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**WORLD HEALTH ORGANIZATION
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No. 227

**TOXIC HAZARDS OF PESTICIDES
TO MAN**

**Twelfth Report
of the Expert Committee
on Insecticides**

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WORLD HEALTH ORGANIZATION

GENEVA

1962

EXPERT COMMITTEE ON INSECTICIDES

Geneva, 23-30 October 1961

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TOXIC HAZARDS OF PESTICIDES TO MAN

Twelfth Report of the Expert Committee on Insecticides

The Expert Committee on Insecticides met in Geneva from 23 to 30 October 1961. Dr P. M. Kaul, Assistant Director-General, opened the meeting on behalf of the Director-General.

Dr J. M. Barnes was elected Chairman and Dr Wayland J. Hayes jr. Vice-Chairman. Dr S. P. Ramakrishnan was appointed Rapporteur.

The provisional agenda was adopted.

1. INTRODUCTION

1.1 Scope of report

The Committee restricted itself to a consideration of the potential toxic hazards to man arising from the use of pesticides in the field of public health, taking into consideration (a) that the hazards arising from the use of pesticides in agriculture and safety in relation to residues in food have been studied by a joint panel of experts of FAO and WHO in Rome (9-16 October 1961); and (b) that the Joint ILO/WHO Committee on Occupational Health will be meeting in April 1962 and the protection of agricultural workers against toxic hazards will be one item on the agenda.

The Committee appreciated that the populations at risk from toxic pesticides include:

- (1) employees in factories and formulating plants;
- (2) field operators; and
- (3) occupants of treated dwellings.

As (1) above concerns occupational health, the Committee restricted itself to (2) and (3).

1.2 Present status of chlorinated hydrocarbon insecticides in public health

The Committee considered the fact that very large amounts of pesticides are in current use throughout the world for the control of a number

of arthropod-borne diseases of man. For instance, in the malaria eradication programme alone, insecticides are being sprayed in the homes of 612 million, or nearly 60 per cent of a total of 1037 million people living in areas of the world that are still malarious. Programmes are ready to be implemented for about 16 per cent, or 170 million people. Malaria eradication has yet to be planned for the remaining 255 million.

The importance of this will be fully appreciated when it is stated that the total amount of chlorinated hydrocarbon insecticides used for malaria eradication alone is estimated at not less than 36 000 tons in 1960 and it is predicted that for the period 1961-65 an average of 65 000 tons per annum will be used. Not less than 200 000 spraymen and supervisors are involved in the spraying operations, and the relevance of this to the problems of the potential or actual toxic hazard from insecticides to man or domestic animals needs no additional emphasis.

The main insecticides that have so far been successfully used in the malaria eradication programmes are the chlorinated hydrocarbons, mostly DDT and to some extent BHC. It appears that no significant toxic hazards have resulted from their use. In view of the unparalleled contribution of DDT in successful eradication of malaria in parts of the world and its continuing efficacy in most eradication programmes, the Committee stressed that a change of insecticides should be made only when absolutely necessary. Since some vectors in a number of countries have become resistant to DDT, the urgent need for alternative insecticides to complete the eradication has been recognized. One such alternative chlorinated hydrocarbon insecticide was dieldrin. However, the use of this insecticide has been abandoned by most countries chiefly because of (a) a significant risk of toxicity to man and his animals and (b) its potentiality for the production of a rapid selection of resistant vector strains.

The Committee considered that except for eradication programmes which will be of limited duration, the routine use of insecticides for vector control was inadvisable. The importance of classical methods in the control of vector-borne diseases such as filariasis and plague was emphasized. The Committee noted the increasing attention being paid to biological methods of vector control as an additional weapon against arthropod-borne diseases.

2. THE NEED FOR ALTERNATIVE COMPOUNDS

The development of resistance to the chlorinated hydrocarbon insecticides among many of the insect vectors of disease has created a serious menace to public health programmes. The number of vector species resistant to insecticides has increased from 2 in 1946 to 52 in 1960. In some instances resistance in insects of public health importance has resulted from the use of pesticides in agriculture.

The problem of insecticide resistance is of particular importance in malaria eradication. During the past two years there has been a tendency in programmes to revert to the use of DDT because of the fact that resistance to dieldrin in *Anopheles* is more frequent and much more intense than DDT resistance and the selection is more rapid. The most difficult situation arises in areas where resistance to both groups of chlorinated hydrocarbons¹ appears in malaria vectors. A recent summary of the extent of anopheline resistance to the BHC/dieldrin group on the one hand and to the DDT group on the other provides the following information: In 1956 only 5 species of *Anopheles* showed any degree of resistance; by the end of 1960, resistance or enhanced tolerance of *Anopheles* to one or the other of the residual chlorinated hydrocarbon insecticides was noted in 29 species, of which 15 are important vectors. Of the latter, 5 have shown resistance to dieldrin, 1 to DDT, and 9 to both insecticides.

The problem of anopheline resistance to insecticides should, however, be viewed in its proper perspective. The human population living in malarious areas where resistant *Anopheles* have been found represents only a small proportion of the people protected by the malaria eradication programmes. Nevertheless, insecticide resistance constitutes an obstacle to the smooth progress of malaria eradication. Insecticide resistance has also become a problem in other fields of public health.

Resistance to DDT of *Aedes aegypti*, the chief vector of yellow fever and dengue of man, was reported first in Trinidad in 1954. Resistant populations of this species occur in Haiti, Venezuela, north-east Colombia, South Viet-Nam, Puerto Rico, Jamaica, Guadeloupe and French Guiana. The loss of effectiveness of DDT against the tropical house-mosquito *Culex fatigans*, vector of *W. bancrofti* filariasis, has created a serious situation in the fight against filariasis and encephalitis, the more so as this species is now resistant to both groups of chlorinated hydrocarbon insecticides. Besides India, DDT-resistant populations of *C. fatigans* occur in Réunion, Venezuela, Taiwan, Brazil, Puerto Rico, Panama, Hawaii, Australia and the Republic of Congo. Dieldrin/BHC-resistant populations of the same species occur in the USA (California), Malaya, East Asia, Panama, South America, Zanzibar and the Congo. *Culex tarsalis*, vector of western equine encephalitis, has developed resistance to both groups of chlorinated hydrocarbons in the USA, and so also has *C. pipiens*, vector of Japanese B encephalitis in Japan.

¹ In their general mode of action and their relation to insect resistance, the chlorinated hydrocarbon insecticides are at present divided into two groups. One group comprises DDT and chemically related compounds such as methoxychlor and DDD; the other group includes BHC and the cyclodiene-derived compounds such as dieldrin and chlordane.

The body louse *Pediculus humanus*, vector of epidemic typhus and relapsing fever, was effectively controlled by DDT initially, but failure became apparent in Korea and Japan in 1951. Now DDT-resistant body-louse populations occur in Egypt, Iran, Turkey, Ethiopia and other countries in Africa, Peru, Chile, France, Yugoslavia, Afghanistan, Mexico and Uganda. In India, DDT-resistant lice have been encountered in the Kashmir valley. BHC/dieldrin resistance has been reported from France, Japan, Iran, West Africa and Tanganyika.

The oriental rat flea (*Xenopsylla* sp.), the principal vector of plague and murine typhus, has developed resistance to DDT in India. Following the appearance of the resistant strain of fleas, recrudescence of human plague has occurred from the erstwhile endemic foci in India after an absence of more than ten years. The dog and cat fleas (*Ctenocephalides canis* and *C. felis*) have also shown extensive selection of resistance to DDT or dieldrin.

