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ASPECTS OF THE ASSESSMENT OF PESTICIDE EXPOSURE AND HAZARDS TO MAN

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Although mammalian toxicity studies are essential in assessing the hazard of any candidate pesticide, the ultimate assessment of the safety in its intended use depends upon studies on exposed people. Those compounds introduced for public health purposes undergo a thorough toxicological scrutiny, and assessment of their safety is made concurrently with their development for a particular use. There is an obvious need to carry out a similar evaluation of hazard to users of agricultural pesticides, in particular those handling pesticides in tropical climates.

While exposure to minute amounts of some more persistent insecticides could be demonstrated in every individual by detecting their presence in human fat and other tissues, adverse effects of pesticides have been observed only within a limited subgroup of the general population exposed to markedly higher dosages of pesticides through their occupation or by misuse and accident. Inappropriate storage and transportation of pesticides of high toxicity, or consumption of seed-grains treated with fungicides has resulted in a number of serious outbreaks of poisoning, and, at the request of governments, WHO has provided assistance in a number of such episodes.

The extent of accidental exposure can seldom be accurately determined and, as a rule, is of limited duration. Generally, most useful information is obtained in studying people occupationally exposed. Studies in workers applying pesticides for public health purposes is of particular toxicological interest for two reasons: 1) if applied indoors such as for malaria vector control the spraymen's exposure is relatively high (1) and 2) the exposure is usually limited to a single compound for a known period of time. In some instances this enables long-term exposure studies to be carried out on a relatively large group of workers.

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TOXICOLOGICAL STUDIES OF INSECTICIDES USED IN VECTOR CONTROL PROGRAMMES

Assessment of the safety of the use of a new insecticide or a newly developed method of application to control arthropod borne diseases is an integral part of the WHO Programme for the Evaluation and Testing of New Insecticides. Evaluation is carried out by a number of colaborating laboratories throughout the world in a programme of seven stages (2) Three of these stages are performed in the laboratory and four in the field. Toxicological assessment begins at the earliest stages and many compounds, although showing great promise with regard to their insecticidal activity, are rejected at this time for toxicological reasons. The remainder receive different kinds of additional safety evaluation depending upon their method of application for vector control. Since skin contamination is the most important source of exposure, the dermal toxicity of a compound is frequently the limiting factor preventing its further development for residual indoor application.

For any new insecticide the hazards can only be assessed on the basis of some knowledge of its mode of action and metabolism in mammals. Provided that the candidate compound belongs to a well studied group, relatively few data are usually sufficient for a provisional assessment of hazard to users. In the case of organophosphates or carbamates, tests such as acute oral and dermal toxicity in rats are carried out to show that the compound behaves as a typical anticholinesterase and does not display unusual or unduly prolonged effects. Repeated doses over short periods are sometimes performed and, in the case of organophosphorus compounds, tests are carried out on hens to exclude delayed neurotoxicity. If a pesticide is to be used under conditions where drinking water might contain residues, special studies are carried out to assess its hazard to the general population.

Only compounds considered safe on the basis of animal tests are ever studied for vector control in the field. In residual indoor application trials a medical toxicologist is always present during the spraying operations and carries out investigations according to a protocol specifically prepared for the trial. It is often during a Stage V (village scale) trial that human exposure to a new compound takes place for the first time under field conditions. Observations, including clinical examination and laboratory tests, are carried out (1) to assess any adverse effect on spraymen and villagers (2) to assess the most important route of absorption and the main causes leading to over-exposure (3) to determine safe techniques of application and protective measures to be observed and (4) to determine the place of any laboratory procedure in monitoring the degree of exposure in order to prevent ill effects.

While a village scale trial employs only a small number of spraymen, usually less than ten, and the spraying operation seldom lasts for more than a week, in an operational (Stage VI) trial, about 20 spraymen are engaged in a spraying round lasting for six to eight weeks. Eventually, in

a large scale trial (Stage VII), four or more rounds of spraying are carried out at three-month intervals by more than 20 spraymen. The protocols for toxicological studies in such trials include the following points: (1) assessment of possible cumulative effects in spraymen (2) establishing that the recommended safety measures are feasible and adequate (3) assessment of any posible adverse effect if the precautions are relaxed for any reason, and (4) evaluation of the adequacy and usefulness of the field method as a routine check for monitoring the degree of exposure.

A number of organophosphorus and carbamate insecticides have been tested in the field trials. These are performed as a rule by WHO field research units in which adequate facilities have been established to allow toxicological observations to be carried out. In most cases the tintometric method (3) is used as a field method for determining blood cholinesterase activity. This method has been adjusted to diminish the reaction of inhibited enzyme when exposure to carbamate insecticides is measured. As a laboratory reference method, at first the electrometric (4) and later, particularly in the case of carbamates, the spectrophotometric method (5) has been employed. The measurement of metabolites in urine has been tried but has not so far shown to be practicable as a monitoring method in the field.

