addition. No masks were worn by the spraymen. The spraymen and mixer washed their hands and faces after spraying or mixing every pump-charge. All had a shower at the end of the day's work.

A clinical toxicologist was present during the spraying operation and carried out a physical examination of the spray personnel. Special attention was paid to the nervous system, reflex function, vibration sense, balance, coordination, and the presence of any tremor. The final examination, on the day after the completion of spraying, consisted of a medical history, especially of sleep and appetite, the measurement of pulse and blood pressure, and the same physical examination.

No complaints were received at any time, and no abnormalities were detected.

Decamethrin

Concurrently with the trial of permethrin, a Stage V trial of decamethrin 50 g/kg water-dispersible powder was carried out in another village near Kaduna. Spraying lasted for 2 days. The insecticide was applied at a target dosage of 0.05 g/m². One bagger, 1 mixer, and 3 spraymen were employed. Protective equipment and precautions and medical surveillance were the same as in the permethrin trial.

No complaints were received from the spraying personnel and no effects of exposure were found on clinical examination.

An extended Stage V trial of decamethrin 50 g/kg water-dispersible powder was carried out near Kaduna in 1978. The insecticide was again applied at a target dosage of 0.05 g/m². During the first round of spraying, which lasted about 5 weeks, 9 spraymen, 3 baggers, 2 mixers, and 2 helpers were employed. They wore similar protective clothing to that worn in the previous trial and, in addition, all spraymen and mixers wore disposable face masks.

A clinical toxicologist was present at the trial site from the start of bagging to the half-way point in the first round of spraying. The surveillance consisted of (1) a medical examination similar to that in the permethrin trial before the start of operations and at the end of the surveillance period and (2) the application of exposure pads to 4 spraymen during a typical day's operation. The exposure pads were applied and the results calculated according to a standard protocol (12).

The results of the exposure-pad tests showed that the average exposure of spraymen during a day in which the pump is charged 8 times is

0.013% of the highest dermal non-lethal dose, which was taken as 800 mg/kg—the highest dose tested in rats without any mortality. The maximum value found on any pad was 0.017%. With organophosphorus compounds, symptoms of intoxication are expected to occur if the value exceeds 1%, but the threshold is not known for pyrethroids.

A number of symptoms were described by 6 of the 9 spraymen. These included itching of the face during spraying, "heat around the eyes", "heat in the face", "heat in the face and upper shoulders", "burning in the eyes", and tiredness—all lasting until the evening. All the baggers and one of the 2 mixers described similar symptoms. There was no observable sign of exposure in any of the men. No complaints of any kind were received from villagers.

It was recommended that exposure be limited to less than 7 pump-charges per day and that the operators be required to comply strictly with the hygiene regimen—the washing of hands and face after the spraying of every pump-charge.

Although the insect-repellent property possessed by some pyrethroids may limit their usefulness for indoor spraying for mosquito control, other uses in vector control show promise—for example, the control of tsetse flies and the prevention of reinfestation by *Simulium* adults in the zones of the Onchocerciasis Control Programme in the Volta River Basin Area.

The toxicological information available at present indicates no serious problem, but a careful evaluation of pyrethroids in the field should continue. Two reactions require special attention—the skin and eye irritation seen particularly after exposure to decamethrin and the slight indication of neuropathy after high doses given to animals. More information is required about the mechanism of action of synthetic pyrethroids, particularly in view of their increasing field use. The Committee recommended that during field trials with pyrethroids medical surveillance should be maintained.

4.2 Larvicides

Larvicides are being increasingly used in public health programmes—particularly the Onchocerciasis Control Programme in the Volta River Basin Area. This programme for the control of *Simulium damnosum* and other programmes for the control of *Aedes aegypti* rely primarily on larvicides. The onchocerciasis control programme, operating over an area of 700 000 km², has used only one product—temephos 200 g/l emulsion concentrate—for its operations, which are directed at the larval

stages of the vector. A search for an alternative product is in progress. Some candidate compounds are azamethifos, chlorphoxim, chlorpyrifos-methyl, decamethrin, diflubenzuron, methoprene, permethrin, and pirimiphos-methyl.

Acute and short-term toxicity studies have been conducted on all candidate compounds at present under consideration as larvicides for *Simulium* control, and long-term toxicity studies on most of them have been completed or are in progress. The data obtained from these studies were reviewed by the Committee. It was noted that considerable progress has been made in assessing the effect of temephos on non-target organisms and on methods of monitoring the environment for residues of temephos.

In view of the importance of developing new larvicides for the control of *Simulium* and *Aedes aegypti*, the Committee recommended that toxicity studies continue on candidate compounds. The toxicological information needed is that normally required for the registration of pesticides likely to leave a residue in human food. Environmental studies on candidate formulations should continue in parallel with tests of their effectiveness against *Simulium* larvae, and chemical methods should be developed for environmental monitoring as the larvicides become operational.