The housefly was the first species to show resistance to the DDT group of compounds and subsequently to BHC and to dieldrin and other cyclo-diene-derived compounds. Resistance of the housefly to chlorinated hydrocarbons occurs in virtually every country of the world, and there is now a serious increase in the number of reports of housefly resistance to the organophosphorus insecticides. The extensive and comprehensive nature of resistance is therefore a very serious obstacle to the insecticidal control of housefly-borne disease in many parts of the world. This situation emphasizes that good sanitation techniques are essential for fly control, as well as new insecticides to meet emergencies.

Similarly the argasid ticks (*Ornithodoros* sp.) have also become resistant to the chlorinated insecticides.

Since insect resistance is a dynamic process and the need for new insecticides is likely to become urgent, the research that has been initiated on the use of alternative insecticides and particularly organophosphorus compounds is of very great importance. The development of new compounds which are safe and which have adequate residual action is of cardinal importance and great urgency.

3. INTERNATIONAL EFFORTS TO DEVELOP SUITABLE ALTERNATIVE PESTICIDES

The Committee noted that WHO is encouraging, and in certain cases actually supporting, intensified research into the mechanisms of insect resistance, so that its full implications can be understood. In addition, the possibilities of developing entirely novel insecticides, and new methods of insect control not necessarily involving chemicals at all, are also being studied.

Meanwhile the Committee was informed that the only immediate solution to the problems of controlling mosquitos or body lice which have become virtually immune to DDT or dieldrin is to turn to alternative existing insecticides, such as malathion or Baytex. However, these compounds are only two of many developed by the chemical industry for use as pesticides, mainly for the agricultural markets. Very few have been adequately evaluated for the rather specialized properties required of an effective and safe public health insecticide.

The World Health Organization has therefore set up and is co-ordinating a scheme of collaboration between the chemical industry and certain independent research laboratories. This scheme provides for an impartial evaluation, on a confidential basis where the manufacturer requires this, of promising new compounds for ultimate use as pesticides in vector control or eradication programmes. It embraces a very thorough series of studies including tests of toxicity to susceptible and resistant vectors, chemical stability, acute and chronic toxicity to mammals, and field trials. The scheme is operating successfully, and if the present spirit of cooperation continues, there is every hope that WHO will be in a position to recommend alternatives together with data for their safe application when the existing pesticides have to be abandoned on account of resistance or danger to man.

The Committee was informed that nearly 500 compounds had already undergone preliminary evaluation by the collaborating laboratories. The majority of these compounds are phosphorothioates or phosphonates. Two of these compounds are considerably less toxic to mammals than Baytex on the basis of preliminary data and yet are comparable in their effectiveness against the larvae or adults of resistant houseflies or mosquitos. There are also some new chlorinated hydrocarbons, carbamates, and synthetic esters related to the pyrethroids.

It would be premature to suggest that these particular new compounds can be finally recommended. However, they provide evidence that new, safer and effective compounds are within the capacity of the chemical industry.

An important feature of the scheme is that it provides not only for the development of new public health pesticides but for an evaluation of established ones. There are several such insecticides which have been widely and successfully used for controlling agricultural pests. Parathion is one example, but its high mammalian toxicity renders it unsuitable as a substitute for DDT. On the other hand, compounds such as Baytex and malathion might be so used, and trials in progress are designed to test their suitability under field conditions. DDVP is being evaluated as an insecticide which, although fairly toxic *per se*, might be applied as a fumigant under carefully controlled conditions so that vector control in dwellings can be achieved with a good margin of safety. The scheme is

thus designed to enable the fullest advantage to be taken of existing insecticides which might otherwise remain neglected simply through a lack of adequate testing under public health conditions and against resistant vectors.

4. ORGANOPHOSPHORUS COMPOUNDS AND CARBAMATES

A considerable number of organophosphorus compounds have been developed as pesticides, and at least one carbamate is widely used for this purpose at the present time.

The organophosphorus compounds vary, in their acute toxicity to mammals, from parathion and Systox (Demeton), which have a single lethal dose of less than 10 mg per kilogram of body weight, to malathion, with one exceeding 1000 mg/kg. Many, like Baytex and diazinon, lie intermediately (see Annex 1). There have been many accidents all over the world from the more toxic compounds; parathion, in particular, has caused hundreds of deaths under a variety of circumstances.

Careful observation on some of these cases has made it possible to delineate accurately the signs and symptoms of poisoning in man, while the efficacy of different kinds of treatment has also been demonstrated. Despite its extensive use, there have been only a few cases of poisoning by malathion.

4.1 Mechanism of action

The effects of the organophosphorus compounds and carbamates in question have been related to the inhibition of blood and tissue cholinesterases and thus to an accumulation of excessive amounts of acetylcholine in effector organs.

The compound may itself bring about this enzyme inhibition. DDVP is an example of such a "direct inhibitor". In many instances the compound has first to be metabolized in the body and converted into the inhibitor; malathion and Baytex are examples of these "indirect inhibitors".

The symptoms of intoxication are mostly, if not exclusively, of a cholinergic nature. Some correlation exists between the rate and degree of inhibition of blood cholinesterase and the severity of the symptoms. This correlation is not strict under all conditions of intoxication. Other mechanisms of action cannot be excluded as the cause of some of the toxic effects.

The duration of symptoms of poisoning depends in part on the rate of the reactivation of the inhibited cholinesterase and the rate at which the inhibitor itself is destroyed or removed from the tissues. Both these factors are related to the chemical structure of the compound.

4.2 Effects

The effects of anticholinesterases have been reviewed at length elsewhere.¹ They are listed in the table on p. 14 and a few notes are added here.

4.2.1 *Local effects*

Miosis is most commonly seen after the eye has been exposed to the vapour or particles of a direct inhibitor, which may also sometimes be present as impurities in commercial preparations of indirect inhibitors. Miosis may be unilateral if particles enter one eye only. It may be accompanied by lachrymation, feeling of pressure in the eye, conjunctival hyperaemia, spasm of accommodation and dim vision.

Salivation, nasal discharge and hyperaemia with excessive bronchial secretion and bronchospasm will result from the exposure of the upper and lower portions of the respiratory tract to direct inhibitors.

If these substances are ingested, gastro-intestinal spasm with colic, hypersecretion, vomiting and diarrhoea are common early symptoms.

4.2.2 *Systemic effects*

These are in general similar following absorption by any route, but differences in their sequence and time course may occur.

4.2.3 *Delayed effects*

A few organophosphorus compounds, such as mipafox (but none in current use as pesticides), have been shown to possess a delayed neurotoxic action.

4.3 Causes of death in anticholinesterase poisoning

As causes of death in poisoning by cholinesterase inhibitors, the following main factors have been shown to be operative:

Respiratory system: increase of secretion, bronchospasm, neuromuscular block of respiratory muscles, paralysis of respiratory centre, asphyxia

Circulatory system: bradycardia, decreased cardiac output, cardiac arrest, paralysis of vasomotor centre

Central nervous system: convulsions

Death appears to be primarily asphyxial in some instances and cardiovascular in others.

¹ Holmstedt, B. (1959) *Pharmacol. Rev.*, **11**, 567.

4.4 Diagnosis of intoxication

Diagnosis of anticholinesterase poisoning can be made from a history of exposure followed by the onset of all or some of the signs and symptoms listed in the table on p. 14. After exposure to the indirect type of inhibitor, the first symptoms may not appear until after the individual has left work. In some instances they may develop during the night, and their association with occupational poisoning may not be immediately recognized.

