Safe use of pesticides

Ninth report of the WHO Expert Committee on Vector Biology and Control

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WHO EXPERT COMMITTEE ON VECTOR BIOLOGY AND CONTROL

Geneva, 11–17 September 1984

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SAFE USE OF PESTICIDES

Ninth report of the WHO Expert Committee on
Vector Biology and Control

INTRODUCTION

The WHO Expert Committee on Vector Biology and Control met in Geneva from 11 to 18 September 1984 to study recent developments in the toxicology of pesticides used in vector control, to advise on their safe use, and to consider other ways in which Member States may promote the safe use of pesticides and reduce exposure to spraymen and the general public. The meeting was opened by Dr S.K. Litvinov, Assistant Director-General, on behalf of the Director-General. He emphasized that since the Committee last met to consider the safe use of pesticides six years previously, there had been more change in the approach to vector control than at any other time. This had arisen from the reorientation of health services in many countries towards the target of Health for All by the Year 2000, which encourages the integration of vector control into the basic health services. Vector control should be viewed broadly as including all methods that could contribute to adequate control of the transmission of vector-borne diseases. Therefore, advice on the safe use of pesticides required a rather different approach from that given previously.

Dr Litvinov also emphasized that Member States were faced on the one hand with pressure to limit the use of pesticides and on the other with increasing resistance of vectors to older chemicals, and with the geographical spread and recrudescence of many vector-borne diseases which were difficult to control; the risks and benefits of using pesticides must therefore be carefully balanced.

1. DEVELOPMENTS IN VECTOR CONTROL:
   HUMAN SAFETY ASPECTS

   Vector control is an integral part of the prevention of endemic diseases. Hitherto, it has been organized at national or regional levels and based on techniques that are often cumbersome and costly.
Recently administrative and other aspects of vector control have undergone a shift in emphasis from vertical organization towards a rather more flexible approach, involving, wherever feasible, well-motivated community participation. There has also been a move towards the integrated approach to control, using environmental management and biological measures in addition to the appropriate use of pesticides; in fact the report of the seventh meeting of the WHO Expert Committee on Vector Biology and Control was devoted entirely to the subject of integrated vector control (1).

1.1 Integrated community vector control

The difficulties inherent in the development of greater individual and community participation in vector control have only recently become a matter of widespread concern. This wider participation has been given an impetus by the development of primary health care. However, there are problems in maintaining even the passive cooperation of communities and individuals in certain programmes of disease control involving, for example, residual insecticide spraying indoors. Even with excellent cooperation, community participation will increase the number of people who are exposed to pesticides. Consequently education on safety aspects will require more attention.

1.1.1 Community participation in vector control

The part that rural communities in many parts of the world are expected to play in vector control must be compatible with their essential daily work. Without incentives, initial participation would be quickly followed by non-compliance.

Primary health care programmes involving community groups, in addition to dispensaries and health centres, may be effectively linked with other more specialized technical services including those for vector control. It has been recommended by the WHO Expert Committee on Vector Biology and Control (1) that a “core group” of technical staff should be formed at central government level (or at regional level in larger programmes). This core group should be entrusted with “the duties of planning, coordination, provision of technical support, and surveillance of integrated vector control programmes”.

6
The integration of vector control by pesticides into primary health care will entail health education at the community level involving, for example, the preparation of simple posters, slides, and films for presentation to adults and schoolchildren, and the provision of simple guides and manuals to schoolteachers, community leaders, and health workers.

1.1.2 Characteristics of modern vector control

The above-mentioned Committee (1) defined integrated vector control as "the utilization of all appropriate technological and management techniques to bring about an effective degree of vector suppression in a cost-effective manner".

Although this concept existed in practice long ago it has been neglected because of the availability of highly effective residual chemical pesticides. However, the concurrent development of resistance to pesticides among the major groups of vectors, concern for the environment and for human safety, and increased costs of insecticides have again led to the view that pesticides must be used in conjunction with other control measures. For many vectors the main components of control are: sanitation, water and habitat management, waste management, reduction of breeding sites, and use of pesticides.

1.1.3 Malaria vectors

Anopheline adults are currently controlled by indoor residual spraying with adulticides through vertically-organized antimalaria campaigns, and this use of pesticides probably will continue for the foreseeable future. Although DDT is still recommended for this purpose, where organochlorine insecticides are no longer effective because of resistance of the vectors, organophosphorus or carbamate insecticides have been substituted. There are also certain ecological and epidemiological circumstances where chemical and/or biological antilarval approaches could be used in a cost-effective way. The following are some specific instances where community action within the context of primary health care could be used to combat malaria: modification of irrigation practices (e.g., intermittent irrigation), community participation in breeding and
distributing predatory fish, spraying of residual insecticides, use of impregnated bednets and impregnated personal clothing, the interposition of cattle shelters between human settlements and insect breeding grounds (zooprophylaxis), and strategic placement of villages and of forest clearance.

1.1.4 Vectors of bancroftian filariasis

The major vector of bancroftian filariasis, Culex quinquefasciatus, breeds in drains, sullage water, ponds, cesspits, septic tanks, and pit latrines—in fact in any collection of water around human habitations. Thus simple sanitary measures that can be organized by the community (e.g., environmental sanitation and reduction of breeding sites by draining, filling, levelling, keeping the drains clear to maintain satisfactory flow, planning at the construction stage, and use of larvicides where necessary) should go a long way towards controlling this mosquito.

1.1.5 Vectors of urban yellow fever, dengue, and dengue haemorrhagic fever

The breeding habitats of Aedes aegypti make it a special candidate for integrated vector control at household and community levels, as there are simple ways to reduce its breeding sites.

Two new types of product, insect growth regulators and biological control agents, are now available in addition to temephos if larviciding is required; these new control agents are discussed in sections 2.4 and 2.5 in this report.

1.1.6 Tsetse flies

The discovery that traps and screens impregnated with insecticides are very efficient tools for controlling riverine tsetse flies in the savannah zones of West Africa and the Congo has opened new approaches to control that can be used by village communities.

1.1.7 Vectors of Chagas’ disease

Recently it was found that thorough wall-plastering substantially reduces Triatoma infestans populations. However, there are certain
socioeconomic factors that govern its acceptance. Community health education should be used to encourage the adoption of wall-plastering, which in the long-run would contribute substantially to the control of Chagas' disease.

1.1.8 Cyclops and dracunculiasis

Guinea-worm infection occurs after ingestion of water contaminated with infested Cyclops; any measure to exclude the vector from drinking-water would therefore control this disease. The ideal, of course, would be the provision of piped water but, in the rural areas of some countries where this may not be immediately feasible, measures described in the operational manual of the Guinea-worm Eradication Programme in India may be used (2). Such measures include: filtering unprotected water through a fine muslin cloth, boiling the water, regular treatment with chemicals that are effective at low concentrations, persuading the community not to enter drinking-water sources, and the conversion of step-wells into draw-wells. All these measures can be achieved with community participation, but success will depend on a good health education programme within the context of primary health care.

1.2 Evaluation of pesticide exposure

The need to evaluate the potential effect of pesticides on different groups of people varies with the toxicity and other characteristics of each compound and with previous experience. With community participation there is the possibility that the level of pesticide application may be variable, and this may make evaluation of its effects more difficult. When a new compound or a really novel method of application is introduced, it is necessary to monitor the spraymen (or other applicators) and the inhabitants of treated premises. It is also important to find out whether any side-effects had been noted during the formulation and manufacture of each compound, and whether the use of pesticides for agricultural purposes had affected the general population. Important aspects of these studies are the determination of the levels of exposure, and the investigation of storage of the chemicals in the body and their eventual excretion.
1.2.1 Measurement of exposure to pesticides

A protocol for the measurement of dermal and respiratory exposures has been issued by WHO;\(^1\) further details on measurement of dermal exposure are provided in Annex 1. Use of the WHO protocol (and earlier versions of it) has shown that, in almost all situations, both dermal exposure and the absorption resulting from it greatly exceed respiratory exposure and the resulting absorption. It is safe to predict that this relationship will continue, but with unusual methods of application of pesticides, e.g., release in the form of a smoke or a vapour, further evaluation may be required.

Measurements have been made of the amount of a pesticide ingested as a result of eating food (such as sandwiches) or smoking cigarettes without first washing one's hands. Although only traces of pesticide were found to be ingested under these conditions, the studies did demonstrate that the prudent worker cannot ignore any aspect of personal hygiene.

Measurements of the levels of pesticides in blood or in tissue offer a very useful indication of the degree of exposure. Some of these measurements were made before 1950. By about 1962 it was possible to measure most of the organochlorine insecticides in blood. Somewhat later, measurement of organic phosphorus compounds and carbamates (mainly as metabolites) became possible. Information is now available on blood and/or tissue levels of many pesticides, including those that are fatal, those that can cause temporary poisoning, and those that are not associated with any illness despite heavy occupational exposure; information is available also for the levels of pesticides in food and in the environment to which the general population is exposed. Thus these measurements give useful background information for evaluating clinical cases as well as the occupational and environmental conditions of exposure.

Less information is available on the concentrations of many compounds or their metabolites in human urine, saliva, or milk, but these values may be as useful as those for blood or tissue.

Total daily absorption associated with occupational exposure has been measured for only a few pesticides. It is difficult to understand how this important matter has been neglected. A satisfactory

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\(^1\) *Field surveys of exposure to pesticides: standard protocol*. Unpublished WHO document VBC/82.1 (1982); available from the Division of Vector Biology and Control, World Health Organization, 1211 Geneva 27, Switzerland.
measurement of total daily absorption for any one compound under
defined conditions of work provides not only valuable information
related to that specific situation but also a basis for the following:
(a) a quantitative comparison of the same compound under different
working conditions; (b) an estimate of total absorption of chemically
similar compounds under similar conditions; and (c) an evaluation
of the probable effects of the same compound when only the extent
of exposure is known (for example, when total intake from food
residues is known or when the total exposure from a vapour-
saturated atmosphere during a given interval of time can be
calculated).

In addition to the case and cohort approaches, there are two kinds
of epidemiological study: (a) those involving relatively brief
exposure such as the village trials of newly developed insecticides
carried out by WHO; and (b) those in which one or more groups
have been exposed for a decade or more. The first kind of study is
usually called monitoring and is to be distinguished from
surveillance, which is the routine assessment of the effects of
exposure to more toxic pesticides (such as fenitrothion) used for long
periods. The value of monitoring for determining whether, and
under what conditions, new compounds are acceptable for vector
control are obvious. Opportunities for carrying out studies of groups
that have been heavily exposed to one or a few related compounds
for many years are limited. WHO has sponsored two studies of DDT
spraymen. In addition, there have been extensive epidemiological
studies of workers exposed to DDT, chlordane, heptachlor, or
dieldrin; these studies have indicated no increase in total mortality
or of mortality due to cancer.