4.3 Insecticides for louse control

The increasing prevalence of head lice and the development of resistance of body lice to organochlorine insecticides and malathion have made the development of effective and safe alternative compounds for louse control an urgent matter. Pesticides for body lice must be in a form that does not permit the hazardous absorption of the chemical through the skin. To minimize the problem of resistance, it is desirable to have insecticides available that belong to a variety of separate chemical groups.

Temephos

Temephos dust (20 g/kg) for the control of lice was considered by the WHO Expert Committee on Insecticides (4) and has since been used effectively and safely for this purpose. The present Committee agreed that the same concentration of temephos, applied for pediculosis capitis in a solvent commonly used for the oral administration of drugs, would present no significant hazard.

Permethrin

With the appearance of resistance of body lice to malathion in Burundi and Egypt, considerable interest has been shown in alternative compounds. Permethrin has been tested in Egypt, and a single application of 10 g/kg dust against body louse infestation provided a high level of control (97%), which persisted for well over a month. In view of the low toxicity of permethrin, the Committee considered that it is safe for use as a 10 g/kg dusting powder against lice.

Malathion

Owing to the possible isomerization of malathion in powder formulations, the Committee recommended that the use of malathion formulations for louse control be limited until the authorities are certain that their content of isomalathion and other toxic contaminants has been reduced to a sufficiently low level.

4.4 Biological control agents

The development of biological control agents for public health use is being sponsored by WHO's Special Programme for Research and Training in Tropical Diseases. Although biological agents are widely used for the control of certain pests in agriculture and forestry, they are not at present being used against disease vectors, although several bacteria, fungi, protozoans, and nematodes are being evaluated for this purpose. WHO is operating a five-stage testing scheme (13). Collaborating centres have been nominated to study candidate agents with special emphasis on isolation, characterization, and safety to mammals and other non-target organisms.

The health hazards of biological agents that might be used in vector control cannot be evaluated entirely by the standard toxicological and biochemical methods used for chemicals, and appropriate procedures are being developed.

4.5 Rodenticides

The Committee reviewed a draft manual on specifications for rodenticides, being prepared by FAO and WHO for publication, to ensure the adequacy of the toxicological information. The Committee considered that the guidance given on pages 38-41 of the twentieth report of the

Expert Committee on Insecticides (4) should be used in the presentation of the specifications, and it made several other suggestions for the improvement of the text.

4.6 Field observations on people exposed to pesticides

Contact between applicator and insecticide is generally much more prolonged in public health than in agriculture, and usually a single chemical is applied by the same people for long periods of time, sometimes exceeding 15 years.

Application of any insecticide as a residual indoor spray—such as in antimalaria programmes—is inevitably associated with significant exposure of the spraymen and measurable exposure of the occupants of treated dwellings. Many other vector control programmes in which insecticides are used lead to significant and unavoidable human exposure to these chemicals. Examples are the direct application of insecticides to the body surface or clothing for lice control, their use as larvicides in outdoor water that is liable to be drunk, and their application in domestic water containers for *Aedes aegypti* control. The number of insecticides used for vector control purposes is relatively small compared to the many used in agriculture since the choice is limited to compounds of low mammalian toxicity.

WHO is carrying out a collaborative programme for evaluating new insecticides with the aim of finding alternative compounds to replace those to which vector resistance has emerged. A number of WHO collaborating centres and field research units have been established throughout the world to carry out this work. As compounds progress through the programme and reach field trials, additional research is undertaken to develop a suitable field method for determining exposure and to explore the relationship of laboratory findings to the signs and symptoms of poisoning. Extensive toxicological studies are carried out to ensure that new compounds developed for malaria control programmes can be applied safely. Many compounds are rejected for toxicological reasons at an early stage in their development. Others are recommended for field trials and an assessment of hazard is made. During the first use of a compound in the field a clinical toxicologist is always present. Protocols for such trials were described on pages 16–19 of the twentieth report of the Expert Committee on Insecticides (4).

This evaluation scheme is largely responsible for the safe and efficient use of insecticides in public health programmes throughout the world. The Committee recommended that the work should continue to ensure

that vector-borne diseases can be controlled without hazard to man and his environment. It also recommended that medical surveillance be continued whenever new pesticides are first applied in the field.

5. PRECAUTIONARY MEASURES AND THE MONITORING OF EXPOSURE

5.1 Precautionary measures

The safe use of pesticides depends on (1) the availability of up-to-date information on the individual pesticides being used, (2) the choice of pesticide, (3) the storage conditions, and (4) the conditions at the sites of use.