A critical review of different methods of measuring exposure during the use of anticholinesterase compounds was published recently (6). The toxicological findings as obtained in WHO field trials are reviewed by the Expert Committee on the Safe Use of Pesticides (7—9). For obvious reasons most of the toxicological assessments have been related to the hazards involved when insecticides are used as residual indoor spray. Some of the highlights of these studies are outlined below.

ORGANOPHOSPHORUS INSECTICIDES

Malathion (diethyl mercaptosuccinate, S-ester with O,O-dimethyl phosphorodithioate), a dimethyl phosphate of low oral and remarkably low dermal toxicity, respective LD_{50} values for rats being 1,000 and > 4,444 mg/kg, was among the first insecticides submitted to the field trials. This compound passed through Stages V—VII in the early 60's without posing any significant toxicological problems (10,11), and its use was approved provided the same precautions as those recommended for DDT were observed. In 1963, fenthion (O,O-dimethyl O-[4-(methylthio)-m-tolyl] phosphorothioate), the new organophosphate being evaluated in the scheme and still under toxicological evaluation, was tested by a national authority in 50 villages. Hardly any precautions were used and initially there was no toxicological supervision. The WHO Consulant, Toxicologist, who arrived after the first round of spraying, reported 30 certain cases of poisoning. Some of these were severe, and while most of the cases involved spraymen, a few villagers occupying treated houses, were also affected. Even during the second smaller round of spraying, which was carried out by new properly trained applicators using protective clothing and appropri-

ate precautions, three cases of mild poisoning were recorded among the operators (12). In view of these observations, fenthion was considered unsuitable for routine residual indoor spraying. It is worth noting that oral toxicity (LD_{50} value in rats being 215 mg/kg) and — what is probably more important — dermal toxicity (LD_{50} of 500 mg/kg) are considerably higher than those of malathion.

Fenitrothion (*0,0*-dimethyl *0*-(4-nitro-*m*-tolyl)phosphorothioate) is a dimethyl phosphate of markedly lower dermal toxicity to rats than fenthion, oral and dermal LD_{50} values being around 500 and 3,500 mg/kg respectively. It has been submitted to a number of field trials within the last decade in which different formulations were evaluated. These studies have provided ample evidence that fenitrothion can be used safely as a residual spray in houses, but certain restrictions regarding spraymens' protective clothing and other precautionary measures have to be carried out. Regular determination of blood cholinesterase activity in spraymen is required, the recommendation being based on the repeated observations of symptomless slight to moderate cholinesterase depression found in most of the spraymen towards the end of the spraying rounds.

Fenitrothion is now being tested for the second year in a Stage VII trial. Weekly determination of cholinesterase activity in spraymen is carried out as one of the means of checking that recommended precautions are observed. No complaints attributable to the insecticide have been reported, but a few spraymen have had to be temporarily withdrawn from the spraying schedule because of lowered cholinesterase activity. A 50% reduction of the preexposure activity is taken as the level at which the operator has to be removed from any work involving exposure to an anticholinesterase insecticide.

CARBAMATE INSECTICIDES

3-isopropylphenyl N-methylcarbamate was one of the first carbamates tested in a village scale trial. The compound had undergone all the preliminary tests for mammalian toxicity, had been used with no adverse effect in experimental huts, and was considered safe to use in an entomological trial. Yet, when used in »real life« conditions, all the spraymen and a few villagers developed symptoms of systematic poisoning. Some of the cases were fairly severe but all of them recovered rapidly except for some skin rashes that persisted for a few weeks (13). Carbaryl (1-naphthyl methylcarbamate), which was tested at the same time, proved to be safe for both the spraymen and villagers. The striking difference between the two compounds in causing systemic poisoning in exposed people was partly due to their acute toxicity but also was partly caused by the much higher volatility of 3-isopropylphenyl N-methylcarbamate — a physical characteristic of a compound to be considered particularly when its use is proposed under hot climatic conditions.

Propoxur (*o*-isopropoxyphenyl methylcarbamate) whose acute toxicity to rats lies between the two above-mentioned carbamates has been studied more extensively than any other carbamate, and a full account of its successful passage through the first six stages of the evaluation programme has been published (14). Observations on the safety of propoxur as a residual insecticide have been carried out in three different parts of the world with a total of more than 4,000 man days of spraying. There were minor symptoms among some spraymen and a few inhabitants in two trial areas. All the patients recovered within a very short time, usually without treatment. Where treatment was given, a few drops of belladonna tincture proved effective.

While symptomless fall in whole blood cholinesterase occurred dailly during work, no evidence of cumulative inhibitory effect was found (15): this is because of the transient nature of the fall. In studies on volunteers, five oral doses of 0.20 mg/kg of propoxur, taken at half-hour intervals produced a symptomless inhibition of erythrocyte cholinesterase down to about 60% of normal with a recovery to 100% activity within three hours after the last dose (16). The depression was approximately the same as the average daily depression recorded in spraymen. In view of these findings, routine cholinesterase determination is of little, if any, practical value in indicating whether a worker should be withdrawn from further exposure to propoxur. On the contrary, minor complaints, from which recovery is spontaneous and rapid, cause the operator to stop work long before a dangerous dose is absorbed.