1.3 Benefit and risk in vector control

1.3.1 Benefits from vector control

The purpose of vector control is the interruption of transmission
of certain important human diseases. Because of the emphasis that
has been placed on vector control, the number of people afflicted by
malaria, yellow fever, Chagas' disease, typhus, and schistosomiasis
has been greatly reduced over the last 40 years, and further
improvement can be anticipated.

It is clear that the benefits of vector control are great. The
improvement and protection of human health, especially in
developing areas, gives a basis for viewing the use of pesticides for vector control in a special way: improved health is not only a benefit in itself but it permits increased economic status both at the personal and at the community level.

1.3.2 Risks associated with vector control

Obviously there are risks involved in vector control, especially when pesticides are used. The risks to man, domestic animals, and wildlife include possible poisoning or even death. Another risk is the contamination of air, water, food, or soil. However, by proper selection of compounds and by their proper use, all these risks can be reduced and usually prevented entirely.

A permanent problem with the use of pesticides is their cost and the cost of the equipment and labour for their application. These costs will determine whether an effective programme can be carried out at national or community level. The need and the demand for the use of pesticides are, however, growing. In a survey carried out in 103 developing countries (many of which were greatly affected by vector-borne diseases because of their tropical climate) the conclusions reached were that 28 pesticides were required for public health, and that the demand would grow from 50,000 tonnes in 1980 to 66,000 tonnes in 1984. Furthermore, the cost of many insecticides is increasing, and many countries and communities face great difficulty in carrying the cost. Despite these difficulties, better use of community resources can be achieved with the help and cooperation of WHO.

1.3.3 Methods of reducing risk

Selection of pesticides. The selection of a pesticide is a primary consideration for any effective pest control programme. The decision is inevitably based on three main factors: cost, efficacy, and safety. Very few preparations are at the same time effective, cheap, and safe; therefore a compromise is often necessary. Unfortunately, compromise is sometimes made to the detriment of safety.

Selection of an appropriate pesticide is becoming an increasingly difficult task because of both the high cost of certain new products

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1 Pesticide requirements for public health. Unpublished WHO document VBC/83.3 (1983); available from the Division of Vector Biology and Control, World Health Organization, 1211 Geneva 27, Switzerland.
and the resistance that has developed against earlier, cheaper pesticides. Vector resistance, which is a dynamic phenomenon, has been spreading and thus affecting many pest-control programmes in various countries. Thus, insect resistance to an otherwise acceptable insecticide is the main reason for searching for new effective compounds, but these are seldom less dangerous to non-target species. For example, the replacement of organochlorine insecticides by more toxic organophosphorus compounds usually considerably increases the acute hazard to workers in the field.

The user will inevitably tend to select the pesticide that is the most effective and at the same time the most economical for his purpose. Often the acute oral toxicity of the active material in rats is the main factor used to assess the hazard to man. However, the relationship between mammalian and pest toxicity usually offers a better indication of risk, i.e., the higher the ratio between the mammalian and pest LD₅₀s, the lower the actual risk to man. Since, from the point of view of occupational exposure, dermal absorption is more important than gastrointestinal absorption or inhalation, measurement of dermal as well as oral toxicity is important. Selection of an acceptable compound is even more important if it is designed for use at the community level.

The extent of exposure. The exposure of spraymen to pesticides in confined areas, as in residual insecticidal spraying, is among the highest in public health, but other techniques of application also have risks. Therefore, it is important to adopt all possible means of reducing the exposure to pesticides of those who apply them.

Duration of work is one of the main factors influencing the extent of exposure. Excessive exposure frequently occurs at the end of the working day or at the end of a campaign, when the workers are tired and consequently fail to take appropriate precautions. It is generally accepted that exposure should not exceed 5 hours a day and 5–6 days a week.

Medical aspects. It is unrealistic to expect that, for every pest control operation, a well-trained medical toxicologist will be engaged to recognize and to treat adverse effects of pesticides. Therefore, ways of controlling and reducing the risks should be made known to responsible workers. Precautions that should be taken include: instituting medical and/or biochemical examinations to detect early signs of overexposure; establishing the most appropriate sequence of pesticide use to avoid cumulative and potentiating effects; organizing first aid in the field; developing a
warning system both in the field and in the nearest medical centre; and securing transport facilities. If all these precautions are taken, the health risks associated with accidental exposure will be considerably reduced.

When selecting workers for a long-term control operation, a thorough medical examination is necessary. It is also crucial to establish normal, pre-exposure values for certain physiological variables, such as the level of blood cholinesterase activity if an organophosphorus insecticide is to be used, so that subsequent values determined during and after exposure can be compared. Selection of personnel is important, and those who are thought to be incapable of handling pesticides safely because of mental illness, low intelligence, alcoholism, or physical handicap should not be employed.

Apart from having personnel available in the field who are trained in first aid, adequate transport facilities to a medical centre should be provided for use in case of an accident; the centre should have properly trained medical staff and a supply of appropriate antidotes. It is most important that the necessary provisions for dealing with an emergency are made before an accident occurs: it may be too late to search for an antidote once it is urgently needed. (The treatment of poisoning caused by several classes of pesticide is discussed in section 5.5 and Annex 3.)

2. REVIEW OF NEW DATA ON INSECTICIDES FOR CONTROL OF VECTORS

The cost of formulating a new insecticide, toxicity testing, and field trials is enormous and has to be made good by large sales. Such investment is unlikely to be undertaken for insecticides used in public health alone and, as a rule, compounds used for vector control, or other public health purposes, have been initially developed for general agricultural purposes. Therefore, considerable data on human safety are nearly always available before compounds are used in public health.

2.1 Pyrethrroids

Since the last report of the WHO Expert Committee on Vector Biology and Control dealing with the safe use of pesticides (3), the
safety of a number of pyrethroids has been evaluated (Fig. 1) and experience of their use in the field has increased.

The pyrethroids have been found to be valuable pesticides with differing stability to light, low volatility, high insecticidal potency, and low toxicity to mammals under normal conditions of use.

Their favourable toxicological properties and proven efficacy have led to a great increase in their use in public health, notably for space spraying but also for personal protection devices and residual applications.

2.1.1 Mammalian toxicity

Many of the pyrethroids are highly toxic to various mammals when they are administered systemically. For example, deltamethrin administered intravenously has an LD$_{50}$ for rats of 2.0–2.6 mg/kg body weight (4.0–5.1 nmol/kg body weight), and for other compounds of this type LD$_{50}$ values as low as 0.35–0.65 mg/kg body weight (1.0–1.9 nmol/kg body weight) have been found. Although there are many different pyrethroid compounds, they produce only two types of symptom in rats: (a) the tremor syndrome consisting of aggressive sparring, sensitivity to external stimuli, and fine tremor progressing to gross whole-body tremor and prostration; or (b) the choreoathetosis/salivation syndrome, consisting of pawing and burrowing behaviour, salivation, coarse tremor progressing to sinuous writhing (choreoathetosis), and long-lasting seizures. Most pyrethroids produce one of these two syndromes, but for a few compounds there is an overlap, e.g., salivation in association with the tremor syndrome.

Although pyrethroids often have high intravenous toxicities, their toxicity when administered by gavage or inhalation is low.

Pyrethroids usually consist of several isomers. In general the cis-isomers are more toxic to mammals than the trans, and it is therefore important to know the isomeric composition of each product; the cis:trans ratio of the insecticide should be kept as low as possible, without decreasing its efficacy. The hazards associated with significant deviations from established ratios should be estimated from acute toxicity studies, and manufacturers should provide such data whenever a pyrethroid is produced with altered isomeric ratios.

There is general agreement that all pyrethroids affect sodium channels in the nerve membrane. In addition, many biochemical and physiological changes in specific areas of the central nervous system
Fig. 1. Structural formulae for pyrethroids

**permethrin (4 isomers)**

**cypermethrin (8 isomers)**

**deltamethrin (1 isomer)**

**bioresmethrin (1 isomer)**

**phenothrin (4 isomers)**

**fenvalerate (4 isomers)**
have been found. However, the mechanism that produces these effects in mammals is not understood.

No pyrethroids have been found to show chronic deleterious effects after short- or long-term administration (up to two years). They appear to be non-carcinogenic in feeding experiments carried out over two years, and the results of bacterial mutagenicity testing, and of host-mediated assays in mice, have been negative. Teratological testing has been negative except for some reduction in implantation and increases in fetal deaths, but only at the highest dose levels (4, 5, 6).

Early work suggested that pyrethroids caused morphological changes in the peripheral nerves that were associated with clinical signs of functional defects. These changes were connected with increases in the level of β-glucuronidase (EC 3.2.1.31) and β-galactosidase (EC 3.2.1.23). However, more recent research using improved techniques has shown that at high doses the morphological changes are minimal, the increases in β-glucuronidase and β-galactosidase activities are small, and the functional defects are slight and rapidly reversible. Although not proven, it seems probable that the effects of pyrethroids on the nervous system occur only at doses sufficient to cause other signs of poisoning.

Administration of high doses of pyrethroids often causes an increase in the liver: body weight ratio. This is not unexpected; it occurs with many lipophilic xenobiotics and is often associated with an increase in the level of mixed-function oxidases or drug-processing enzyme systems. This adaptation may explain why early symptoms of poisoning disappear during long-term dosing.

2.1.2 Metabolism

In mammals, pyrethroids are rapidly metabolized by ester cleavage or as a result of oxidation by the mixed-function oxidases, and the products quickly excreted. The metabolism is complex because many pyrethroids are mixtures of enantiomorphs (sometimes up to 8) and have numerous sites available for hydroxylation. Pyrethroids tend not to concentrate or persist in certain tissues although there are exceptions, e.g., fenvalerate persists in adipose tissue longer than in others.

The unconjugated products of ester cleavage of bioresmethrin and permethrin are apparently more toxic than their parent
compounds. Nevertheless, they are rapidly cleared or are further conjugated or metabolized. The low concentration of cyanide liberated from those pyrethroids containing an α-cyano group is rapidly detoxified to thiocyanate and presents no practical hazard. Hydroxylation anywhere in the molecule before ester cleavage leads to a reduction in insecticidal and mammalian toxicity.

The toxicity of pyrethroids can be increased or decreased by administering substances that influence their metabolic pathways. The fact that the routes and rates of pyrethroid metabolism are different in insects, fish, and mammals explains some of the major variations of toxicity, although other factors such as differing sensitivity of target tissues may play a part.

2.1.3 Human exposure

Experience in spraying these compounds has shown that exposure leads to only local effects on the human skin. Erythema and paraesthesia (an itching and burning sensation on washing in warm water) sometimes persist after exposure. Inhalation of sprayed particles sometimes leads to bronchiolar irritation.