Simple tests to evaluate and monitor the mammalian toxicity of pesticides after prolonged storage would be particularly useful in developing countries, where facilities for pesticide analysis are not readily available. Since these would be screening tests, it might sometimes be necessary to resort to chemical analytical methods for confirmation. The Committee proposed that WHO should prepare protocols for simple bioassays of mammalian toxicity that might be used in the field.

To prevent unnecessary and prolonged storage of pesticides, care should be taken that stocks are used in the order in which they are received.

The Committee felt that the key to good safety practice is control of the level of exposure to a given pesticide. This level is usually subject to wide variations depending on some or all of the following conditions :

- type of formulation applied ;
- method and rate of application and equipment used ;
- environmental conditions, such as prevailing winds, temperature, and humidity ;
- physical posture of and constraints on individuals caused by variables such as the height of crop or type of houses to be sprayed ;
- duration of work ;
- protection of the potential portals of entry, e.g., skin, respiratory passages ;
- attitude of the operators.

The Committee emphasized that many workers involved in the use of pesticides in developing countries may be illiterate and hence written

precautionary measures may be inadequate. The training of spraymen and supervisors in the safe use of pesticides forms the first line of defence against pesticide hazards. Courses should be provided to enable supervisors to identify and describe the various pesticides commonly used, mix various formulations and apply them, and repair and maintain spraying equipment. Supervisors should also be able to train spraymen in the field using a variety of visual techniques.

The main constraints in the use of protective clothing are climatic conditions and the attitude of individuals. Protective clothing and maintenance of personal hygiene are among the most important safety measures and clothing and facilities should be provided according to the pesticide used, the type of application, and the tasks to be done. Some examples are given below (see also section 4.1).

(1) *Mixers and baggers*. Since they come in contact with technical materials and concentrated formulations they should wear rubber boots, gloves, aprons, and masks. They should be given an adequate supply of soap. All clothing should be washed after each use.

(2) *Spraymen*. Those applying residual insecticides should be provided with canvas shoes or boots, overalls, and caps with downturned brims, they should be given an adequate supply of soap, and all their clothing should be washed after each use.

Those engaged on ultra-low-volume space treatment with 20 g/l diesel oil solution of bioresmethrin synergized with pyperonyl butoxide need be provided only with overalls and masks because experience indicates that the hazard to the operators is very low.

Those engaged on larviciding with temephos or larvicidal oil need no special protective clothing because the risk of toxicity from these two substances appears to be very low.

A medical examination is advisable, including the determination of blood cholinesterase, of those applying organophosphorus compounds. Regular medical surveillance of seasonal spray operators should be undertaken. The Committee was of the opinion that this type of supervision should be mandatory.

Spraymen, mixers, and baggers should be instructed to report any symptoms of illness promptly to the supervisor. The supervisor is responsible for finding out any cases of illness and providing first aid.

The officer in charge of the programme in the area must be given the following directions :

(1) Before the start of spraying operations, alert all medical services likely to be called upon to treat any cases of poisoning.

(2) Make available to the medical personnel all relevant information on the insecticides in use.

(3) Ensure that adequate facilities are provided for emergency care of people poisoned by pesticides.

(4) Ensure the permanent provision of washing facilities.

5.1.1 *Information*

Detailed and up-to-date instructions on the safe application of a given pesticide are prepared by WHO in the form of information sheets on the safe use of pesticides in public health. The instructions are usually grouped in five parts covering (1) information for the project leader ; (2) directions to field supervisors ; (3) directions for operators to ensure their own safety ; (4) directions for operators to ensure the safety of inhabitants ; and (5) instructions to be given to inhabitants in the project area. They are translated as needed into the language used in the project area and are communicated and explained to the inhabitants to ensure their full collaboration during the spraying period.

Information sheets have been prepared on the safe use of

- fenitrothion, malathion, and propoxur water-dispersible powder formulations for residual indoor application
- fenitrothion for ultra-low-volume ground application.

They are distributed to all those concerned with WHO trials and antimalaria projects and may be obtained on request by those responsible for other trials or projects. In some instances a sheet prepared for one insecticide has been used for another insecticide of similar toxicity and mode of action. These information sheets have been very beneficial, and the Committee recommended their wider distribution and their adaptation to other methods of application.

5.2 **Methods of monitoring exposure**

The most practical method available of assessing exposure to organophosphorus insecticides is the monitoring of blood cholinesterase. During the past few years the tintometric field kit (produced by Tintometer Ltd., Salisbury, England) has been widely used for determining whole-blood cholinesterase activity. The Committee reviewed and approved the instructions regarding the interpretation of the tintometric results of cholinesterase activity, with particular reference to exposure to feni-

trothion prepared as part of the relevant information sheets described in section 5.1.1. In this connexion the Committee stressed that the severity of poisoning is determined not only by the degree of reduction of cholinesterase activity but also by other factors such as rate of inhibition of cholinesterase and type of active ingredient (inhibitor).