The diagnosis can be confirmed by determination of the activity of the blood cholinesterases. This, however, may not be depressed in cases where local symptoms follow exposure to direct inhibitors, as would be brought about by a splash of DDVP concentrate on the face and eyes.

The determination of the activity of the blood cholinesterases is of even greater value as an index of exposure, because it is possible to have depression of activity in the complete absence of symptoms.

Several methods are available for determining cholinesterase activity.¹ The Committee agreed that a separate determination of the plasma and red-cell cholinesterase gives the most accurate information. Whole-blood tests may be easier to perform in the field but are less sensitive and subject to greater experimental errors, making it difficult to detect small fluctuations in activity. The advantage of determining the activity of plasma cholinesterase alone was recognized, because few organophosphorus compounds are known which do not depress activity in the plasma before that in the red cells.

Because the Tintometer method developed by Edson² is practical under field conditions and experience in its use has been gained, this method should continue to be used at the present time. The Committee recommended, however, that an attempt be made to modify the method so that plasma cholinesterase can be determined separately. They also hoped that information on the field method used in the USSR for determining the activity of plasma cholinesterase would be made available.

Research should also be encouraged to develop stable cholinesterase preparations for use as standards for field test methods.

For the convenient collection and transport of blood specimens from the field to the laboratory, the Committee recommended that the method using blood dried on filter paper after being taken from the finger tip should be further investigated.

The Committee recommended that the activity of blood cholinesterases be determined regularly in operators exposed to the organophosphorus

¹ Augustinsson, K. B. (1957) Assay methods for cholinesterase. In: *Methods in biochemical analysis*, London, Interscience; Barnes, J. M., Hayes, W. J. & Kay, K. (1957) *Bull. Wld Hlth Org.*, 16, 41.

² Tintometer Ltd. (1956) The rapid field determination of cholinesterase in whole blood. In: *Colorimetric chemical analytical methods*, Salisbury, England.

compounds of intermediate or greater toxicity. They further recommended that operators be withdrawn from exposure if the activity of their blood cholinesterase decreases by 25 per cent or more from a well-established pre-exposure value.

The insecticidal carbamates give rise to a more rapidly reversible cholinesterase-inhibitor complex. This makes it impossible to use estimates of cholinesterase activity made *in vitro* as an accurate index of the activity of this enzyme in the tissues.

4.5 Therapy of poisoning by cholinesterase inhibitors

The correct treatment of anticholinesterase poisoning includes—in addition to the use of drugs—removal of the toxic agent and decontamination of exposed skin with an alkaline solution or soap and water. Suction of the airways, tracheotomy, and positive-pressure artificial respiration may be necessary at a later stage. These measures have been dealt with extensively in various reviews.¹ It must be stressed that all drug treatment is liable to fail if the other measures are not properly observed. Drugs used for this purpose fall into several groups as follows :

4.5.1 *Atropine*

Atropine sulfate is recommended as first aid in the case of poisoning with organophosphorus compounds or carbamates.

Atropine should be injected immediately after the appearance of any local pulmonary or systemic signs of anticholinesterase poisoning, in doses somewhat larger than those employed for other purposes.

When signs or symptoms produced by an anticholinesterase compound are *mild*, 1-2 mg of atropine should be injected intramuscularly and repeated, if necessary, at 30-minute intervals until symptoms are relieved. Any patient sick enough to receive even one dose of atropine should be under medical observation for at least 24 hours, because the symptoms may reappear.

When symptoms of poisoning are *moderately severe*, 2-4 mg of atropine should be injected intravenously or, if this is not feasible, intramuscularly. Repeated doses of 2 mg at 10-minute intervals should be given until symptoms are relieved.

When *severe* symptoms are present (particularly respiratory difficulties, marked slowing of the heart or convulsions), 4-6 mg of atropine should be injected intravenously or, if this is not feasible, intramuscularly and repeated in doses of 2 mg at 3- to 8-minute intervals until the severe symptoms decrease markedly or cease. In severe anticholinesterase poisoning the effect of each injection of atropine may be transient, lasting only 10-30

¹ Holmstedt, B. (1959) *Pharmacol. Rev.*, **11**, 567.

minutes. The patient must therefore be observed as closely as possible for recurrence of signs of poisoning, and atropine must be repeated at appropriate intervals for at least 48 hours if his clinical condition requires it. In severe poisoning as much as 24-28 mg of atropine may be required the first day. Respiratory failure requires immediate artificial respiration.

Attention ought to be given to the fact that treatment with atropine may reduce heat loss, due to inhibition of sweating. Under hot environmental conditions this may be dangerous, particularly in young children. It is therefore advisable that the hospitalized patient be kept cool and quiet. Under no circumstances must a person who has received even one dose of atropine be allowed to perform muscular work, and he must be kept under observation for at least 24 hours or until he is fully recovered.

Devices, including automatic injectors of reliable construction, are now available for the administration of atropine or other drugs of similar solubility and stability. It was recommended by the Committee that a supply of these injectors should be at hand during spraying operations but should not be issued to the individual sprayers.

4.5.2 *Alternatives and supplements for atropine*

In addition to the oximes (see 4.5.3 below), substitutes or supplements for atropine include atropine analogues, anticonvulsants such as Tridione, and a series of compounds derived from benactyzine that also have antidotal action.¹ Parsidol and Diparcol have also been suggested.

Although some atropine analogues may be superior to atropine for treating poisoning by specific compounds, none has been found that is better in all respects. Anticonvulsant drugs are important, but because of lack of complete information, the Committee could reach no decision about them. It recommended that WHO collect any data available on the experimental study and clinical use of atropine substitutes and supplements. The data, together with small quantities of the drugs in current use, should be made available to members of the Expert Advisory Panel on Insecticides to enable them to advise the Director-General on their therapeutic value in poisoning by organophosphorus compounds.

4.5.3 *Reactivators (oximes)*

In recent years it has been demonstrated that certain oximes, when used in combination with atropine, provide more effective therapy than atropine alone in poisoning with some anticholinesterases.² These drugs reactivate phosphorylated cholinesterase and thus tend to correct the biochemical lesion rather than merely relieve symptoms. Of the oximes,

¹ Anichov, S. S. (1961) *Ann. Rev. Pharmacol.*, **1**, 21.

² Holmstedt, B. (1959) *Pharmacol. Rev.*, **11**, 567, Table 4.

2-pyridinium aldoxime methiodide (2-PAM-iodide) has been used in man in accidental poisoning by organophosphorus compounds. The intravenous administration of 2000 mg of 2-PAM-iodide to man at the rate of 100-300 mg/min. produces no signs or symptoms and no change in blood pressure or cardiac rate. The safety of the compound is shown by the fact that repeated doses totalling over 40 g have been given intravenously without side-effects in a case requiring this tremendous dose for recovery.

Because of its low solubility in water (5% w/v), 2-PAM-iodide can be administered intravenously only. N-methylpyridinium-2-aldoxime methane sulfonate (P2S) (70% w/v) and 2-pyridinium aldoxime methochloride (2-PAM-chloride) (100% w/v) are much more soluble. The manufacture and distribution of these more soluble salts should be encouraged.

It has been demonstrated that the results obtained with an oxime in relation to a particular organophosphorus compound are not necessarily applicable to other organophosphorus compounds, even those closely related chemically. The potential usefulness of the 2-PAM salts and other reactivators should, therefore, be investigated when new insecticides of the organophosphorus type are introduced.