Conventional studies of nerve conduction in workers exposed to various pyrethroids have failed to detect any abnormalities. However, experiments on conduction in the sensory nerve fibres in the tails of rats treated with deltamethrin have shown that the subnormal phase of excitability seen in control animals is replaced by a markedly prolonged supernormal phase that extends up to 200–400 ms; a diminished effect was found 24–28 hours after a single intravenous dose. It has yet to be established whether this technique may be used to monitor human beings exposed to deltamethrin; however, it is not apparently applicable to cismethrin, a pyrethroid not containing an α-cyano group.

There are no simple methods of measuring exposure. Excretion of pyrethroid metabolites can be used as an indicator but the technique is complex. Measurement of thiocyanate (derived from cyanide released from the α-cyano group) in blood or in saliva cannot be used to monitor exposure because the background concentration varies according to the intake from food and from smoking.

In the unlikely event of poisoning, treatment should be symptomatic. It has been shown that mephenesin is an effective treatment for rats who have been given a lethal dose of deltamethrin,
and somewhat less effective in the case of cismethrin. Although this observation may be of significance in trying to understand the mechanism of action of pyrethroids, mephensin itself is not a practical therapeutic agent because it has to be given by continuous perfusion.

2.2 The use of permethrin for aircraft disinsection

The Committee considered the use of permethrin for aircraft disinsection.

Disinsection trials with a 2% solution of permethrin (cis:trans ratio of 25:75) had been carried out using a Freon-propelled spray. Satisfactory disinsection was obtained with an aerosol concentration of 0.7 mg a.i./m³ and, in a separate trial, a residual application of 0.2–0.5 g/m².

Having reviewed the likely exposure of passengers and crew, the Committee considered that the safety margin for such treatment is very large and recommended permethrin formulations at the above levels for aircraft disinsection.

2.3 Anticholinesterase compounds

Since the Expert Committee's last report on the safe use of pesticides (3) only one compound in this group, bendiocarb, has reached operational use.

Bendiocarb is a broad-spectrum pesticide developed for the control of insects and arthropod pests of public health significance. Like other N-methylcarbamates, it is a fast-acting anticholinesterase compound, and its acute mammalian toxicity is relatively high. However, from the toxicological viewpoint, N-methylcarbamates have two inherent safety features: (a) the rapid spontaneous reactivation of carbamoylated cholinesterase; and (b) their relatively flat dose–response curve.

The mammalian toxicology of bendiocarb has been reviewed and summarized (7). Studies of human volunteers have shown that the threshold oral dose for reducing whole-blood cholinesterase activity and causing associated symptoms (vertigo, nausea, and sweating) lies between 0.15 and 0.20 mg a.i./kg body weight. The symptoms

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reverse 0.5 hours after dosing, and whole-blood cholinesterase activity is restored in 4 hours. Repeated ingestion of 0.1 mg a.i./kg body weight at hourly intervals does not cause symptoms.

Bendiocarb ingested at a rate of approximately 0.12 mg/kg body weight was rapidly eliminated (99%) in the urine of a male volunteer in 22 hours; the plasma half-life was estimated as 3.5 hours. Dermal absorption was low but enhanced by occlusion of the skin (7).

Bendiocarb is an extremely effective insecticide and consequently can be used at low concentrations. When applied at 0.4 g a.i./m², it has been found to be effective as a residual insecticide for the control of malaria vectors. The lack of any visible deposit and odour at this rate of application makes it acceptable to the householder.

After a preliminary evaluation of bendiocarb in which a spray was prepared from a 5% water-dispersible powder, a trial was carried out in Central Java with the collaboration of WHO, the national government, communities, and industry. For safety reasons pre-weighed sachets containing 80% bendiocarb water-dispersible powder were used. All surfaces up to a height of about 3 m were sprayed, and spraying lasted 12 days. Protective clothing consisted of an overall that was laundered daily and a broad-brimmed hat. Spraymen also wore ankle-length canvas shoes and were provided with gauze face-masks. Safety assessment of the spraymen consisted of: (a) medical surveillance for signs and symptoms of carbamate poisoning, (b) measurement of whole-blood cholinesterase activity, (c) collection of urine for analysis of bendiocarb metabolite levels, and (d) estimation of the total dermal exposure using pads as outlined in the standard protocol.²

To determine the level of absorption of insecticide, urine collections were obtained from some villagers for 24 hours after they had returned to their sprayed homes.

During the first day of spraying, one sprayman developed signs of acute intoxication, i.e., excessive salivation, vomiting, and headache. Although his whole-blood cholinesterase was found to be 62% of baseline, he recovered spontaneously in less than 3 hours. One other sprayman developed a unilateral miosis after a drop of spray fell into his eye; his eye returned to normal after 2 hours.

² See footnote on page 10.
There were no other complaints of adverse effects from spraymen or from village residents.

Several spraymen had asymptomatic, slight to moderate inhibition of whole-blood cholinesterase activity, with a mean value of 87% of pre-exposure levels.

The calculated dermal exposure for a full day's spraying (4.5 hours) ranged from 6.1 to 157 mg with a mean of 31.8 mg. The mean urinary excretion of bendiocarb equivalent (measured as 2,2-dimethyl-1,3-benzodioxol-4-ol) was 0.94 mg. Maximum excretion of 10.4 mg occurred in the intoxicated sprayman previously mentioned. A good correlation was observed between the amount of bendiocarb applied by the spraymen (mean 47.4 g a.i. daily) and both the extent of cholinesterase inhibition (mean reduction of 31.8% after 4.5 hours of spraying) and the amount of bendiocarb equivalent excreted in the urine (mean 0.94 mg daily). In the urine samples collected from the villagers, excretion of bendiocarb equivalents was quite variable, ranging from non-detectable (less than 0.01 mg) to 1.98 mg; 5 samples exceeded 1 mg. As the collection of urine may have been incomplete, these figures must be regarded as conservative.

Several small ducklings were poisoned during the trial, indicating their high susceptibility to bendiocarb.

The results of these trials demonstrated that bendiocarb may be safely applied by trained personnel using adequate precautions, a rate not exceeding 0.4 g/m², and pre-weighed sachets. The Committee considered that the use of sachets containing 80% bendiocarb water-dispersible powder reduced handling in the field (bagging) and was a major contribution to overall safety. As with other carbamates, monitoring exposure by measuring cholinesterase activity is impracticable.

2.4 Insect growth regulators

The term “insect growth regulator” is sometimes used in a restricted sense to mean insect juvenile hormones and their analogues but usually means all compounds that regulate insect growth. Three main classes are now recognized: (a) juvenile hormones and their analogues; (b) chitin-synthesis inhibitors; and (c) certain triazine compounds.

In addition, some butyl-substituted phenols and certain carbamates have produced morphogenetic effects on mosquitoes and
flies similar to those of juvenile hormone analogues, but apparently none has been developed commercially.

Insect juvenile hormones are terpenoids. Some plants produce terpenoids that show hormonal activity in insects; thus, a terpenoid called "the paper factor" found in the balsam fir is a naturally occurring analogue of insect juvenile hormone. Structurally, the synthetic compound methoprene is more like the juvenile hormones produced by insects than "the paper factor". Methoprene and the naturally occurring insect juvenile hormones are both rapidly metabolized. This is not necessarily true of those synthetic analogues that contain nitrogen, a benzodioxole moiety, or, in particular, chlorine substitutions; the metabolism of such compounds must be tested individually.

Each immature insect larva has an absolute requirement for juvenile hormones if it is to pass through the usual stages of development. Then, in order for the larva to metamorphose into a sexually mature adult, the concentration of the hormone must become very low. If an analogue is administered during the last larval stage, the insect cannot form a pupa and eventually dies. In insects subject to selection pressure by analogues of juvenile hormones, resistance to these compounds has been associated with a marked increase in mixed-function oxidases. In separate experiments it has been shown that mixed-function oxidases of houseflies are controlled genetically, and thus the basis for resistance to juvenile hormone analogues becomes clear.

2.4.1 Methoprene

The chemical and physical properties of methoprene, its toxicity, and the precautions that should be associated with its use have been reviewed in a WHO/FAO data sheet.1 The growth regulatory action of the compound, its impact on non-target species, its stability in soil, water, and living organisms, and the tendency of target organisms to develop resistance to it have been reviewed at much greater length by Mian & Mulla (8).

Methoprene is a juvenile hormone analogue with remarkably little difference from known, naturally occurring juvenile hormones. Even under laboratory conditions, it is selective, affecting some

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insect larvae far more than others. Methoprene is stable during storage and under certain environmental conditions. However, the fact that it is subject to chemical and biological decomposition in water, especially at high temperatures, and that it is destroyed by sunlight, undoubtedly contributes to the specificity of the compound under actual conditions of use. The compound has practical value for control of flood-water mosquitoes and of fleas, and slow-release formulations of methoprene have given good control of *Aedes aegypti* that breed in containers when it is applied at 1 mg a.i./litre.

A feature that makes methoprene so attractive for public health use is its extremely low toxicity. The oral LD₅₀ for dogs is 5000–10 000 mg/kg body weight, and for rats it is even higher, i.e., 36 000 mg/kg body weight. Rats remained healthy and reproduced normally through three generations while maintained on a dietary level of 2500 mg of methoprene per kilogram of feed. The results of studies of the dermal and inhalation toxicity of methoprene in animals are equally favourable. Appropriate studies have indicated that methoprene is not irritating, sensitizing, neurotoxic, mutagenic, carcinogenic, or teratogenic.

The only forms of wildlife that have shown adverse effects under conditions resembling those in the field are insects and crustaceans. The Committee considered that, because of its extremely low toxicity to mammals, methoprene can be safely added to drinking-water at a rate of 1 mg a.i./litre.

2.5 Biological control agents

A review of biological agents for vector control, and recommendations for their development and potential use, have been given in the sixth report of the WHO Expert Committee on Vector Biology and Control (9). Substantial support has been given to WHO Collaborating Centres to carry out safety testing of promising microbial control agents and to develop standard protocols for such tests.

Unlike the situation with most chemical pesticides, the developmental research and safety testing of biological control agents are performed mostly by non-industrial institutions. Many scientists have argued for some time that the test protocols developed for chemical pesticides are inappropriate for microbial control agents. A new approach in safety testing of biological control agents was discussed at a consultation held in Geneva in
1980 under the auspices of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The Committee considered that the proposals for safety evaluation in the WHO Memorandum published after this consultation (10) are adequate.

Although many aspects of the safety evaluation of microorganisms are based on the principles and methods developed for chemical pesticides, important additional studies are required, e.g., infectivity for non-target species, including mammals. The evaluation of immunological response to proteins associated with microbial agents is also very important. As pointed out in the WHO Memorandum (10), there is a pressing need to develop suitable standard protocols for studying the possible immunological effects of microbial control agents since they may become more widely used in public health and agriculture.

2.5.1 Present status of safety testing

An in-depth review of the present status of developmental research within and outside the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases was undertaken at the seventh meeting of the Scientific Working Group on Biological Control of Vectors, which met in March 1984.\(^1\) Among several biological agents being developed for vector control, the Committee noted that one, *Bacillus thuringiensis* serotype H-14, was already commercially available and that production of another, *Bacillus sphaericus*, was being considered.