Recently a spectrophotometric field kit for determining cholinesterase activity has been developed, as recommended in 1972 by the WHO Expert Committee on Insecticides (4). A document describing the details of the kit and assay procedures (14) was approved by the present Committee.

The kit which is available from WHO ⁴ consists of basic equipment, accessories, and preweighed chemicals sufficient for about 1000 whole-blood and 1000 plasma cholinesterase determinations. A single experienced operator can carry out 40 whole-blood and 40 plasma cholinesterase assays in a day.

It has been the practice to measure enzyme activity in whole blood and plasma, but the level of erythrocyte cholinesterase is a better indicator of cholinesterase activity at nervous synapses. Technical difficulties of separating erythrocytes in the field, however, limit its applicability. Further research is needed to simplify the determination of erythrocyte cholinesterase in whole blood.

The development of this spectrophotometric field kit is an important step forward because it may be possible to adapt it to monitor exposure to other pesticides in the field, e.g., carbamates, dinitrophenols, paraquat, and possibly some pyrethroids. It should be borne in mind that the spectrophotometer has many other uses in public health apart from the monitoring of pesticides.

6. OTHER ASPECTS OF THE SAFE USE OF PESTICIDES INCLUDING EDUCATION AND TRAINING

6.1 Field surveys of pesticide exposure

Little objective evidence exists for the value of protective measures other than locally available protective clothing and good hygienic practice. Surveys have therefore been organized to study exposure in actual field conditions in both agriculture and public health, and WHO

⁴ Orders should be sent to the Division of Vector Biology and Control, World Health Organization, 1211 Geneva 27, Switzerland.

has designed a standard protocol for the survey of exposure to organophosphorus pesticides in agriculture (12). In the three years since the protocol was issued it has been used on several occasions, particularly in India, Sri Lanka, and Sudan.

Some of the results obtained in these surveys were reviewed by the Committee, which recommended that further surveys be carried out so that definitive conclusions might be drawn and safety measures improved. It further recommended that similar protocols be designed for surveys of exposure to other types of pesticide.

6.2 Treatment of insecticide poisoning

The treatment of poisoning due to carbamates and organophosphorus compounds was summarized in Annex 2 of the sixteenth report of the Expert Committee on Insecticides (5) and was updated in the annex to the twentieth report of that committee (4), which also included organochlorine compounds. In both cases, the annex was reprinted as a leaflet and widely circulated in English, French, and Spanish. There have been few major developments in the treatment of insecticide poisoning in recent years, but there have been some changes in emphasis. A new text has therefore been prepared and is annexed to the present report (Annex 2).

6.3 Expertise in toxicology

There is a need for international coordination in toxicological research and for a sharing of expertise in order to increase the research capacities of the developing countries. WHO has been attempting to ascertain, through a chain method, the names of physicians and scientists active in this field. However, this method has its disadvantages, and the lack of contact through governments has led to some gaps in the information collected. The societies of toxicology in several countries have published comprehensive lists of members and their fields of interest, and the European Society of Toxicology is proposing to widen its list in collaboration with other national societies. The Committee suggested that WHO collaborate with the toxicological societies in this activity and maintain and periodically distribute a list of institutes and departments active in this field, categorized according to the specialties of the staff, together with the name of the director or a corresponding member.

The most important aspects of such a list would be the detailing of expertise and the willingness of corresponding members to help with the problems of WHO.

6.4 Development of WHO recommended classification of pesticides by hazard

In 1975 the Twenty-eighth World Health Assembly adopted a recommended classification of pesticides by hazard (15, 16) and at the same time requested the Director-General to continue to develop the classification. The scope of the classification was confined to the *acute* risk to health that might be encountered accidentally by any person handling the product in accordance with the manufacturer's directions or in accordance with the rules laid down for storage and transportation by competent national and international bodies.

It took some time for the classification to be accepted on a general basis, partly because too much had been expected of it and partly because its scope as set out above had been overlooked. However, the classification has been adopted by a number of developing countries and (in 1977) by the Council of Europe (17).

One effect of the adoption of the classification by developing countries was a number of informal requests to assist them in the classification of individual compounds. This need had been anticipated to some extent in the annex to the classification, but it became clear with time that this was not sufficiently comprehensive or up to date. Recently, therefore, WHO has issued guidelines to the classification of pesticides (18). Over 500 pesticides have been classified according to a single suggested LD₅₀ figure for each. The opportunity has been taken to adjust the position of a number of pesticides in the classification where this seemed to be indicated for the reasons stated in the document and in accordance with the principles set out in the classification itself.

In 1976, members of the WHO Expert Advisory Panel on Vector Biology and Control were consulted on the development of the classification, as requested by the World Health Assembly. A number of alternative methods of classification were suggested, such as parallel classification, the formulation of toxicological profiles, and the arbitrary valuation of toxicological effects and their summation. No agreement was reached on any of these suggestions, and several members of the panel thought that the classification was adequate for present needs, particularly as an aid to legislation in developing countries.