After poisoning by some organophosphorus compounds, the intravenous administration to man of 500-2000 mg of 2-PAM-iodide ameliorates generalized weakness to a moderate degree, reduces muscular fasciculations and relieves neuromuscular block. Improvement may begin within 30 seconds after injection of oxime and become maximal in 5-10 minutes. Approximately 20 minutes later there may be some return of weakness and fasciculations, but not to the original level. A second injection of oxime then results in further improvement. There is some reversal of the inhibition of blood cholinesterase. In connexion with parathion poisoning treated by 2-PAM-iodide, the reversal is confined largely to the red-cell cholinesterase and, in some cases, is permanent after a single dose. Since respiratory weakness may develop rapidly in the course of severe anticholinesterase intoxication, mechanical measures to sustain respiration are still needed for some patients.

It must be stressed that the 2-PAM salts and other reactivators are of limited value if not accompanied by other therapeutic measures such as atropine and artificial respiration. It was recommended that 2-PAM-iodide, 2-PAM-chloride, P2S or a similar compound be included in the kit for medically trained toxicologists who accompany spraying teams using organophosphorus insecticides.

In severe intoxication by an organophosphorus compound, 1000mg of one of the 2-PAM analogues should be slowly injected intravenously after the previous administration of atropine. The dose may be repeated after 20 minutes if weakness is not relieved or if it recurs. In moderate intoxication half the above dose should be used and similarly repeated.

The following drugs *must not be given* to people poisoned with anticholinesterases: morphine, barbiturates or tranquillizers.

[1.000 mg]

SIGNS AND SYMPTOMS OF ANTICHOLINESTERASE POISONING *

<i>Site of action</i>	<i>Signs and symptoms</i>
	<i>Following local exposure</i>
Pupils	Miosis, marked, usually maximal (pin-point), sometimes unequal
Ciliary body	Frontal headache, eye pain on focusing, slight dimness of vision, occasional nausea and vomiting
Conjunctivae	Hyperaemia
Nasal mucous membranes	Rhinorrhoea, hyperaemia
Bronchial tree	Tightness in chest, sometimes with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, cough
Sweat glands	Sweating at site of exposure to the liquid
Striated muscle	Fasciculations at site of exposure to the liquid
	<i>Following systemic absorption</i>
Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, dyspnoea, slight pain in chest, increased bronchial secretion, cough
Gastro-intestinal system	Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness (? cardiospasm) with "heartburn" and eructation, diarrhoea, tenesmus, involuntary defecation
Sweat glands	Increased sweating
Salivary glands	Increased salivation
Lachrymal glands	Increased lachrymation
Heart	Slight bradycardia
Pupils	Slight miosis (occasionally unequal), later more marked
Ciliary body	Blurring of vision
Bladder	Frequent or involuntary micturition
Striated muscle	Easy fatigue, mild weakness, muscular twitching, fasciculations, cramps, generalized weakness including muscles of respiration, with dyspnoea and cyanosis
Sympathetic ganglia	Pallor, occasional elevation of blood pressure
Central nervous system	Giddiness ; tension ; anxiety ; jitteriness ; restlessness ; emotional lability ; excessive dreaming ; insomnia ; nightmares ; headache ; tremor ; apathy ; withdrawal and depression ; bursts of slow waves of elevated voltage in EEG especially on over-ventilation ; drowsiness ; difficulty in concentrating ; slowness of recall ; confusion ; slurred speech ; ataxia ; generalized weakness ; coma with absence of reflexes ; Cheyne-Stokes respiration ; convulsions ; depression of respiratory and circulatory centres with dyspnoea, cyanosis, and fall in blood pressure

* From Holmstedt, B. (1959) *Pharmacol. Rev.*, **11**, 567.

5. PRESENT STATUS OF RESEARCH ON ORGANOPHOSPHORUS COMPOUNDS FOR USE IN PUBLIC HEALTH

5.1 Malathion [S-(1,2-diethoxycarbonylethyl)-O,O-dimethyl phosphorodithioate]

This is one of the least toxic of the organophosphorus compounds which has been shown to be effective as a residual insecticide. It is an indirect inhibitor of cholinesterase. Its acute toxicity to mammals is considerably less than that of DDT, but it shows a greater tendency to be absorbed through the skin. However, urinary excretion of malathion-derived material is proportional to dosage, and excretion falls to undetectable levels by the third day or even sooner after the last dermal exposure.¹ Thus malathion, unlike the chlorinated hydrocarbon insecticides, is not stored to any significant degree. Studies have shown that the daily application of 10% malathion dust to the human skin for several weeks is slightly irritating but produces no more serious clinical effect. This massive dosage produces little or no inhibition of blood cholinesterase activity.

Its sorption and consequent inactivation in mud walls limits its usefulness for malaria eradication, although it is effective on impervious surfaces such as thatch or bamboo.² Malathion is especially promising for the control of body lice. Limited field trials have indicated that two applications of 30-40 g 1% dust each, applied two weeks apart, will reduce the lice to a level at which typhus would not be transmitted. These two applications would appear to be adequate treatment for a year.

In view of the wide margin of safety of malathion, the Committee approved its use in those public health programmes in which it is needed.

5.2 Baytex [O,O-dimethyl O-(3-methyl-4-methylthiophenyl) phosphorothioate]

The organophosphorus compound known as Baytex has physical and chemical properties which make it promising for use as a residual insecticide. Several studies have shown the effectiveness of Baytex against a wide range of insects and the Committee concluded that, given satisfactory evidence that its use would not involve significant health hazard to operators or to householders, it could be regarded as a good substitute for DDT where resistance to that compound occurs.

¹ Hayes, W. J., Mattson, A. M., Short, J. G. & Witter, R. F. (1960) *Bull. Wild Hlth Org.*, **22**, 514.

² Unpublished WHO working paper.

From animal experiments, Baytex is regarded as an organophosphorus insecticide of intermediate toxicity. The toxicity of Baytex depends on its conversion in the animal to an inhibitor of cholinesterase.

The Committee was informed that 300 tons of Baytex had been used in 32 operations in different parts of the world ; according to the information made available to the Committee it appeared that no illness had resulted from its use.

In 1960, during trials by the Insecticides Testing Unit¹ in Lagos, which further established the effectiveness of Baytex against malaria vectors, evidence was obtained of some reduction of the blood cholinesterase activity in some of the small number of spraymen and in a considerable number of inhabitants of sprayed houses. There was some uncertainty about the significance of these findings because the cholinesterase activity was measured on whole blood. Anaemia is known to be common and might have contributed to the low whole-blood cholinesterase activity. It is also known that defective liver function, not uncommon among undernourished people, can be associated with erratic levels of plasma cholinesterase activity. Consequently, in further trials carried out by the Insecticides Testing Unit in 1961 special attention was paid to possible exposure of the inhabitants of the sprayed houses to Baytex. The activity of plasma cholinesterase and that of erythrocyte cholinesterase were estimated separately both in spraymen and in the inhabitants of sprayed houses.

Only one of the eight spraymen showed definite depression of plasma cholinesterase. None had inhibition of the erythrocyte enzyme. Most of the residents had a moderate depression of plasma cholinesterase activity one week after their houses had been sprayed, and in the majority this depression was still evident one month later. In no case was the red-cell cholinesterase inhibited, nor were there any symptoms of organophosphorus intoxication. It was concluded from these studies that while application of Baytex was evidently safe under these conditions, there was clear evidence of its absorption by the inhabitants.

The Committee agreed that determinations of plasma cholinesterase activity represent a sensitive index of absorption of Baytex that might be used in future trials, not only to safeguard the health of operators and inhabitants, but also in suitably planned investigations to help to establish the most important routes of absorption. It might then be possible to recommend modification in the techniques used in the application of pesticides that would reduce the absorption of the material by those living in treated dwellings.