Extensive studies have been carried out with *B. thuringiensis* H-14\(^2\)\(^-\)\(^3\) and *B. sphaericus* (11).\(^4\) *Bacillus thuringiensis* has passed safety tests for operational use and *B. sphaericus* for application in


The above documents are available from the Division of Vector Biology and Control, World Health Organization, 1211 Geneva 27, Switzerland.
large-scale field trials. Safety evaluation included tests for: acute infectivity by oral, intraperitoneal, and intracerebral routes of application; dermal and ocular irritation; and acute inhalation and allergy. In addition, an aqueous solution of the *B. thuringiensis* H-14 endotoxin, when tested *in vitro* with and without an activation system, had no mutagenic or toxic effects on *Salmonella typhimurium*.¹ A review of the information on the safety of *B. thuringiensis* H-14 for non-target organisms, including man and other vertebrates (as well as insects of economic importance such as silkworms), was recently issued.² In view of the favourable results, the Committee recommended that the development of these agents for vector control should proceed.

The Committee considered that the addition of live microorganisms to drinking-water is undesirable. Accordingly, only the asporogenic form of *B. thuringiensis* H-14 should be used to control *Aedes aegypti* in vessels containing drinking-water.

2.5.2 Issues raised by the development of new mutants and by genetic engineering

Advances in genetic engineering have resulted in new methods of producing the *B. thuringiensis* H-14 toxin—even from different organisms. Modern techniques make it possible to characterize the toxin entomologically and immunologically and to determine its chemical structure. The Committee considered that variants of *B. thuringiensis* (including the asporogenic strain) producing the same toxin would not require additional safety evaluation. However, a strain producing a modified toxin, possibly with altered biological activity, would require some additional evaluation of the live microorganism and full safety evaluation of the toxin. When the toxin-producing gene is transferred to another microorganism (e.g., *Escherichia coli*), complete safety evaluation would be required. Similar principles would apply in the examination of new isolates, and monitoring of exposed populations would be essential.


The above documents are available from the Division of Vector Biology and Control, World Health Organization, 1211 Geneva 27, Switzerland.
3. REVIEW OF SELECTED COMPOUNDS FOR CONTROL OF RODENTS AND MOLLUSCS OF PUBLIC HEALTH IMPORTANCE

3.1 Rodenticides

The safe use of rodenticides in public health was discussed by an Expert Committee in 1972 (12). That Committee emphasized the safety of warfarin-type rodenticides, but discussed in greater detail the acute rodenticides.

3.1.1 Anticoagulant rodenticides

The development of widespread resistance to warfarin and other classical rodenticides has led to the development of a second-generation of anticoagulants that are potent toxicants and effective against warfarin-resistant strains. A particular advantage is that such compounds are slowly metabolized and excreted in rodents, and this prolongs the inhibition of prothrombin synthesis so that a toxic dose may be ingested even at a single feeding.

Phytomenadione (vitamin K₁) remains an effective antidote for cases of human intoxication with either first- or second-generation anticoagulants, but it may take time to become effective and prolonged therapy may be required to avoid hypocoagulation. For emergency treatment, transfusion of even a small volume of cross-matched blood or plasma may be effective.

Three second-generation anticoagulant rodenticides are commercially available: brodifacoum, bromadiolone, and difenacoum. These compounds inhibit prothrombin synthesis and cause bleeding, which may be occult. They are primarily absorbed from the gastrointestinal tract but dermal absorption is possible. Although highly toxic, they are not hazardous to man when used in baits at low concentration (e.g., 100 mg/kg of bait); however, concentrated forms are particularly hazardous and their availability should be restricted. Only trained personnel should prepare the baits, which should contain a suitable marker-dye. To prevent contamination, the baits should not be used in domestic, public, or industrial situations where they can come into contact with food or water, and unnecessary distribution into the environment should be avoided.
Anticoagulants are relatively selective in their action, usually because of differences in behavioural reaction to the bait and the greater body-size of the non-target species rather than because of their intrinsic toxicological properties.

3.1.2 Acute rodenticides

The safety and effectiveness of acute rodenticides have previously been discussed \((12, 13)\). In general, they are less selective than anticoagulants. Nevertheless, acute rodenticides are widely used (especially against warfarin-resistant strains) because of their efficacy, low cost, and availability.

Although pyrifenuron is effective against rodents resistant to anticoagulants, there are marked species differences in its toxicity and, unfortunately, man is susceptible. Reports of severe autonomic and peripheral neuropathy, diabetes mellitus, and death after ingestion of pyrifenuron appeared soon after its introduction in the mid-1970s. In view of the established danger to human health, the Committee recommended that pyrifenuron should not be used. However, zinc phosphide, another acute rodenticide, continues to be effective and has a good safety record.

3.2 Molluscicides

In 1972, the WHO Expert Committee on Insecticides discussed the safety aspects of niclosamide, trifenmorph, Yurimin, and organotin compounds \((12)\). Since then, the use of organotin compounds to control the snail hosts of *Schistosoma* spp. has been developed further.

3.2.1 Tin compounds

Although inorganic compounds of tin are widely distributed in nature, organotin compounds rarely occur naturally. No conclusions about the toxicity and safety of organic tin compounds can be drawn from experience with inorganic tin compounds.

Organotins have been found to produce gastrointestinal disturbances, tremor, convulsions, paralysis, and death in animals, but their actual mode of action remains unknown. Closely related organotin compounds can have markedly different toxic effects; for example, trimethyltin causes neuronal necrosis in certain areas of the
brain, triethyltin causes oedema of the central nervous system, and
diethyltin causes hypertrophy of the bile duct in some species.
Similarly the same compound may be highly toxic to one species and
essentially harmless to another; for example, dibutyltin is highly
toxic to rats but not to guinea-pigs. The tetraorganotin compounds
are also particularly hazardous since they are rapidly metabolized
to the triorganotins, and are lipid-soluble and volatile.

Triorganotin compounds have some importance as fungicides,
and they have been proposed as insecticides or anti-feeding
compounds for insects. So far, their use has not led to reports of
serious side-effects. However, any tin compounds prepared for use
as a pesticide should be studied with particular care because (a) their
mechanism of action is not understood and (b) they are easily
absorbed.

Bis(tributyltin)oxide. The chemical and physical properties of
bis(tributyltin)oxide, its toxicology, and the safety precautions
necessary for its use have previously been reviewed.¹

Bis(tributyltin)oxide is highly toxic, its intravenous LD₅₀ for mice
being 6 mg/kg body weight, and its intraperitoneal LD₅₀ for rats
being 7.2 mg/kg body weight. Oral absorption is moderately
efficient, this being indicated by the fact that the oral LD₅₀ values
in mice and rats are only about 10 times greater than the
Corresponding intravenous or intraperitoneal values. Dermal
absorption is less efficient, as is indicated by LD₅₀ values of 900 mg/
kg and 11 700 mg/kg body weight in rats and rabbits respectively.
The compound is highly irritating to the eyes, and its systemic
toxicity by this route approaches that by the intravenous route.

When fed to rats for 30 days, a dietary level of 320 mg/kg of feed
led to marked refusal of food, loss of body weight, and death. At
a dietary level of 100 mg/kg of feed, growth was suppressed even
though food consumption was normal.

Animals poisoned by single or repeated small doses of
bis(tributyltin)oxide die of respiratory or cardiac failure, often in
coma. The compound prevents energy conservation by
mitochondria by several mechanisms and it affects other enzyme
systems also. However, it is not known for certain how these
biochemical changes are related to specific symptoms and to death.

¹ Data sheet on pesticides, No. 65. Bis(tributyltin)oxide. Unpublished WHO/
FAO document VBC/DS/85.65 (1985); available from the Division of Vector Control
and Biology, World Health Organization, 1211 Geneva 27, Switzerland.
Most ingested bis(tributyltin)oxide is excreted unchanged in the faeces; however, some is absorbed and is either metabolized or enters the enterohepatic circulation. Initial excretion of $^{14}$C-labelled compound by mice has a half-life of 1–2 days, but later excretion of the material in the enterohepatic circulation has a half-life of 3–4 weeks. The highest concentration of bis(tributyltin)oxide is found in fatty tissue.

Bis(tributyltin)oxide was found to be mutagenic in tests using Drosophila and mammalian cell cultures. Six-month dermal application tests for carcinogenicity in mice were negative for both bis(tributyltin)oxide and tributyltin fluoride (a closely related compound), but long-term studies are necessary before these results can be confirmed. An oral carcinogenicity study in rats is currently in its final stages.

The effect of the compound on reproduction, including possible teratogenic effects, remains to be explored.

There are no reports of human illness associated with the use of bis(tributyltin)oxide as a mollusicide. In the rubber industry it has produced severe eye irritation as well as irritation of the upper and, to a lesser degree, the lower respiratory tract without any change in pulmonary function. Application of undiluted compounds to the hands of volunteers produced follicular inflammation and pustules that usually healed within seven days.

Bis(tributyltin)oxide is toxic to a wide range of organisms, but it has been suggested that a concentration of 0.0001 mg/litre would be safe for fish.

Bis(tributyltin)oxide is being considered for use as a molluscidic in slow-release formulations only. Although it is soluble in water to the extent of 100 mg/litre, it is rapidly adsorbed by surfaces, especially those of organic matter. It may be that the compound is more effective for snail control when adsorbed on surfaces than when it is in solution. From field studies it seems that the concentration required to kill snails is safe for fish.

The Committee concluded that studies are needed to find out the range of concentrations of bis(tributyltin)oxide in water under different conditions of use. These studies should give additional information on the effectiveness of the compound for control of schistosomiasis and should determine levels of possible human exposure and thus assess its safety before it is used on a large scale. Studies of its effects on reproduction should also be performed.
4. PROTECTION OF PEOPLE WHO USE PESTICIDES

It is well known that spraymen (and other applicators) are at risk from pesticides and that they must take adequate safety precautions. There is little risk to the occupants of treated houses if pesticides are applied properly. However, an increasing number of protective methods and devices, e.g., repellents, bednets impregnated with insecticides, mosquito coils, and fumigation mats, are used by individuals and by families. The amount of chemical exposure associated with the use of such devices needs to be evaluated, and an education programme to reduce possible risks should be implemented at various levels.

4.1 Personal protection against exposure to pesticides used in agriculture and public health

Personal protection can minimize or even eliminate a possible hazard, and is vital when handling, mixing, or applying pesticides. Although the use of protective clothing and other safety devices offers considerable protection, other precautions are still necessary —especially personal hygiene. Although the Committee was aware that recommendations to implement relevant safety measures and to protect workers exposed to pesticides have been made by previous Expert Committees (3, 12, 14), it felt that the topic should be discussed again because compliance with earlier recommendations had been poor.