The Expert Committee noted that the guidelines to the classification of pesticides (18) included some new elements, such as the addition of notes on unusual effects and the adjustment of the classification for those compounds that may produce irreversible effects.

The Committee recommended that the presentation of the classification described in the guidelines should be continued, with the inclusion of further data as they become available.

Although the Committee did not at present favour the formulation of a parallel classification to cover long-term and/or cumulative effects, it considered that any new method of incorporating this aspect of toxicity into the classification should be examined. The efforts being made in some countries to devise other effective schemes of classification of toxic chemicals should be kept under review.

6.5 Assistance in poisoning outbreaks

Disturbed by the increasing number of accidental releases of chemicals into the environment, resulting in adverse effects on health of epidemic proportions, the Thirtieth World Health Assembly requested the Director-General to study the problems and long-term strategies in this field and "to examine the possible options for international cooperation, including the financial and organizational implications, with a view to . . . providing rapid and effective response in emergencies and in developing arrangements for mutual assistance between Member States" (19).

The Expert Committee took note of WHO's arrangements for meeting requests from Member States for technical cooperation after outbreaks of pesticide poisoning.

Because of the increasing number of toxic compounds it is often impossible to have within a single country specialists capable of dealing with all situations. The Committee recommended that WHO establish and maintain a list of specialists (see section 6.3) who are willing to help when outbreaks of pesticide poisoning occur. In making the selection of experts, WHO may consider collaborating with national and international societies of toxicology, the European Medical Research Council Advisory Sub-group on Toxicology, and other international organizations involved in poison control and assistance after chemical accidents.

The Committee also urged Member States to notify WHO of such accidents promptly and to request assistance as early as possible since it will then be most effective.

To assist Member States in their investigation of poisoning outbreaks and other monitoring surveys, guidance on sampling and despatching specimens is given in Annex 3.

It must be recognized that, when all has been done to alleviate suffering and infirmity, such outbreaks provide opportunities for studying pesticide toxicology in man and the epidemiological circumstances of poisoning. These studies are particularly useful in improving preventive measures.

6.6 Information and training

Two information services—the issue by FAO and WHO of data sheets on pesticides and the distribution by WHO of information sheets on the safe use of pesticides in public health—have already been described (sections 2 and 5.1.1), and the Expert Committee now considered other means of conveying information to those responsible for the use of pesticides in the field.

International seminars have been held in the past and have probably had some impact on legislation and on interministerial cooperation at the national level. However, in many cases the educational content of these seminars has not found its way to those actually working with pesticides in the field.

The responsibility for disseminating information must rest with national authorities since only they can translate the message into their own cultural and linguistic terms. Courses sent by mail have proved to be particularly useful in Latin America to solve the problem of isolation. A course on the safe use of pesticides, using a tape and slides and produced in one country, may be found useful with little modification in others, provided there is no language problem.

All avenues of education on the safe use of pesticides should be used, including the inclusion of the subject in the curricula of schools and universities and the organization of national campaigns. In this respect, the Committee suggested that a future World Health Day might be devoted to the theme of the prevention of poisoning, so providing a valuable opportunity for emphasizing the safe use of pesticides to the general population. The continuing education of agricultural extension workers and of others concerned with the distribution of pesticides in rural areas should be stressed, and in this area, collaboration with FAO and ILO is of great importance. WHO should also collaborate with non-governmental organizations such as the International Federation of

Poison Control Centres in order both to receive data on intoxication and to disseminate information.

The Committee noted that WHO has adopted an innovative approach to education with the production of a modular course on the safe use of pesticides, which is particularly suited for use in developing countries in collaboration with the national authorities. The basic course is divided into over 100 modules, each with a text and a visual aid, and a selection may be made from these modules appropriate to the level and experience of the group under instruction. The courses will be produced in national languages and adapted to local conditions. Self-administered courses are being adapted from the basic course.

The Committee strongly supported the modular concept and recommended its continued development in collaboration with national authorities. It seemed to fill a much-felt need, particularly in the developing countries.

7. SUMMARY OF RECOMMENDATIONS

7.1 Recommendations for national authorities

1. Establish an interdepartmental control agency for the registration of pesticides and the improvement of coordination between government agencies concerned with the use of pesticides. The agency would also act as an advisory body for all concerned with the use of pesticides (section 2).

2. Ensure good manufacturing practice, adequate control of quality of pesticides, and adequate control of use of pesticides and their formulations (section 2).

3. Develop technical services for safety evaluation and pesticide analysis in order to make legislation effective (section 2).