If Baytex is ultimately recommended for use on a wide scale, the Committee recommended that WHO collect information on the effect of long-term exposure of mammals to this insecticide.

¹ The Insecticides Testing Unit is a field research unit established in Lagos by WHO in collaboration with the Nigerian Government.

5.3 DDVP (dichlorvos¹) (O,O-dimethyl-2,2-dichlorovinyl phosphate)

This differs from most other organophosphorus insecticides in that it produces an insecticidal concentration of vapour in a way that makes it promising for the interruption of malaria transmission and for the disinsection of aircraft.

DDVP is a direct inhibitor of cholinesterase. A review of the extensive study that has been made of its toxicology has failed to reveal any other mode of action or any side-effects. The acute and chronic toxicity of DDVP is less than that of Parathion (see Annex 1), but contact with concentrated liquid formulations must be avoided.

Under the conditions of repeated systemic absorption, there is a wide margin of safety between dosages of DDVP that produce a measurable degree of inhibition of cholinesterase activity and dosages that produce illness. Thus rats can withstand for 90 days, without any sign of intoxication, 20 times as much DDVP in their diet as the amount required to produce definite lowering of the activity of both plasma and red-cell cholinesterase. The compound is rapidly metabolized and excreted.

The rate of vapour formation and the rate of hydrolysis and loss of DDVP vapour are such that it is not possible to produce an acutely dangerous concentration of vapour under practical conditions. Men exposed during their work to concentrations very much greater than those needed for insect control have shown neither illness nor even a depression of blood cholinesterase activity. The highest concentration of DDVP to which people can be exposed for a very long time without any inhibition of cholinesterase activity becoming evident is not known, but there is extensive evidence that such a concentration is greater than that necessary for the control of anopheline mosquitos or for the disinsection of aircraft.

The Committee examined the two types of vaporizer now being tested for mosquito control and the interruption of malaria transmission. Studies of safety, including measurements of the concentration in the air of the dwelling and determinations of the blood cholinesterase activity of the residents, that have been carried out in connexion with limited field trials were reviewed. The Committee agreed that since the concentration of DDVP achieved in the air was low in relation to the concentration of DDVP causing toxic effects the programme should go forward, but the medical officers concerned should keep alert for any side-effects that may appear under field conditions.

The Committee went on to discuss the way in which DDVP might be used for the disinsection of aircraft. Briefly, DDVP would be introduced

¹ The common name recommended by the International Standards Organization (ISO).

as a vapour at a controlled concentration for half an hour during normal ventilation in flight, and it would then be removed by the continuing ventilation. The insecticidal concentration of DDVP is non-irritating and odourless, unlike the aerosols so often ineffectually used today.

The Committee considered the information available on DDVP. It came to the conclusion that there are, at this time, insufficient data to permit it to reach a firm conclusion and to make positive recommendations regarding application and technique on a broad scale or on a full operational basis (see Recommendation 8). The Committee recommended that when adequate information becomes available the Director-General submit it to selected members of the Expert Advisory Panel on Insecticides and request them to advise him whether the Organization should recommend these procedures with one or other of the two types of dispensers on an operational basis. In the event of their reporting favourably, these operations should then be carried out on a larger scale under such conditions that further information on their safety would be obtained, so that a full picture could be presented to the Expert Committee on Insecticides on some future occasion with the view of obtaining firm and positive recommendations.

6. PROTECTION AGAINST EXPOSURE TO INSECTICIDES

6.1 Protection of operators

The Committee considered the general measures that should be taken for the protection of the health of operators applying pesticides in public health programmes. They also formulated some precise recommendations, including some related to the introduction of new pesticides. The protection of operators was dealt with fully in the 1956 report of a Study Group¹ in the light of information then available. Where appropriate, the recommendations of that group are repeated here together with such modifications as can be made on the basis of experience and knowledge gained since 1956.

After years of use with the minimum of safety precautions and absence of any evidence of poisoning, DDT was replaced in some programmes by dieldrin without any realization of the fact that the known mammalian toxicity of dieldrin made it probable that its use under such conditions would present a greater hazard to operators if they handled it in the same way as they had handled DDT. Casualties—fortunately with few, if any, fatalities—from dieldrin poisoning have been reported from almost every

¹ World Health Organization (1956) *Toxic hazards of pesticides to man*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, 114).

programme in which the material has been applied in indoor spraying for any length of time. Some casualties occurred even in spray teams where discipline was good and the precautions suggested in the report of the Study Group were observed.

These cases of poisoning among spray operators have led to a greater realization of the possible hazards to which these men may be exposed in vector-control programmes. Because of the limitations that must apply to the application of the findings in studies of acute and chronic toxicity on laboratory animals, it is now realized that exposure to a potentially hazardous material must be first undertaken in carefully supervised programmes in which a special watch is kept on the health of the spray operators.

Following the recommendation made in the 1956 report, work has been carried out to assess the nature of the hazards to which indoor sprayers applying water-dispersible-powder suspensions are exposed.¹ These studies show that vastly more of the deposit falls on the body surface than is inhaled, but the amounts falling on the skin itself will naturally depend upon the degree to which this is protected. Light cotton cloth provides an adequate protection from water-dispersible-powder suspensions.

The amount of pesticide absorbed by the dermal route will depend not only upon the area of exposed skin but also upon the readiness with which the particular pesticide penetrates the skin. The inhalation hazard will depend mainly on the size of the particles; with wettable powders it is found that by the time they reach the area of the face of the operator they are virtually dry and of a size greater than that which will reach the depth of the lungs. Material of this nature, after entering the nose, is ultimately swallowed. Further experiments showed that substantial protection of both the airways and the exposed skin of the face could be achieved by wearing a light veil held away from the face on a broad-brimmed hat. Vision through the veil is not obstructed by spray deposit as it is with a plastic visor.

Absolute protection of the skin and respiratory tract imposes physical limitations that would make house-spraying in hot climates impossible. It is therefore necessary to ensure that the precautions recommended are adequate to meet the likely hazard and that their exercise will allow the work to be effectively carried out. The strangeness of the attire of a suitably protected operator should not be allowed to interfere with the spraying programmes merely because the protected population does not appreciate its significance. In this context the importance of public health education must be stressed. It is encouraging to note that certain protective

¹ Wolfe, H. R., Walker, K. C., Elliott, J. W. & Durham, W. F. (1959) *Bull. Wild Hlth Org.*, 20, 1.

equipment is acceptable because its possession adds to the worker's comfort and to his prestige.

6.1.2 *General aspects of hazard*

Apart from the risks involved in the handling of bulk shipments, to which spray operators will not normally be exposed, hazards may arise (a) in transferring pesticide at headquarters stations from bulk packages to smaller containers, and in carrying it to the site of spray operations; (b) in the preparation of spray concentrates; (c) by continued exposure to droplets in the course of spraying; (d) by accidental contamination at any stage.

6.1.3 *General precautions for all spray operators applying pesticides*

Without attempting to formulate a complete code of practice, the Committee recommended the following as *minimum precautions* for operators handling pesticides in public health work. *All pesticides are toxic to some degree, and care in handling all types should be routine practice.*

(1) All operators handling pesticides should be informed of the risks involved in their use and receive instructions for handling them safely.

(2) There should be adequate technical and medical supervision of operators, together with the provision of facilities for the treatment of any casualties. Supplies of atropine, some in special syringes ready for immediate injection and some in tablet form, should be available in all first-aid kits when anticholinesterase insecticides are being applied. The Committee agreed that no issue of atropine to spraymen for self-medication should be made, but that the supervisor of the field operations should be trained to administer atropine in emergencies.