Unfortunately, ideal protective clothing that is cheap, cool, flexible, easy to wear and, at the same time, fully protective is not available. Truly impermeable materials are usually thick, heavy, uncomfortable to wear, and expensive; they may even prove impossible or even dangerous to wear under hot and humid conditions. Cotton fabric appears to be more suitable than other materials since it is absorbent, easily washed, and offers sufficient protection to the skin.

All protective equipment including clothing, wide-brimmed hats, gloves, boots, aprons, and face-shields should be thoroughly and regularly washed with soap and water. Whenever possible, clothing should be washed immediately after work or exchanged for clean work-clothes (supplied by employers or other authorities) for the next day’s work.
Personal hygiene is particularly important and should be encouraged by the provision of soap and water as near as possible to the place of work.

Whatever personal protection is considered essential for the application of a particular pesticide, education and guidance are necessary to explain to the workers why these precautions are required and the probable consequences of non-compliance.

4.2 Safety of repellents and/or insecticides used for personal protection

Personal protection against contact with insects is of major importance in integrated vector control. Such protection may include the use of repellents, bednets, mosquito coils, and fumigation mats. These devices should be suitable for widespread use without any special restrictions, and they should be so manufactured that their proper use does not pose any hazard to users. However, there may need to be restrictions on the use of the technical materials in the manufacture of these protective devices.

4.2.1 Repellents

Chemicals with repellent properties may be applied directly to the skin, clothing, or bednets. It has even been suggested that they be applied to the walls of homes to repel mosquitoes. If a repellent is to be used on the skin its dermal toxicity must be practically zero. This may be achieved if the intrinsic toxicity of the active material is very low, if its dermal absorption is negligible, or if its concentration in the preparation is extremely low. If a repellent causes skin irritation it is unsuitable for dermal application.

Each repellent should be tested according to generally accepted principles for compounds intended for wide domestic use. The fact that registered repellents are used by small children and pregnant women should be taken into account when assessing their safety. Potential allergenic properties of repellents should also be considered.

Diethyltoluamide (deet) has long been known as a repellent of biting insects. It is used widely in preparations that are applied to the skin at a concentration of 500–1000 g/litre. All exposed parts of the body such as the legs, arms, face (excluding the eyes), ears, and neck should be treated. Deet feels less oily on the skin than other
repellents and is sufficiently effective to permit some dilution with alcohol, which increases its cosmetic acceptability. Specifications for deet have been established by WHO (15). Other repellents applied to the skin are dimethyl carboxylate, dimethyl phthalate, ethohexadiol, and butopyronoxyl.

Repellents are used primarily in situations where other chemical control methods are not feasible and where individual protection is essential. In addition to the above, the following compounds are known to have repellent properties: benzyl benzoate, butyl ethyl propanediol, chlorodiethylbenzamide, alicyclic carboximides of heterocyclic amines, and permethrin.

Repellents applied to the skin are effective for only a few hours. However, if clothing is impregnated with repellent the duration of effectiveness can be increased to several weeks.

Deet and butopyronoxyl are applied to clothing to repel ticks. Benzyl benzoate and dibutyl phthalate, alone or in combination, are the best repellents for treating clothing because they are the only compounds that can withstand leaching by water and remain effective after the clothing has been washed once or twice. The standard rate of impregnation is 20 g/m², or 70 g of active ingredient for a jacket (or shirt), trousers, and socks.

When a chemical is applied to clothing, contact with the skin is only indirect; the degree of absorption through the skin, if any, is therefore considerably less than with direct applications. Taking into account the generally low dermal toxicity of these chemicals, it is unlikely that impregnated cloth should pose any hazard to the wearer.

The Committee concluded that the use of repellents should be encouraged only when their efficacy and safety have been established. There is no indication that the chemicals currently in use are harmful under ordinary conditions. The Committee therefore recommended the establishment of specifications for compounds other than deet, and expressed the opinion that the use of traditional repellents such as citronella should be explored.

4.2.2 Impregnated bednets

The effectiveness of cheap personal protection devices such as bednets is increased if they are impregnated with a repellent or an insecticide. Both types of compound should be of very low toxicity to mammals. Recently, the use of permethrin to treat bednets has
been suggested. To achieve the uniform distribution of up to 200 mg of permethrin per square metre of fabric, the bednet should be soaked in an appropriate concentration (usually about 1%) of the compound that has been made up from an emulsifiable concentrate. Preparation of the dilute formulation requires handling permethrin concentrate, and care should be taken to avoid overexposure. It should be the responsibility of local authorities to ensure that the treatment of bednets is carried out safely.

Properly treated bednets should pose no hazard to those who use them. The acute oral toxicity of permethrin in aqueous solution for rats is very low, the LD₅₀ being over 4000 mg/kg. Dermal toxicity is so low that it could not be demonstrated. Permethrin has a very low vapour pressure and hardly evaporates. In addition, the total amount of permethrin applied to a bednet usually does not exceed 1 g, an amount that is highly unlikely to cause any harm to man.

4.2.3 Mosquito coils

There are many different brands of mosquito coil, but most are produced to smoulder for 7–10 hours under normal conditions of ventilation. The content of active ingredient depends upon the brand; for example, two coils that are commercially available in different countries were found to contain 1.9–3.1 g/kg of pyrethrins and 70–130 g/kg of DDT, respectively. Many coils now contain synthetic pyrethroids such as bioallethrin and (S)-bioallethrin. Mosquito coils are usually used at night for individual protection against biting mosquitoes, a smouldering coil being placed under the bed. The coils are also quite extensively used in the evenings to protect people sitting in rooms or on a veranda.

Whether inhalation of the fumes produced by a smouldering coil has any toxic effects depends upon the chemical composition of the device. Generally, the extent of exposure is rather modest. In an ordinary sleeping-room that is not specially insulated, with the door and the windows closed, the rate of air exchange is at least once an hour. In the tropics, air exchange may be 10 or more times faster. Thus ventilation, together with the size of the room and the concentration of insecticide in the coil, should be taken into account when calculating the degree of exposure. However, mosquito coils release other noxious by-products when burnt, and exposure to these, as well as to insecticides, should be considered when assessing their safety.
The Committee considered that, as far as the pesticides discussed above were concerned, there should be no chance of users suffering from overexposure if the devices were used in the recommended ways. The Committee recommended that non-insecticidal constituents should be such that when burnt they do not produce fumes that may pose a threat to human health.

4.2.4 Fumigation mats

The fumigation mat is a relatively recent product that is rapidly replacing the use of mosquito coils in rooms where there is an electrical supply to operate them. Whether or not fumigation mats are as entomologically effective as mosquito coils is not known, but sales promotion is certainly making them more fashionable than coils.

The active ingredients in fumigation mats are synthetic pyrethroids such as bioallethrin and (S)-bioallethrin which are discharged into the atmosphere as a vapour over an 8-hour period at average concentrations of 0.2 and 0.1 mg/m³, respectively. Unlike the smouldering mosquito coils which release a relatively uniform dosage, the active ingredients of fumigation mats are discharged unevenly during the 8-hour period, rising to a maximum shortly after a mat heats up and then tailing off.

The Committee agreed that the use of bioallethrin and (S)-bioallethrin in fumigation mats was unlikely to present significant toxicological problems to the user.

4.2.5 Aerosols

The types of insecticide used in hand aerosol-sprays and their low concentration should pose no hazard to man under normal conditions. However, natural pyrethrin present in such sprays may occasionally cause respiratory problems in people who have become sensitized. Other known problems of pressurized hand-sprays are related to the propellants and not to the insecticides.

The addition of perfume to mask the insecticidal odour may in some instances result in misuse of aerosols.

The Committee was of the opinion that all household pesticide sprays should be registered.
4.3 Education in use of protective measures

Inevitably, all vector control measures involving the use of pesticides and repellents are potentially hazardous to the population. The risks are minimal, but the community must be aware that they exist, and they should be instructed in the basic, simple precautions that are necessary to reduce exposure. This is especially important with increasing community participation in vector control. Information on the safe use of pesticides will be useful not only in vector control but also in agriculture.

In this respect the role of primary health workers is of the utmost importance. These health workers are drawn from the community and are given a standard course of education and training that enables them to work at the primary health care level; their work is mainly preventive. The technical information given to them must be simple, practical, and well-formulated, and it must allow them to grasp the basic concepts of the use of pesticides in public health and agriculture. (An extract from the syllabus for training Sudanese community health workers in the prevention of pesticide poisoning is given in Annex 2.)

4.4 Education in the selection, legislation, and safe handling of pesticides

In recent years, there has been a growing realization that education regarding protective measures in pesticide application cannot be confined to the upper echelons of ministries of health and agriculture but must be given at all levels. While international efforts to this end are increasing, it is clear that more work still has to be done.

National multilevel courses on the safe use of pesticides have been introduced in a number of countries. Such courses in Egypt, Oman, and Sudan (in Arabic); Nigeria and the Republic of Korea (in English); Pakistan (in Urdu); Brazil (in Portuguese); and in a number of South and Central American countries (in Spanish) were based on a WHO document available only in connection with the establishment of national courses.¹ Similar courses are organized by FAO.

A course on the safe use of pesticides is being prepared by the World Bank, and other courses, based on an agromedical approach to pesticide use, have been given by the Universities of California and Miami and by the Oregon Consortium in Indonesia and in the Caribbean. The Tropical Development and Research Institute, United Kingdom (formerly the Tropical Products Research Institute) has also been involved in training in several countries. This list is not exhaustive and many other similar courses could be added.

Among the many booklets that have been prepared by national and international organizations, those issued in English, French, and Spanish by the International Group of National Associations of Agrochemical Manufacturers (GIFAP) are noteworthy. These include: *Guidelines for the safe handling of pesticides during their formulation, packing, storage and transport, Guidelines for the safe and effective use of pesticides, and Guidelines for emergency measures in cases of pesticide poisoning*.

A manual on prevention, diagnosis, and treatment of insecticide poisoning for use by primary health workers has recently been produced and widely distributed by the Division of Vector Biology and Control, WHO. The Committee felt, however, that it should be revised to include more pesticides.

A rather different type of training may be needed in the future since many countries now have some form of pesticide registration scheme but lack the expertise to evaluate applications for registration. To some extent, they rely on proof of prior registration in developed countries, but this may not be relevant to the needs of some developing countries, especially in tropical areas. Scientists in registration centres therefore need to be trained so that they can assess the vast number of company reports and statements by environmental and consumer groups that are submitted; training in toxicology is particularly important.

The syllabus should cover the elements of good laboratory practice; the statistical evaluation of results; and the principles of toxicology, which should be specially related to a thorough understanding of the definitions of terms and of dose–effect relationships.

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1 International Group of National Associations of Agrochemical Manufacturers (GIFAP), Avenue Hamoir 12, 1180 Brussels, Belgium.

A course lasting up to 3 months may be required for those with a sound scientific background. Whenever possible the course should be complemented by a visit to an existing national organization for pesticide registration.