4. Undertake training in the safe and effective use of pesticides at all levels (section 2).

5. Notify WHO of poisoning outbreaks and, if required, to request early assistance (section 6.5).

7.2 Recommendations for WHO

1. Continue field trials of new insecticides to ensure that those chosen for public health programmes are used efficiently and safely (sections 4.1 and 4.6).

2. Promote environmental and toxicological studies on candidate compounds or formulations for the control of vectors of onchocerciasis, trypanosomiasis, and yellow fever (section 4.2).

3. Encourage studies on the summation and potentiation of toxicity of pesticides by chemicals (section 3.2).

4. Prepare protocols for simple tests for evaluating and monitoring mammalian toxicity of pesticides in the field following prolonged storage (section 5.1).

5. Undertake the wider distribution of information sheets on the safe use of pesticides in public health and adapt them to methods of application other than residual spraying and ultra-low-volume application (section 5.1.1).

6. Continue to issue the FAO/WHO data sheets on pesticides (section 2).

7. Further develop protocols for surveys of pesticide exposure of operators in the field (section 6.1).

8. Compile a directory of institutes and departments active in pesticide toxicology research (section 6.3) and a list of specialists willing to help in the laboratory or in the field in case of poisoning outbreaks (section 6.5).

9. Maintain the existing presentation of the WHO recommended classification of pesticides by hazard, with the inclusion of further data as they become available (section 6.4).

10. Continue the development of the WHO modular course on the safe use of pesticides, in collaboration with national authorities (section 6.6).

11. Maintain close collaboration with FAO, ILO, and UNEP, with emphasis on the provision of education and training and the carrying out of field surveys in developing countries (section 1).

7.3 Recommendations for future research

1. Investigate the toxicity of formulated pesticides after subjecting them to accelerated or long-term tropical storage (section 3.2).

2. Study the toxicology and enzymology of impurities in organophosphorus pesticides containing carboxyl ester moieties and try to develop an enzymic test for undesirable impurities in field samples of these insecticides (section 3.2).

3. Investigate the toxicity and mechanism of action of pyrethroids (section 4.1.2).

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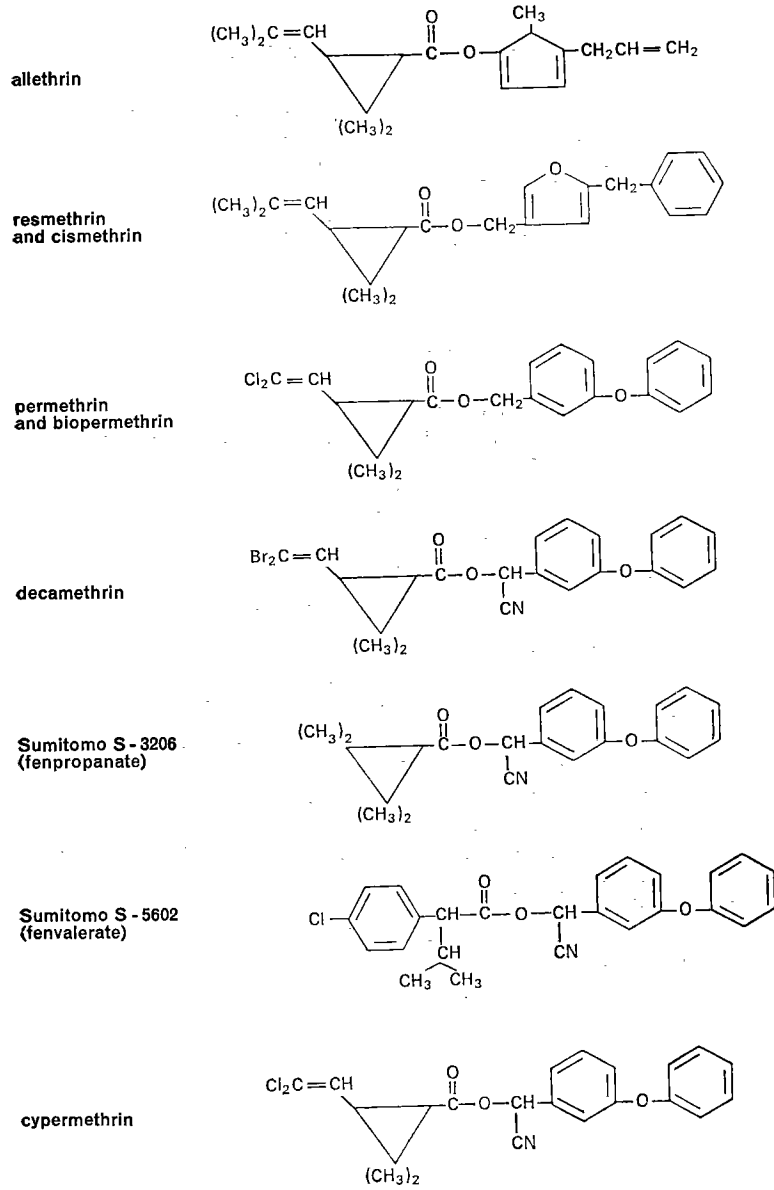
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REFERENCES