(3) Operators applying pesticides of all types should wear some form of impervious head covering, which should be regularly cleaned. A broad-brimmed hat with a veil together with an impervious cape to cover the shoulders should be worn in all programmes where new pesticides are being applied, since the pesticides may offer a hazard appreciably greater than that presented by DDT or malathion.

(4) Operators having scratches on the skin or skin irritation at places likely to be exposed to the insecticide should not be permitted to work, since such damage is known to facilitate the penetration of the pesticides into the body.

(5) Facilities, including soap, should be provided for washing the skin and clothing. Compulsory washing after the daily work should be a supervised routine in all spraying operations.

(6) Operators should not be exposed to a pesticide for more than 4-5 hours during a normal working day if the application of that pesticide by the same operator is going to take place day after day over long periods.

(7) Separate working clothes should be used ; they should be changed and washed as frequently as possible. An occasional rinse in kerosene will effectively remove deposits of chlorinated hydrocarbon pesticides not taken out by soap and water. Ordinary washing soda is a better decontaminant for the organophosphorus insecticides than any of the modern detergents in use.

(8) Workers should not smoke during their work nor eat without first washing their hands, and they should take other simple precautions in places where pesticides are handled.

(9) Recognizing that, in all pesticide work, the greatest hazard lies in the handling of concentrates, the Committee drew attention to and endorsed the recommendations for safety made in Section 9 of the Sixth Report of the Expert Committee on Insecticides¹ (see Annex 3). Further, the Committee recommended that, in the transferring of concentrates from drums, either threaded taps or drum-pumps of standard design be employed.

(10) Equipment used in spraying should conform to the general and specific recommendations with regard to design and maintenance included in the *Specifications for Pesticides*.²

(11) All pesticide containers should be adequately labelled to identify the contents and show, *in a form comprehensible to the operator*, the nature of the material and the precautions to be employed.

(12) It is important to ensure the safe disposal of empty or nearly empty containers. They must not be allowed to go astray or be removed by unauthorized people possibly for use as containers of food or drinking water, especially in areas where such containers may be scarce.

The following procedure is known to be effective in decontamination of used containers, provided that they have not been allowed to become rusty.

The drum is rinsed two or three times with water and the sides scrubbed. For drums that have contained organophosphorus compounds an additional rinse should be carried out with 5% washing soda and the solution allowed to remain in the drum overnight. Rubber gauntlets should be worn during this work, and a soakage pit should be provided for the rinsings.

¹ World Health Organization (1956) *Expert Committee on Insecticides, sixth report*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, 110).

² World Health Organization (1961) *Specifications for pesticides*, 2nd ed., Geneva.

On the possible need for the use of masks when spraying organophosphorus compounds, the Committee considered reports in which it was claimed that operators spraying Diazinon showed some depression of blood cholinesterase activity unless masks¹ were worn; falls of blood cholinesterase activity were also recorded in some men in another project who had sprayed Baytex over a period of weeks, even when respirators and protective clothing had been provided. However, in two short-term spraying operations in the Insecticides Testing Unit where the men wore impervious clothing and hats but no respirators, the majority showed no fall in blood cholinesterase. The Committee noted that a malaria-eradication field project using Baytex will be carried out by the Government of Iran with the collaboration of the World Health Organization, and that a close watch will be kept on the levels of blood cholinesterase activity and the general state of health of the spraymen. If falls in cholinesterase activity occur despite the use of the precautions listed above, the Committee recommended that tests to see whether the wearing of a mask will prevent absorption of Baytex should be carried out before any final recommendation on the use of this insecticide is made.

6.1.4 *Clinical surveillance of operators*

A sprayman should always have ready access to a medical man so that notice may be taken of any symptoms that may indicate acute over-exposure to the pesticides or harmful effects of long-term exposure. Apart from clinical examination, the Committee also considered what quantitative biochemical tests could be carried out in an attempt to assess and so to control the degree to which the men were exposed.

A traditional method in occupational medicine is the examination of the urine in order to detect the excretion of the ingested foreign material or its metabolites. The Committee noted that methods had been established for the measurement of DDA, a metabolite of DDT, and of hitherto unidentified metabolites of dieldrin and malathion in the urine of men who had been exposed to these three pesticides. None of these techniques was at present suitable for field use nor, with the exception of DDT, was there enough information to make it possible to decide whether such examinations would be useful in providing a guide to the exposure which the sprayman had undergone. The Committee expressed the hope that in countries where vector-control programmes were being carried out in reasonable proximity to suitably equipped research laboratories, further work on the examination of the urine of exposed operators for pesticides and their metabolites might be initiated. It was not possible to foresee how important

¹ The masks were Dräger Model 71/624-A701.

surveillance by this means might become as new pesticides were introduced into public health programmes.

The significance and importance of regular determination of blood cholinesterase activity where organophosphorus compounds are used have been discussed elsewhere. Equipment for carrying out this test in the field is available, and methods may be further improved as experience is gained.

In view of individual differences and the lack of knowledge of the average levels of activity of the blood cholinesterase in populations living in different parts of the world,¹ it is essential that pre-exposure levels be determined on all operators, and some attempt should also be made to assess any fluctuations occurring during the observation period in unexposed members of the population.

Very clear details have been provided of the techniques for measuring the exposure of spray operators.² The Committee hoped that where facilities exist, an opportunity of extending our knowledge of the hazards run by spraymen would be taken by making measurements in the manner outlined.

The recommendations which are included in this section of the report involve the provision of more facilities than were outlined in the report of the Study Group on the Toxic Hazards of Pesticides to Man. This makes it all the more important that the responsibility for providing these facilities and for taking care of the health of spray operators should be clearly delineated before a spray programme is started.

With the increased awareness of the possibility of hazard, it is likely that the care of spray operators will form an important part of programmes involving the application of pesticides until such time as it is possible to use chemicals that present no hazard to those who handle them.

6.2 Exposure of residents

The determination of blood cholinesterase activity has provided a very sensitive index of the absorption of organophosphorus insecticides, and as described in Section 5.2, the residents of certain dwellings in Nigeria which had been sprayed with Baytex showed some depression of plasma cholinesterase activity. This indicates that they had absorbed some of the deposit applied to their homes. There seems no reason to doubt that they would also absorb other pesticides applied in a similar manner. The exact way in which the pesticides are absorbed is not known, but the Committee noted that in Italy, where houses were sprayed with diazinon,

¹ Barnes, J. M., Hayes, W. J. & Kay, K. (1957) *Bull. Wld Hlth Org.*, 16, 41.

² Durham, W. F. & Wolfe, H. R. (1962) *Bull. Wld Hlth Org.* (in press). Reprints of this paper will be available on application to WHO.

determinations of blood cholinesterase activity were made with negative results. Further observations are needed in order to discover the factors which influence the degree to which sprayed materials may be absorbed by residents of treated premises. The application of pesticides as residual fumigants demands that a very careful watch be kept on those exposed to this type of insecticide during preliminary trials of its efficacy.

The Committee considered the use of dieldrin-cement briquettes for the control of mosquito larvae in small domestic water containers. They were informed that in some areas at the present time this was the only effective way of controlling certain vectors of filariasis. The Committee recommended that accurate determinations of the concentration of dieldrin in the water under field conditions should be made. If the practice is introduced, steps should be taken to keep a watch on the health of the people and to secure urine samples from them in order to ascertain whether any significant level of dieldrin metabolites can be detected. However, the Committee had some reserve about the safety of this procedure and considered that its use for larval control should be restricted to the shortest possible time. The Committee recommended that the development of alternative methods be promoted as soon as possible.