The Committee recommended that the development of such training programmes should be given priority.

4.5 Education in toxicology

The growth in the use and transport of potentially dangerous chemicals, including pesticides, has increased the risk of exposure of the community. It is therefore important to increase the number of experts in toxicology, particularly in developing countries.

Courses are available that provide in-depth postgraduate education in toxicology and often give opportunities for research. Few countries can afford the high cost of providing such education, and it would therefore probably be better if courses were organized on a regional basis. Several lists of the courses that are available have been compiled.\(^1\), \(^2\), \(^3\) The Committee recommended that WHO should encourage toxicological education of suitably qualified scientists from developing countries. The establishment of professorships in toxicology in leading universities to promote awareness of the subject and of related disciplines would help in the recruitment and training of scientists who, in turn, would be able to give advice to the community on the safe use of new chemicals.

5. PREVENTION AND TREATMENT OF POISONING

5.1 The WHO Recommended Classification of Pesticides by Hazard, and Guidelines to classification

Since it was first adopted by WHO in 1975, The WHO Recommended Classification of Pesticides by Hazard has become

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\(^3\) LAURER, R. Survey of training programmes in toxicology and of toxicology courses in ten countries within the European Region. Copenhagen, WHO Regional Office for Europe, 1982 (unpublished document).
widely accepted (16). It was subsequently adopted by the Council of Europe, and it is now used as a basis for pesticide control in many developing countries, including a consortium of American countries. It was recommended for use by the FAO Second Government Consultation on International Harmonization of Pesticide Registration Requirements, held in Rome in October 1982.1

Guidelines to classification, which includes tables and explanatory notes, first appeared in 1978 and replaced an annex of examples in the original classification. Since then, it has been revised four times. The most recent edition has been issued in a new format, and now covers 554 compounds, together with 85 national synonyms.2 It is clear that Guidelines to classification needs to be revised regularly at approximately 18-month intervals. The WHO Recommended Classification of Pesticides by Hazard is based on acute hazards only. Suggestions have been made in the past that the definition by “hazard” should be extended to include other types of risk, such as carcinogenesis. The Committee decided not to do so. However, in view of repeated requests, it recommended that the following paragraph be included in Guidelines to classification.

“While the classification deals only with the acute risk to health, evaluations of chronic effects, including cancer, have been completed for many compounds for registration purposes. The results are noted in the ‘Remarks’ column. With the exception of arsenous oxide, none of the technical products listed in Tables 1–5 is known to be carcinogenic for man.”

5.2 Packaging, labelling, and storage of pesticides

Packaging, labelling, and storage should be given particular attention by those responsible for the efficient and safe use of pesticides. Pesticide poisoning would be greatly reduced if packaging, labelling, and storage practices met specific safety requirements.


The Committee noted that the Second Government Consultation on International Harmonization of Pesticide Registration Requirements, in which WHO participated, dealt with these subjects.\footnote{See footnote 1 on page 38.} After the consultation, FAO published guidelines on the packaging and storage of pesticides (17), labelling practice (18), and the disposal of surplus pesticides and pesticide containers (19).

WHO has recommended labelling requirements for each technical product or pesticide formulation for which specifications have been issued (15). They include minimal cautionary notices which should be shown on the label. These notices are continuously reviewed and updated (20).

5.2.1 Packaging

The packaging of pesticides must withstand transport, handling, and the climatic and storage conditions to which they will be exposed. Specifications for packaging are therefore not limited to the transport period and the associated handling, but must ensure the integrity of the container for the whole period from packing by the manufacturer to the application of the pesticide in the field. The packaging of pesticides should be strong enough to resist breakage or leakage for at least two years when stored under adverse conditions, such as those found in the tropics. Metal drums are generally better than other types of packaging; however, great care must be taken to prevent them from rusting if they are exposed to a wet climate for a long time. In addition, the protective coating inside the drum must not deteriorate during storage. Drums must be tightly sealed to avoid leakage and evaporation of solvents. The use of barrels with tops sealed with ring clamps should be discouraged because the tops are easily loosened during transportation. Drums should always be used for emulsifiable concentrates.

As a rule glass containers should not be used for bulk shipment of pesticides.

It is recommended that the size of containers should be limited to that which can be easily lifted (when full) by one man. Experience has shown that 20- and 40-litre containers arrive with little or no apparent damage whereas 250-litre drums are often badly dented.
Water-dispersible powders for public health use must be packaged in moisture-proof plastic bags to maintain their good suspensibility for use in pressurized spray tanks.

In some countries, formulations are repacked locally into smaller containers for domestic or agricultural use. Repacking must be subject to regulations to avoid poisoning of workers and mislabelling of packages. The new packaging must be of sufficient quality to prevent leakage or adulteration of the product.

5.2.2 Labelling

Proper labelling is essential to the safe use of pesticides. Careful attention should be paid to the design, content, and quality of labels to ensure that they will easily be understood by users. As a rule, appropriate labelling is mandatory and part of national registration requirements.¹

As an absolute minimum, a label must give information on the product itself, i.e., approved name and content of active ingredient, proprietary name, net weight of contents, batch or reference number, date of manufacture, name of manufacturer, and a reference to WHO or FAO specifications (20).¹ It must also give information on the toxicity of the product, its safe use, and the emergency treatment of poisoning. Minimal cautionary notices are given in WHO’s Specifications for pesticides used in public health (15).

It was suggested that the date of manufacture should be printed in large bold letters, in indelible ink, on the top of containers as well as on the side. The Committee recommended that pesticide labels should include the hazard class of the contents given in The WHO Recommended Classification of Pesticides by Hazard in addition to any internationally or nationally required symbols.²

Labels must be printed in a language—or languages—that will be understood by users and those responsible for safe handling and transport of the pesticide. Use of graphics may prove useful to instruct illiterate workers in the safe use of the contents of the package.

The same stringent regulations for labelling should be applied when pesticides are repacked locally into smaller containers.

¹ See footnote 1 on page 38.
² See footnote 2 on page 38.
The Committee recommended that further studies should be carried out on the techniques and effectiveness of using graphics for labelling pesticide containers.

5.2.3 Storage

It is not uncommon for pesticide containers to be unprotected from the weather for long periods during trans-shipment or storage. Such exposure should be kept to an absolute minimum.

As pesticides are valuable but hazardous commodities, facilities should be made available for their safe and secure storage. Proper facilities should be constructed for central as well as regional storage of full pesticide containers and of empty containers awaiting disposal. The containers should not be in direct contact with the ground, and should be stored at a level that is high enough to avoid flooding. They should be protected from the sun and rain by a roof or other impervious covering.

Volatile pesticides must always be kept separate from other pesticides to avoid cross-contamination, and be stored in a well-ventilated area.

The storage area should be inspected regularly, and the general public should be prevented from entering it by means of a secure fence or by guards.

Clean-up operations and decontamination should always be done quickly and safely; the necessary equipment for the control and clean-up of leaks from containers should be kept at hand. Information on decontamination procedures, if not provided, should be sought from the manufacturer.

Owing to the dangers of pesticide fires, special attention should be given to their prevention and control. Protective and safety equipment, such as protective clothing, respirators, and fire blankets, should be readily available and maintained in serviceable condition. All employees should have access to qualified medical aid and should be trained in safety procedures.

5.3 Disposal of pesticides

All countries that use pesticides should keep under review the adequacy of their facilities for handling and disposing of hazardous wastes; these facilities should include an incinerator capable of
destroying various toxic chemicals and at least one hazardous-waste disposal site.

Many countries are faced with the problem of disposing of large quantities of unusable pesticides. The principal means of disposal are burning and burial. In arid climates burial is probably the safest method because the risk of leaching or flooding is minimal; in tropical zones with abundant rainfall burning is advisable.

The possibility of storing unwanted pesticides in impervious containers in disused mineshafts or burning them in cement kilns should be investigated.

National authorities should make available information on established methods for disposal and their effectiveness, and should develop systems for the disposal of unwanted pesticides, if necessary in collaboration with international agencies.

5.4 Disposal of used containers

The cleaning and disposal—or recycling—of pesticide containers is a serious problem in developing countries. Some practical guidelines for container disposal have been proposed; however, in some countries, certain conditions make it difficult to follow the guidelines. For example, in many developing countries, metal containers are extremely useful for many different purposes and therefore tend to be retained by the community. In most cases, people do not recognize the dangers they face in reusing these containers, even if the risks of poisoning are clearly indicated on the label in the local language. Another major problem is that few developing countries have the necessary facilities to clean and recycle containers.

Most of the pesticides that are used in developing countries are packaged in metal, glass, paper, or plastic containers. Paper or plastic containers holding solid formulations should be shaken to ensure that all the contents are emptied into the spray solution. Small quantities of empty paper or plastic sacks should be burnt on site, or collected and brought to a central storage area for subsequent burning or burial. Glass or rigid plastic containers should be crushed and then buried or disposed of in conventional landfill sites or dumps.

As the first step in decontamination, used metal containers should be rinsed as soon as they are emptied; whenever possible, the rinsate should be used as a diluent for the next spray solution or safely
disposed in a soak-pit. This simple step will usually reduce the residue in a drum to less than a few grams of active ingredient so that, in most cases, it no longer presents an acute toxic hazard.

The rinsed containers should be resealed, collected, and brought to a secure storage site at the end of each day. Unless the containers are stored securely, they will almost certainly “disappear”, and be used for a multitude of purposes by the local people.

National authorities should investigate systems for providing an incentive to ensure the safe disposal of metal containers.

WHO has carried out some studies to evaluate a simple method of decontaminating metal drums. Drums that had contained emulsifiable concentrates of different pesticides were filled with water and allowed to stand for 24 hours before being emptied; the process was repeated three times, and samples were taken from the third rinse. The results of these preliminary studies are shown with some extrapolations in Table 1.

It must be emphasized that results have been obtained for only a few compounds and that they may not apply to other pesticides. The Committee recommended that WHO, in collaboration with industry, should promote further studies on decontamination of used containers, and that the results should be made available to national authorities. To speed the acquisition of this information, national authorities should make decontamination tests one of the requirements for registration of new formulations.

5.5 Treatment of pesticide poisoning

There are very few specific antidotes for the treatment of pesticide poisoning and, in some countries, those that do exist are not readily available. The Committee was of the opinion that antidotes should be routinely available wherever pesticides are used and that every effort should be made to increase their availability.