1. WHO Technical Report Series, No. 620, 1978.
2. *Safe use of pesticides*. Geneva, International Labour Office, 1977 (Occupational Safety and Health Series, No. 38).
3. BAKER, E. L. ET AL. *Lancet*, **1** : 31 (1978).
4. WHO Technical Report Series, No. 513, 1973.
5. WHO Technical Report Series, No. 356, 1967.
6. RAY, D. E. & CREMER, J. E. *Pesticide biochemistry and physiology* (in press).
7. VERSCHOYLE, R. D. & BARNES, J. M. *Pesticide biochemistry and physiology*, **2** : 308 (1972).
8. ALDRIDGE, W. N. ET AL. *Biochemical pharmacology*, **27** : 1703 (1978).
9. WOUTERS, W. ET AL. *European journal of pharmacology*, **43** : 163 (1977).
10. GAUGHAN, L. C. ET AL. *Journal of agricultural and food chemistry*, **25** : 9 (1977).
11. RUZO, L. O. ET AL. *Journal of agricultural and food chemistry*, **26** : 918 (1978).
12. Unpublished WHO document VBC/75.9.
13. WHO Technical Report Series, No. 561, 1975.
14. Unpublished WHO document WHO/VBC/78.692.
15. *WHO Handbook of resolutions and decisions*, Volume II, 3rd ed., 1979, p. 75 (resolution WHA28.62).
16. *WHO Chronicle*, **29** : 397 (1975).
17. *Pesticides*, 4th ed. Strasbourg, Council of Europe, 1977.
18. Unpublished WHO document VBC/78.1.
19. *WHO Handbook of resolutions and decisions*, Volume II, 3rd ed., 1979, p. 90 (resolution WHA30.47).

Annex 1

CHEMICAL STRUCTURE OF SOME NEW PYRETHROIDS



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Annex 2

TREATMENT OF POISONING DUE TO ORGANOPHOSPHORUS, CARBAMATE, AND ORGANOCHLORINE INSECTICIDES

Successful treatment depends on the rapid and simultaneous application of measures for :

- (1) alleviation of life-threatening effects ;
- (2) removal of non-absorbed material ; and
- (3) symptomatic treatment and the administration of antidotes if these exist.

The alleviation of life-threatening effects

For the removal of secretions and maintenance of a patent airway, arrange the patient in a prone position with head down and to one side, the mandible extended, and the tongue pulled forward. Clear the mouth and pharynx with a cloth or by suction. Use an oropharyngeal or nasopharyngeal airway or endotracheal intubation if airway obstruction persists. Artificial ventilation should be applied if required. Mouth-to-mouth respiration is to be avoided when it is suspected that the patient has been intoxicated by mouth because vomited material may contain dangerous amounts of toxic substances.

The removal of non-absorbed material

Depots of toxic material may be present in the gut or on the skin, from which absorption may continue for days. The condition of intoxicated patients who have become free of symptoms may deteriorate when newly absorbed toxic material reaches the circulation. Where intoxication has occurred by mouth, gastric lavage is imperative. If the clothing or exposed skin is contaminated by insecticide or by vomit, the clothing must be removed and the skin washed with soap and water for at least 10 minutes. Contamination of the eyes is treated by irrigation of the conjunctiva with water for 10 minutes.

Symptomatic treatment and administration of antidotes if these exist

Intoxication with organophosphorus compounds

On signs of systemic absorption, both atropine and reactivators must be given parenterally.¹

Persons with or 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 by slow intravenous injection (adult doses). More atropine (with or without the reactivator) may be given, depending on the severity of the intoxication and the response to the first dose. After the administration of oximes, less atropine may be required.

In cases of severe intoxication, 4–6 mg of atropine sulfate should be given initially to adults, followed by repeated doses of 2 mg or as much as is required to maintain full atropinization. Whenever possible, this treatment should be performed concurrently with measures for the alleviation of life-threatening effects and the removal of non-absorbed material. 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 intervals of 5–10 minutes. Every 2-mg dose should give 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. There may also be a short-lasting diminution of miosis. Cases are described in the literature in which several hundred milligrams of atropine have been given during the first 24 hours. Usually, however, it is not necessary to exceed 50 mg per day. Continuous intensive observation of patients is essential since symptoms may recur and, if untreated, may cause death. In every case, observation should be maintained for at least 72 hours after initial improvement.