In this context it also wished to reiterate the statement made in the report of the Study Group on the Toxic Hazards of Pesticides to Man :¹

“Water, including supplies of drinking-water, is a breeding place for a number of insect and mollusc vectors of diseases of man. The Group emphasizes that, as a general public health principle, drinking-water should, as far as possible, be free from pesticides. Nevertheless, it recognizes that for the proper control of a number of diseases of different types it may be necessary to introduce certain of these chemicals into water supplies.”

The Committee stressed, however, that the choice of such a pesticide should be made with great care, taking into account the possible effects of long-term exposure of the consumers.

6.3 Third parties

Accidents to children and others often arise from inadequate care in the safe custody of pesticide concentrates. Those in charge of programmes using pesticides must ensure that the responsibility for the custody of stocks and the disposal or treatment of empty or half-empty containers is unambiguously placed upon the shoulders of suitably qualified people. The diversion of pesticides for personal or domestic use has led to a number of accidents.

¹ World Health Organization (1956) *Toxic hazards of pesticides to man*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, 114).

7. ACCIDENTS ARISING FROM EXPOSURE TO INSECTICIDES AND LEGISLATIVE CONTROL

The Committee considered that public health programmes should clearly recognize the importance of accidental poisoning within the community. While pesticides contribute to this experience, it can be noted that pharmaceutical preparations, together with household chemicals, are usually of much greater significance. In this connexion, the accidental poisoning of children is a major problem.

It was the opinion of the Committee that the development of poison-control programmes could be achieved only on the basis of well-designed legislation, soundly administered and supported by appropriate health education programmes.

The design of legislation relating to the control of poisons should take into account new developments and the increasing numbers of poisonous substances, while at the same time recognizing the value of the controlled use of these substances. Legislation must include practical and realistic measures which protect the public in general and children in particular. It should prevent dangerous levels occurring residually in food supplies and provide proper standards for the protection of those who use these materials.

The Committee saw considerable merit in the registration of pesticides and reaffirmed the view previously expressed¹ that adequate labelling through some form of registration of all pesticides was necessary. The Committee recognized the special importance of pesticide formulations put on the market for use by the general population. Control, or even restriction of distribution to the public of the more toxic substances, should be the basis of regulation.

The Committee reaffirmed that labels written in the language of the country where the pesticide would be used should provide the minimum information recommended in the 1956 report,¹ namely :

- (1) the name of the manufacturer ;
- (2) the common name as recommended by the appropriate committee of the International Organization for Standardization ;
- (3) the type of formulation, with concentration of ingredients ;
- (4) the recommended uses and, where appropriate, cautions against undesirable applications ;
- (5) the basic precautions to be employed ;

¹ World Health Organization (1956) *Toxic hazards of pesticides to man*, Geneva, p. 29 (*Wld Hlth Org. techn. Rep. Ser.*, 114).

(6) a suitable indication of hazard, including a pictorial symbol for highly toxic substances ;

(7) the recommended treatment in case of intoxication ;

(8) the proper disposal of the container.

Emphasis should also be given to methods of packaging and storage, to prevent contamination of food supplies and access by unauthorized persons, particularly children. Great attention must be given to the avoidance of poison containers which can be mistaken for food containers and of a presentation of poisons in a form that can be confused with sweets or pharmaceutical preparations. Care must be given to the disposal of empty pesticide containers in such a manner as not to endanger any person or animal or contaminate water supplies.

The safety of workers in industry and agriculture will in many countries be the responsibility of the occupational health section of the public health administration. Codes of practice and legislation have been enacted in many countries. The Committee recommended that WHO publicize the relevant legislation in the *International Digest of Health Legislation* and at an early opportunity review the whole position in order to provide a guide to countries contemplating setting up similar legislation. However, in many countries where disease-eradication programmes are planned there will be little, if any, legislation of this type covering pesticide operators. For this reason the Committee felt it necessary to specify in some detail the recommendations given in Section 6.1 for their protection.

Not only should first-aid advice be given on the label, but workers using pesticides should be clearly instructed in appropriate first-aid measures.

The Committee was of the opinion, however, that aerial spraying applications came into a special category and that effective aerial application and pilot safety must be considered together, along with such matters as the avoidance of contamination of public water supplies, and it commended a system described to it under which pilots not holding a special rating or licence are precluded from commanding aircraft engaged in the dropping of pesticides. Under this system the pilot is required (a) to be the holder of a commercial pilot's or higher class of licence, (b) to have completed an approved course of instruction, the syllabus for which includes a section dealing with the toxicology of pesticides and safety measures to be adopted, and (c) to have passed an appropriate examination.

Such a pilot's rating should properly be supplemented by regulations for the employing companies, possibly under an operations-manual scheme, the scope of which would include organization, supervision of operators and flight checking, flight conduct, equipment, handling and storage of chemicals, operational landing strips, operating limitations, aircraft operations, emergencies and special flight technique.

8. INFORMATION ON PESTICIDES AND ITS DISTRIBUTION

The Committee was of the opinion that the competent authorities should demand, and that industry has a clear obligation to provide, all the available information on the composition of pesticides, together with all available toxicity data. This can be supplemented with information obtained through registration procedures, by notification of poisoning from doctors and hospitals, and from a variety of other sources.

It was recognized by the Committee that many national administrations would welcome summarized but comprehensive information on the various pesticides in use, and it calls attention to the publications listed in Annex 2.

The Committee commended the information circular at present issued by WHO and would welcome steps to improve the range of information contained therein; and to this end it recommended to WHO that Member States be invited to report, on a uniform reporting basis, cases of poisoning occurring from the use of pesticides.

When poisoning by a pesticide is reported which might seriously limit the effective use of the compound concerned, it was recommended that WHO should consider investigating the report.

9. CONCLUSIONS AND RECOMMENDATIONS

(1) In view of its unparalleled contribution in the successful eradication of malaria in parts of the world and its continued efficacy in most present eradication programmes, DDT remains the insecticide of choice on the grounds of safety, and other insecticides should be used only when absolutely necessary.

(2) The application of BHC by the generally recommended methods for vector control is also acceptable on grounds of safety.

(3) Cases of intoxication by dieldrin among spray operators have drawn attention to the hazards to which spraymen in public health programmes may be exposed when certain pesticides are used. As a result the whole question of operator safety is now receiving greater attention.

(4) On the grounds of its safety, malathion may be used as a substitute for DDT, either as a residual insecticide or for direct dusting under clothing for louse control. The example of malathion illustrates the important principle that the introduction of organo-phosphorus insecticides does not necessarily introduce any greater hazard than that presented by insecticides hitherto in common use in public health programmes. Indeed, in some

cases the hazards may be considerably less, since early evidence of absorption can readily be obtained by a simple field test before intoxication occurs.

(5) Despite its promise as a substitute for DDT in mosquito control, there is not yet sufficient evidence of the safety of Baytex under conditions in which field operators will be subjected to prolonged exposure to enable the Committee to make firm recommendations about its wide-scale use where other insecticides fail in eradication programmes. It is hoped that the evidence to be collected in a malaria-eradication field-research project will provide a basis for a definite decision.

(6) The evidence obtained that the inhabitants of at least some types of dwellings have absorbed some of the Baytex applied as a residual spray does not in itself provide a basis for objecting to the use of Baytex; these observations do, however, point to the desirability of making further investigations designed to reduce any absorption of residual spray materials, possibly by improved techniques of application.