The treatment of poisoning by organophosphorus, carbamate, and organochlorine insecticides was outlined in an annex to a previous report of this Committee (3). However, in view of the importance of the subject and the use of the information by Member States, the Committee decided that it should be reprinted in this report with the addition of paragraphs on the treatment of poisoning by anticoagulant rodenticides and by paraquat (Annex 3).
<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>Chlorpyrifos</th>
<th>Pirimphos-methyl</th>
<th>Cypermethrin</th>
<th>Permethrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of pesticide in final rinsate</td>
<td>mg/litre</td>
<td>0.31</td>
<td>2.8</td>
<td>0.34</td>
<td>0.12</td>
</tr>
<tr>
<td>No effect level (NEL)*</td>
<td>mg/kg body weight per day</td>
<td>0.03</td>
<td>0.5</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>NEL as % oral LD₅₀ in rats</td>
<td>%</td>
<td>0.022</td>
<td>0.025</td>
<td>0.125</td>
<td>0.125</td>
</tr>
</tbody>
</table>

**Adults** (average weight 40 kg)
Water intake: normal 1.5 litres; maximum 5.0 litres

<table>
<thead>
<tr>
<th>Potential intake of pesticide*</th>
<th>Unit</th>
<th>mg</th>
<th>mg</th>
<th>mg</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>mg</td>
<td>0.47</td>
<td>4.2</td>
<td>0.51</td>
<td>0.18</td>
</tr>
<tr>
<td>Maximum</td>
<td>mg</td>
<td>1.55</td>
<td>14.0</td>
<td>1.70</td>
<td>0.60</td>
</tr>
<tr>
<td>NEL</td>
<td>mg</td>
<td>1.2</td>
<td>20</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

| Potential intake as % NEL      | %    | 39     | 21     | 0.25   | 0.09   |
| Normal                         | %    | 129*   | 70     | 0.85   | 0.30   |
| Maximum                        | %    | 200    | 200    | 200    | 200    |

**Infants** (average weight 3 kg)
Water intake: normal 160 ml/kg; maximum 800 ml/kg

<table>
<thead>
<tr>
<th>Potential intake of pesticide*</th>
<th>Unit</th>
<th>mg</th>
<th>mg</th>
<th>mg</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>mg</td>
<td>0.05</td>
<td>0.45</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Maximum</td>
<td>mg</td>
<td>0.25</td>
<td>2.24</td>
<td>0.27</td>
<td>0.10</td>
</tr>
<tr>
<td>NEL</td>
<td>mg</td>
<td>0.09</td>
<td>1.50</td>
<td>15.00</td>
<td>15.00</td>
</tr>
</tbody>
</table>

| Potential intake as % NEL      | %    | 55     | 30     | 0.33   | 0.13   |
| Normal                         | %    | 278    | 149    | 1.80   | 0.66   |
| Maximum                        | %    | 129*   | 70     | 0.85   | 0.30   |

* NEL based on 2-year feeding studies in rats.
* Calculation of potential intake is based on the assumption that the third rinsate is used as drinking-water.
* NEL reached with intake of 3.5 litres.
6. SUMMARY OF RECOMMENDATIONS

6.1 Recommendations for national authorities

1. In providing guidance for community participation in integrated vector control, governments should consider the safety aspects. Education in the safe use of pesticides in public health and agriculture through primary health care workers and/or agricultural advisers will be required and will need to continue indefinitely. The health of pesticide workers and the efficacy of vector control measures should be monitored concurrently (section 1).

2. On the basis of the results of special trials with bendiocarb (section 2.3), which has relatively high toxicity, and of more recent experience with pyrethroids the Committee recommended that low concentrations of these compounds might be applied safely by trained operators.

3. Permethrin is recommended as safe for aircraft disinsection at a concentration of 0.7 mg a.i./m\(^2\), or as a residual application of 0.2–0.5 g/m\(^2\) (section 2.2).

4. The Committee considered that, because of its extremely low mammalian toxicity, methoprene can be applied safely to drinking-water at a target dose of 1 mg a.i./litre (section 2.4.1).

5. The addition of live microorganisms to drinking-water is undesirable. Accordingly, the use of Bacillus thuringiensis H-14 for control of Aedes aegypti in drinking-water should be restricted to the asporogenous form (section 2.5.1).

6. Second-generation anticoagulants (e.g., brodifacoum, bromadiolone, and difenacoum) are so toxic that they must not be used in circumstances where contamination of food or water may occur. In their concentrated form, these materials should be available only to licensed pest-control operators trained in bait preparation and use (section 3.1.1).

7. The acute rodenticide, pyrinnuron, should not be used in public health or in agriculture (section 3.1.2).

8. Devices impregnated with permethrin or deet that are intended to be used for personal protection should not pose a hazard to users. The safety of treating bednets should be the responsibility of local authorities (sections 4.1 and 4.2).

9. Every effort should be made to provide adequate medical facilities for the treatment of pesticide poisoning and antidotes if they exist (section 1.3.3).
10. Governments should develop national systems for the disposal of unwanted or surplus stocks of pesticide, if necessary in collaboration with international agencies (section 5.3).

11. National governments should investigate systems for providing economic incentives to ensure the safe disposal of metal pesticide containers (section 5.4).

12. Effective, simple methods for the decontamination of durable pesticide containers should be developed. All national authorities should require information on decontamination before new formulations can be registered for use in agriculture or public health (section 5.4).

6.2 Recommendations for WHO

1. The Committee recommended that collaboration between WHO, national governments, and industry in village-scale trials, such as with bendiocarb, should be encouraged (section 2.3).

2. The following paragraph should be added to the next edition of Guidelines to classification:

"While the classification deals only with the acute risk to health, evaluations of chronic effects, including cancer, have been completed for many compounds for registration purposes. The results are noted in the 'Remarks' column. With the exception of arsenous oxide, none of the technical products listed in Tables 1–5 is known to be carcinogenic for man." (Section 5.1.)

3. WHO should encourage the education in toxicology of suitably qualified scientists from developing countries. The establishment of professorships in toxicology in leading universities in order to promote awareness of the subject and of related disciplines would help in the recruitment and training of scientists who, in turn, would be able to give advice to the community on the safe use of new compounds (section 4.5).

6.3 Recommendations for future research

1. Total daily absorption of pesticides by workers under specified, practical conditions of work should be measured for as many compounds as possible (section 1.2).
2. Additional epidemiological studies of workers who have had prolonged, heavy exposure to any compound used in vector control should be encouraged (section 1.2).

3. In view of the favourable results already obtained with *B. thuringiensis* H-14 and *B. sphaericus*, these biological agents for vector control should be developed further and used (section 2.5).

4. Each new laboratory strain of a bacterium that produces a modified toxin should require full evaluation of the safety of the toxin and some additional evaluation of the live microorganism. Also, when a new strain is isolated or when a toxin-producing gene is transferred to another microorganism (e.g., *Escherichia coli*) complete safety evaluation is essential (section 2.5.2).

5. Studies are needed to determine the range of concentrations of bis(tributyltin) oxide in water under different conditions of use as a molluscicide. Studies of its effects on reproduction should also be performed (section 3.2.1).

6. The efficacy and safety of traditional repellents such as citronella should be explored (section 4.2.1).

7. Further studies should be carried out on the techniques and effectiveness of using graphics for labelling pesticide containers (section 5.2.2).

ACKNOWLEDGEMENTS

The Expert Committee acknowledges the valuable contribution to its work made by the following: Mr R. Bahar, Equipment Planning and Operations, World Health Organization, Geneva, Switzerland; Dr R. Cabral, International Agency for Research on Cancer, Lyons, France; Dr D. A. Muir, Malaria Action Programme, World Health Organization, Geneva, Switzerland; Dr A. Pelfiérne, Pesticide Development and Safe Use, World Health Organization, Geneva, Switzerland; Dr C. P. Pant, Ecology and Control of Vectors, World Health Organization, Geneva, Switzerland; Dr G. Quélencé, Pesticide Development and Safe Use, World Health Organization, Geneva, Switzerland; and Dr A. Smith, Ecology and Control of Vectors, World Health Organization, Geneva, Switzerland.

REFERENCES


Annex 1

ASSESSMENT OF EXPOSURE BY DIRECT AND INDIRECT MEANS

1. Collection of samples for direct measurement of dermal exposure

1.1 Disposable overalls and gauntlets

To assess dermal exposure a worker is required to wear a new disposable overall and gauntlets for a minimum period of one hour during any one day's spraying. If significant exposure of the head is likely, a head-pad, as described below, or a disposable hat should also be worn. Care should be taken to ensure that the overall or gauntlets do not become saturated with pesticide spray; if this does occur a fresh overall and gauntlets must be worn. The exact duration of exposure and amount of pesticide used must be accurately recorded.

At the end of each assessment period the overalls and gauntlets should be carefully taken off by an assistant to avoid cross-contamination. Each gauntlet should be put in a separate plastic bag, and the overall (or overalls) cut into the following six parts: legs (above and below knee separately); arms (above and below elbow separately); and torso (front and back). Care should be taken to ensure that the instrument used for cutting the overall is not contaminated. Each part of the overall should be put in a separate plastic bag. Until they can be analysed, all the bags should be stored in a place that is out of direct sunlight and as cool as possible. They should be clearly labelled with the worker's number, the date, and other necessary details of exposure.

1.2 Exposure pads

Exposure pads consist of pieces of α-cellulose, measuring 10 × 10 cm, that are backed with glassine paper or aluminium foil. When monitoring the degree of exposure to oily formulations, aluminium foil can be used by itself. A white absorbent paper backed with polyethylene\(^1\) has also been successfully used as an absorbent pad.

\(^1\) Manufactured by Whatman Biochemical Ltd, Springfield Mill, Maidstone, Kent ME14 2LE, UK.
Prior extraction of pad material is often necessary to remove substances that may interfere with the analysis of pesticide residues.

2. Biological monitoring as an indirect measurement of exposure

2.1 Levels of compounds and metabolites in blood and urine

Although any substance may accumulate in the body if the daily intake is great enough, the body can break down or excrete relatively large amounts of most organic chemicals, including some pesticides. The likelihood of pesticides accumulating in the body is therefore small.

Biological monitoring provides a quantitative measurement of pesticide absorption from all routes of exposure. The objective of biological monitoring is to relate the concentration of a particular compound, or of a specific representative metabolite, in biological material to the total uptake by the body. This requires specialized and sensitive methods of analysis. Under field conditions, where facilities are limited, samples of blood or urine (or both) are usually analysed.

Since it may not always be possible to analyse the specimens at the field station, facilities for preserving and dispatching the samples should be made available.

The time and frequency of sampling and the volume of the specimen depend on the properties of the compound being monitored, the method of pesticide application, the specific conditions of the study, and the sensitivity of the analytical methods used. Therefore, detailed guidelines on sampling cannot be given, although some general principles do apply.

(1) Samples must be taken and analysed before exposure to establish reliable baseline concentrations.

(2) During the period of exposure the number of samples collected should be sufficient to provide a good measure of the total uptake and an indication of possible transient retention.

(3) Sampling should be continued for sufficient time after exposure to provide data on the pattern of pesticide elimination.

(4) When monitoring urinary metabolites, the decision to collect spot samples or 24-hour urine samples depends on the properties of the pesticide, the rate of its absorption, and the analytical requirements. To check that a 24-hour schedule has been respected, the creatinine content of the sample should be measured.
(5) Safeguards should be taken to avoid contaminating samples with the parent compound.