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 for treatment 36 hours or more after intoxication, oxime therapy may be less effective. Reactivators

¹ When symptoms occur prior to medical attention being available, atropine with or without obidoxime can be given by intramuscular injection. For this purpose automatic injectors loaded with atropine sulfate or with a combination of atropine sulfate and obidoxime chloride are available. For pharmaceutical reasons, the combination of atropine and a pralidoxime salt is impracticable.

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 carbamates

The signs and symptoms of carbamate poisoning resemble those of organophosphate poisoning, but since they disappear comparatively rapidly atropine treatment is often not necessary by the time the patient reaches a 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 organochlorine compounds

The organochlorine compounds that commonly cause poisoning are endrin, aldrin, and dieldrin.

There is no specific antidote. Treatment is aimed at controlling the symptoms, especially hyperreactivity 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, since this is at present a lengthy and highly specialized procedure, treatment should never be deferred pending the result of a laboratory test.

Note

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 a food item or drinking-water should be borne in mind.

SAMPLING IN POISONING OUTBREAKS

Primary samples should be collected with the idea of determining the identity of the toxicant and the rate of dosage. For example, if there is evidence that poisoning has occurred through the contamination of flour used to make bread, then primary samples would consist not only of suitable samples from patients but also of samples of the suspect formulation, the suspect flour, and the suspect bread. There might be good reason to collect, as secondary samples, other ingredients of the bread as well as other kinds of food and drink in order to rule out the possibility of multiple contamination or as a precaution in the event that flour was not really the source of poisoning. However, secondary samples that probably contain no poison should be so labelled and their analysis postponed until the identity and approximate concentration of the poison in primary samples has been established. This procedure will greatly increase the efficiency of chemical analysis.

The primary set of samples, therefore, should consist of the following, where appropriate :

- the suspect formulation, which should be sent to the laboratory under completely separate cover from the remaining samples, because of the possibility of cross-contamination ;
- remnants of the specific food, water, or other material assumed to have been the direct cause of poisoning ;
- vomitus or lavage fluid ;
- blood ;
- urine ;
- stool specimens ;
- skin washings ;
- expired air ;
- bile (especially for narcotics) ;
- various tissues (especially the stomach and its contents, the liver, the kidney, the brain, and the storage tissue peculiar to the suspect compound) provided death has occurred and an autopsy has been performed. Samples of fat sufficient for analysis may be taken from living patients by needle biopsy without danger ;
- other specimens as required.

Poison may have been spilled on the clothes. Vomitus may have contaminated clothing or sheets or it may have been mopped up with a towel or other cloth. Any fabric known or suspected to contain poison, vomitus, or even urine should be sent to the laboratory.

It is most important that formulations and any other specimens suspected of heavy contamination be sent to the laboratory under separate cover, otherwise it may be difficult to exclude the possibility that a trace of poison found in a tissue sample may have entered the sample as a contaminant during transport.

A number of plastics and rubbers contain extractable impurities that may be difficult to distinguish from pesticides if, as is likely, the specimens are analysed by gas chromatography. The impurities can be separated and identified, but the procedure complicates and delays analysis. All solid and liquid specimens should preferably be collected in glass bottles or jars with ground glass stoppers or with screw caps lined with aluminium foil. If such containers are not available, however, it should be remembered that it is better to have imperfect specimens than none at all.

All samples should be labelled carefully. The following information is generally required :

- name of patient
- date of birth
- weight of sample
- date sample taken
- hour sample taken
- place sample taken
- name of referring physician.

Samples that remain under the same administrative control may be labelled by code number.

If there is any possibility that a sample will be of medicolegal importance, it must be sealed and transmitted in such a way that its identity and validity can be established in court. Lids and corks may be secured by adhesive tape and then labelled in indian ink or some other suitable writing material in such a way that the writing crosses two or more strips of tape. Then the closure cannot be removed without removing the tape, and the tape cannot be removed and replaced without the tampering being obvious.

Some samples such as flour, hair, and other dry materials require no preservation. Other samples such as blood, tissues, excreta, and many foods must be preserved unless they can be transferred to the laboratory

immediately. Unpreserved samples may undergo chemical change, the importance of which in relation to diagnosis depends on the compound. Furthermore, putrid samples may be refused by the laboratory. Refrigeration is always an acceptable means of preserving samples. It may be achieved by shipping the material in an insulated container with a refrigerant or with crushed ice in plastic bags to prevent leakage. It may be technically easier to use dry ice, but freezing destroys red blood cells and prevents their separation from plasma. Separate measurements of plasma and red cells are valuable in connection with several heavy metals and with cholinesterase activity. Dry ice will last much longer if it is in an insulated container.

It is usually satisfactory to preserve urine with a few drops of a 1:10 dilution of formalin (i.e., 40 g/l formaldehyde solution) without refrigeration. Tissues may also be preserved with the same dilution of formalin if organochlorine insecticides are the only compounds to be analysed.

Specimens should be conveyed to the laboratory by the most rapid means available.