(7) Although continued vigilance is needed in the trials at present in progress, the evidence so far available indicates that the use of DDVP as a residual fumigant is safe and that present investigations should be extended in view of the apparent efficacy of DDVP in killing mosquitos. Special attention should be paid to infants, old people and invalids who may remain all day within the treated houses.

(8) The controlled release of DDVP offers promise as a satisfactory means of aircraft disinsection. At present there is no evidence to indicate that the procedure is dangerous for the passengers. When adequate information becomes available, the safety of the crew should be finally assessed.

(9) The health of spray operators should be adequately safeguarded if the precautions laid down in some detail in Section 6.1 of this report are followed and an adequate clinical surveillance of the men is maintained.

(10) Regular determinations of blood cholinesterase activity should be made in all spray operators in public health programmes who are working with an organophosphorus compound until the safety of the compound has been established, as in the case of malathion.

(11) The field test method for determining blood cholinesterase activity is appropriate for general surveillance, but in cases where serious depression occurs, blood samples should be sent to a laboratory where a more complete analysis may be made. When there are initial symptoms or when a depression in cholinesterase activity of 25 per cent or more from a well-established pre-exposure value is discovered, the operator(s) should be taken off any work involving handling of the pesticide. Attention should also be paid to any special circumstances that might have led to over-exposure.

(12) The responsibility for organizing and for maintaining surveillance of the health of the spray operators should be assigned and clearly defined before programmes are started.

(13) The Committee recognized the value of long-term surveillance of the health of operators who have used pesticides for long periods. Such studies are very important in assessing the possible long-term effects of these materials. In view of the difficulties in setting up and continuing such surveys for pesticide operators in public health programmes, the Committee recommends that WHO should seek advice on how such investigations can be made.

(14) To assist countries that may wish to introduce or to improve their legislation in order to control the distribution and use of pesticides, it is recommended that steps be taken to collect, publish and review such legislation as has already been promulgated in different countries.

(15) Some countries may not have suitably qualified experts to advise them on the safety of pesticides which commercial enterprises wish to introduce into their territories. The appropriate authorities should be encouraged to demand full data from the manufacturers. If necessary they might sometimes be assisted, through WHO, to make contact with other authorities with experience in the use of the same compounds. The information at present disseminated by WHO on the toxicity of pesticides is very valuable, and it is hoped that this service will be maintained.

(16) To assist countries that may be called upon to provide services for the safety of operators applying organophosphorus compounds in public health programmes, the Committee recommends that WHO should

(a) select on the basis of advice from the appropriate experts the most suitable type of injector to be recommended for the administration of atropine in the field ;

(b) obtain information on the sources and availability of supplies of suitable oxime preparations or other reactivators.

(17) During the deliberations of the Committee a number of suggestions were made for further research likely to improve the control of hazards arising from the use of pesticides. The following are worthy of special mention :

(a) More information on the actual exposure which an operator undergoes by the inhalation or deposition of sprayed material in different operations should be obtained by methods now adequately described.¹

(b) The value of determining amounts of pesticides or their metabolites in the urine of men occupationally exposed to pesticides should be assessed by planning the appropriate studies in field operations where suitably equipped research laboratories are accessible.

¹ Durham, W. F. & Wolfe, H. R. (1962) *Bull. Wild Hlth Org.* (in press).

(c) When opportunity arises, the level of pesticides deposited in human fat should be analysed so as to obtain evidence of either special occupational exposure or the extent to which members of a community might be casually exposed to these materials. The offer of the laboratories of the United States Public Health Service in Atlanta, Ga. to carry out certain of these analyses was noted with appreciation.

(d) Attempts should be made to adapt the field test kit for cholinesterase so that plasma cholinesterase activity may be determined separately. There is also need for stable preparations of cholinesterase to serve as standards with this technique.

(e) The filter-paper method for collecting and transporting blood samples should be re-examined for its applicability to the needs outlined in this report.

(f) More research is needed on the therapeutic value of different drugs in poisoning by anticholinesterase compounds.

(g) The availability of certain isotopically labelled pesticides through WHO was noted as a facility that might be of great value to certain research laboratories interested in studies of the mammalian toxicity of pesticides.

(18) In respect of the evaluation and prevention of acute, subacute and long-term toxicity risks to man from the use of pesticides, the Committee stresses the desirability of close and continuous cooperation, as well as an exchange of information, between national agencies and international organizations such as WHO, FAO, and ILO concerned with public health, agricultural, food-protection and occupational-health programmes and recommends that the Director-General explore how this may be even better achieved.

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Annex 1

**MAMMALIAN TOXICITY
OF SOME ORGANOPHOSPHORUS INSECTICIDES**

Test animal	Parathion	Systox (Demeton)	DDVP	Diazinon	Baytex	Malathion
LD ₅₀ , Single oral dose (mg per kg of body weight)						
Rat (M)	12.5	10	80	150	215	1 375
Rat (F)	3.5	4	56		615	1 000
Mouse	25.0			80	150	3 000
Guinea pig	32.0			320	> 800*	570
Rabbit				130	150*	
Hen	5*	20*		25*	40*	500*
LD ₅₀ , single skin application (mg per kg of body weight)						
Rat	21		75		500 (M & F)	> 4 400
Rabbit	40	24		> 4 000		
Concentration tolerated in diet without gross effects (p.p.m.)						
Rat	25	20	1 000	1 000	250	1 000

* Approximate figure.

Annex 2

**PUBLICATIONS DEALING WITH PESTICIDES
IN CURRENT USE**

1. Association of American Pesticides Control Officials, Inc., *Pesticide chemicals, official compendium* (Copies may be obtained from the Secretary-Treasurer, A. B. Heagy, Box HH, University P.O., College Park, Md., USA)
2. Martin, H. (1961) *Guide to the chemicals used in crop protection*, 4th ed., [Ottawa], Research Branch, Canada, Department of Agriculture (Pesticide Research Institute, University of Western Ontario Sub-Post Office, London, Ont., Canada)

3. Dormal, S. & Thomas, G. (1960) *Répertoire toxicologique des pesticides*, Gembloux, Ducolot, p. 86
4. Fabre, R. & Truhaut, R. (1962) *Toxicologie des produits phytopharmaceutiques*, Paris, Sedes (2nd edition in press)

Annex 3

PRECAUTIONS TO BE OBSERVED WHEN PREPARING SOLUTIONS OR SUSPENSIONS OF PESTICIDES ¹

“ In preparing concentrations of water-dispersible powders, use must be made of deep mixing-vessels and long-handled mixers to protect the operator from splashing and to permit stirring from a standing position.

“ For the dilution of solid pastes, electrically operated or power appliances are satisfactory and permit the dilution to be prepared in a closed vessel. Where such appliances are not available, long-handled mixers and tall vessels should be provided. No vessel shall be filled to a point where the operator will be endangered through splashing. Operators employed in the mixing of concentrates should, in addition to [protective clothing and devices recommended for spraymen] be provided with impermeable aprons. Long-handled dippers or scoops should be used for transferring the insecticide from one vessel to another

“ Liquid concentrates should be supplied in strong cans, not easily damaged in transportation, tightly sealed to avoid any leakage, but with a cover that may be easily removed.

“ For transportation of the liquid concentrates, use may be made of military-type tanks provided with pressure caps and a small aspiration tube so as to avoid a sudden flow when drawing off.”

¹ Extracted from the Sixth Report of the Expert Committee on Insecticides (*Wld Hlth Org. techn. Rep. Ser.*, 1956, 110, p. 21).