The assessment of total body absorption from the amounts determined in blood or urine requires some knowledge of the pharmacokinetics of the compound, preferably in man.

2.2 Measurement of daily absorption associated with occupational exposure

There are no efficient field methods of measuring absorption that do not have practical disadvantages or require some degree of extrapolation. In field trials, high degrees of correlation between the results are not usually found. Conditions in the factory workplace tend to be more stable, but here also uncontrollable variables may influence the levels of exposure and considerable scatter must be expected in the results. The field investigator must therefore make allowances for this unavoidable scatter and decide whether additional measures to reduce exposure are required.

2.3 Measurement of enzyme activity in blood

It is possible to determine the degree of absorption of organophosphorus pesticides by measuring the level of cholinesterase activity. There are three main methods of doing this:

(1) The colorimetric test paper method. This method measures activity in plasma; however, facilities are not always available in the field to separate blood plasma.

(2) The colorimetric tintometric method. This method measures whole-blood cholinesterase activity, which is a more relevant indicator of toxicity than plasma measurements.

(3) Spectrophotometric methods. Some of these methods are suitable for use only in the laboratory, but others are suitable for field use, particularly when more accurate results are required.
TRAINING OF COMMUNITY HEALTH WORKERS IN THE PREVENTION OF PESTICIDE POISONING

The following is an extract of the syllabus used for training community health workers in the Sudan.\(^1\) It illustrates the national approach to the prevention of pesticide poisoning.

Definition

The following simple definition given in clear terms is intended for primary health workers. “Pesticides” are chemicals used to kill “pests” (insects, fungi, weeds, rodents, etc.,) that damage crops or cause disease. These chemicals kill by stopping or changing the normal life processes of the pest.

Poisoning can also occur in man, and causes various degrees of illness or death. For this reason, pesticides must be handled with great care.

Routes of entry

For pesticides to cause illness or death in a worker or citizen, they must get into the body. This can occur in one of three ways: through the skin, the lungs, or the alimentary tract.

Primary health workers should know the following.

Skin

If a pesticide comes into direct contact with the skin, it can pass quickly through the dermis and epidermis into the blood. This is the most common route of entry into the body, as contamination of the skin can occur easily and often goes unnoticed.

Such skin contact may be a result of:

1. spills or splashes on to the skin when handling a pesticide;
2. wearing clothes, gloves, hats, boots, or socks that have pesticide on them;
3. cleaning or handling equipment that has pesticide on it; and

\(^1\) Also included in the syllabus but not reproduced here is a section on the effects of pesticides on the body and on symptomatology.
(4) being accidentally sprayed either directly or by spray drifting from the next field.

The danger of pesticides entering through the skin is greatest when:

(1) the temperature is high;
(2) the skin is wet; and
(3) the skin is broken (cuts, sores).

Lungs

Pesticide that is present in the air is breathed into the lungs. The pesticide passes from the lungs into the blood and is then carried all over the body.

Lung contact may occur:

(1) during mixing and preparation of pesticides for spraying;
(2) during spraying; and
(3) when entering a treated area before the dust settles or the spray dries.

Alimentary tract

When pesticides are taken directly into the mouth and swallowed, they enter the body from the stomach and intestines. While most people would not intentionally eat or drink a pesticide, they may do so by:

(1) consuming food or drink that have been contaminated by spills of pesticide or by being stored near pesticides;
(2) consuming food or drink that has been prepared or stored in empty pesticide containers;
(3) handling and eating food with hands that are contaminated with pesticide; and
(4) touching the mouth with contaminated hands.

Labels

There are many types of pesticide; they act differently on the pests and some are more hazardous to man than others.

Valuable information is given on the label of each pesticide container. The label should be read carefully before the pesticide is used and all recommendations and precautions should be followed.
When seeking medical attention for pesticide poisoning, be sure to take the label or container to the medical centre because it gives important information on treatment.

**Work practices**

The way in which people work can determine whether the risk of pesticide poisoning is large or small. A worker who is careful usually follows the advice of the primary health worker (the occupational health supervisor) and thereby reduces the risk of poisoning.

Primary health workers should teach all workers the following guidelines.

**Handling containers**

(1) Inspect pesticide containers before handling them. If there are any leaks, wear full protective clothing to move and empty the containers and to clean up any pesticide that has been spilt.

(2) Avoid damaging containers while handling them.

**Opening, pouring, and mixing**

(1) Work only in the designated area.

(2) Do not work alone when handling pesticides.

(3) Work on stable surfaces where containers will not tip.

(4) Use only the tools provided for opening containers. Do not tear bags open as the uneven rips make spills more likely.

(5) If necessary use suitable tools for pouring and mixing.

(6) Pour carefully from an opening at the top of the container to avoid splashing.

(7) Open, pour, weigh, and mix in a well-ventilated area. Be sure that the dust is drawn away from the working area or keep upwind of all opening, pouring, and mixing operations.

(8) Do not use the mouth to siphon materials or to blow out clogged spray nozzles.

(9) Clean up any spills immediately.

(10) Collect spills of dry pesticides into a plastic bag and put in a special waste container.

(11) Spread adsorbing material on top of spills of wet pesticides, wait for spills to be soaked up, and then shovel the contaminated adsorbing material into a special waste container.

(12) DO NOT USE WATER TO WASH AWAY SPILLS.
When the job is finished

1. Use soap and water to wash all surfaces and equipment that have come into contact with pesticides.
2. Wash empty pesticide containers several times and then damage them so that they cannot be used by anyone else because the residues that remain in the container could cause illness or death.

Spills on the skin or clothing

If pesticide is splashed on skin or clothing, the following instructions should be followed immediately:
1. Remove contaminated clothing;
2. Quickly wash the affected area with soap and water. Then scrub the area again thoroughly, including the fingernails, toenails, and hair if necessary;
3. Wash again with soap and water;
4. Rinse with clear water;
5. Wash the contaminated area with rubbing alcohol to remove any remaining pesticide. This is even more important if the pesticide has been on the skin for some time;
6. Put on clean clothing;
7. Burn contaminated clothing; and
8. Obtain the label from the pesticide container and take it to the medical center if symptoms of poisoning appear.

Splashes in eyes

Pesticide splashed into the eyes is a very serious problem: pesticides enter the body rapidly in this way and there is also a risk of permanent eye damage. If splashes occur, flush the eyes with plenty of water for 15 minutes. Then get medical attention immediately.

Personal cleanliness

Personal cleanliness plays an important part in preventing pesticide poisoning by making sure that small amounts of pesticide are washed off before they can enter the body.

1. Do not rub the eyes or touch the mouth while working with pesticides.
(2) Wash the hands before eating, drinking, smoking, or using the toilet.
(3) Do not keep food, drink, or tobacco anywhere near pesticides; do not even keep them with you while you work.
(4) Do not eat, drink, or smoke in the work area.
(5) Wash thoroughly at the end of the working day and change into clean clothes.
(6) Throw away gloves that leak or contaminated shoes or boots.
(7) Change clothes and bathe as soon as you arrive home to prevent continued contamination of skin or contamination of family members.

Field workers

Field workers may be exposed to pesticides:
(1) by working in a recently sprayed field;
(2) by handling sprayed crops;
(3) by accidental spraying;
(4) by the wind carrying spray from an adjoining field; and
(5) by entering a sprayed field too soon.
TREATMENT OF POISONING DUE TO ORGANOPHOSPHORUS, CARBAMATE, AND ORGANOCHLORINE INSECTICIDES, ANTICOAGULANT RODENTICIDES, AND PARAQUAT

Successful treatment of pesticide poisoning depends on the rapid and simultaneous application of measures for: (a) alleviation of life-threatening effects; (b) removal of non-absorbed material; and (c) symptomatic and/or specific treatment.

1. 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.

2. The removal of non-absorbed material

Deposits 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. When intoxication has occurred by mouth, gastric lavage is imperative. If the clothing or exposed skin is contaminated by pesticide, 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 15 minutes.

1 After: WHO Technical Report Series, No. 634, 1979 (Safe use of pesticides: third report of the WHO Expert Committee on Vector Biology and Control), Annex 2; with additional material.
3. Symptomatic and/or specific treatment

3.1 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 may be given, depending on the severity of the intoxication and the response to the previous 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 dose of 2 mg 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 (pulse rate over 140 beats per minute). 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 treatment is not given, death may result. 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-methyl poisoning, reactivation of the enzyme activity of the red

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1 When symptoms occur before medical attention is 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.
blood cells may be observed within 1 hour, but, if the patient comes for treatment 36 hours or more after intoxication, oxime therapy may be less effective. 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. Intravenous injections of oximes should be given slowly, especially in small children.

3.2 Intoxication with carbamates

The signs and symptoms of carbamate poisoning resemble those of organophosphorus 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 available. 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.

3.3 Intoxication with organochlorine compounds

There is no specific antidote. Treatment is aimed at controlling the symptoms, especially hyperactivity and in some instances convulsions. Artificial ventilation may be required. Anticonvulsant treatment with soluble barbiturates, diazepam, or paraaldehyde 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.

3.4 Intoxication with anticoagulant rodenticides

The principal management of intoxication by conventional or second-generation anticoagulant rodenticides is administration of phytomenadione (vitamin K₁). After blood samples have been taken for differential diagnostic tests, including the measurement of prothrombin levels, phytomenadione (vitamin K₁) in a dose of 5–10 mg should be given three times on the first day of treatment.
irrespective of symptoms. The vitamin should be diluted with an injectable 5% solution of dextrose or sodium chloride and given intravenously, preferably by infusion. Intramuscular administration of smaller doses of phytomenadione should be continued until the prothrombin time has reached normal. In addition to the vitamin, a seriously ill patient should initially be given a transfusion of carefully matched whole blood (as little as 50 ml may be effective); transfusions should be repeated daily until the patient has returned to normal. Prolonged observation of patients affected by second-generation anticoagulants (coumarin derivatives) is required because these compounds are metabolized slowly and repetitive therapy may be indicated. In any event, the progress of the patient should be assessed by monitoring the prothrombin time of blood samples taken at least twice a day; monitoring should continue until a return to normal is clearly established.

3.5 Intoxication with paraquat

No antidotes currently exist and management essentially relies upon the use of adsorbents to prevent absorption from the gut and upon the removal of absorbed paraquat from the body. One litre of a suspension of fuller's earth (about 300 g/litre) or bentonite (about 70 g/litre) should be administered orally as soon as possible and repeated in doses of 200–500 ml every two hours for several days. In an emergency, use of ordinary soil may be beneficial if these adsorbents are not available. The removal of circulating paraquat by forced diuresis and peritoneal dialysis has been attempted. Administration of oxygen is contraindicated in acute poisoning because paraquat is more toxic in the oxygenated lung. In the chronic and fibrotic phase of poisoning, the use of oxygen should be delayed for as long as possible.

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