This property of propoxur, of having a »built-in warning system« is based on the kinetics of inhibition of cholinesterase by monomethylcarbamates and is shared by other members of this class of compounds. While inhibition in early stages is rapid, it is difficult to produce a severe degree of inhibition by carbamates because the rate of reactivation approaches that of inactivation (16, 17). Thus, there are certain important characteristics of carbamate insecticides which distinguish them from organophosphorus compounds (see Table), and renders them more advantageous from the safety point of view of the user.

STUDIES ON WORKERS WITH PROLONGED EXPOSURE TO DDT

DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane) has been used as a residual indoor spray in vector control programmes for about 30 years. It has an unmatched safety record. Over 150 factory workers with heavy and prolonged exposure to DDT have been subjected to exhaustive medical examinations. The only relevant findings were those that could be predicted, i. e. increased storage and excretion of DDT and its metabolites and a mild stimulation of the microsomal enzymes of the liver (18).

WHO is undertaking or supporting studies on long-term exposure to DDT. The studies are carried out in India and Brazil and a further extension of the study to a group in Mexico is now being planned. In this

Table 1

Toxic properties of carbamates as compared to organophosphorus compounds

	Organophosphorus compounds	Carbamates
Action in the body	*»indirect« inhibitors of cholinesterase;* active inhibitor is formed in the body from the original compound*	*»direct« inhibitors of cholinesterase;* original compounds possess high affinity to the enzyme
RECOVERY OF INHIBITED CHOLINESTERASE	SLOW	RAPID
(a) after a single exposure (b) after successive exposure	(a) within several hours or days** (b) within several days or weeks**	(a) and (b) within several hours or within one day**
Effect of successive daily over-exposures	cumulative inhibitory effect on cholinesterase may produced dangerous depression of enzyme activity	cumulative effect is too small to play a significant role in producing dangerous depression of cholinesterase activity
Onset of symptoms after exposure	may be delayed for several hours	usually immediate
Dose producing incapacitating symptoms	not far from the dangerous (lethal) dose	far from the dangerous (lethal) dose
Recovery from illness	slow (within several hours or 1—2 days)**	rapid (within several hours)
Therapy	as a rule required when syptoms occur; atropine and oximes	atropine (the use of oximes might be harmful) seldom required;

* This statement applies to phosphorothioates only
** Depending on the degree of cholinesterase inhibition.

way, information on people with different nutritional status to those studied in the United States, is being obtained. The study groups comprise spraymen in malaria eradication campaigns who have been exposed to DDT for a minimum of five years before admission to the study. These groups are matched against controls with only community exposure to DDT and it has been demonstrated that blood levels of DDT and its analogues in the exposed group exceed those in the control groups by a factor varying between four and ten. About 350 people belonging to the exposed group are under surveillance with a total of more than 3,500 man-years exposure to DDT.

The survey in Brazil commenced in 1968 and thus the survey group consists of men now exposed for over 10 years. In addition, subgroups of men exposed for a large number of years during the 1950's, and of people living in sprayed houses are included in this survey. Full histories and clinical examinations form the basis of this survey and blood levels of DDT are determined on a sampling basis.

In India, the main study was carried out in 1971 on an intensively exposed group, consisting of history, clinical examination and blood levels on each man and control. A follow-up study was carried out in 1973. This group ceased exposure to DDT at the end of 1971, when the insecticide used in the malaria campaign was changed to HCH. Based on the results of the 1973 follow-up, it seems likely that after the 1975 follow-up study, it will be possible to determine the degradation curve of DDT in man when high exposure is discontinued.

The results of these studies up to 1972 were considered by the Expert Committee on the Safe Use of Pesticides and are outlined in their report (9). At that time and subsequently, no differences in morbidity and mortality have been identified in men with levels of DDT considerably in excess of those found in any general population.

AGRICULTURAL PESTICIDES

It has been well demonstrated in the assessment of hazards due to pesticides used in public health, that the ultimate safety assessment has to be made on exposed people. A far greater quantity of insecticides is used in agriculture and the compounds used are often of considerably higher mammalian toxicity. To protect those who apply these pesticides there is an obvious need to extend the type of toxicological assessment used for public health pesticides to those used in agriculture. In particular, the hazard posed by agricultural pesticides should be assessed under tropical conditions where the means of protection, as described on labels, are seldom feasible. WHO has initiated investigation of these problems in association with representatives of industry and a standard protocol for such studies is under preparation. By extending the toxicological aspects of the evaluation scheme from public health to agri-

culture, we hope in the future to be able to see the human hazards posed by the proper use of pesticides in the totality, thus encouraging the safe use of pesticides where they are needed for improving human nutrition and health.

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Sažetak

OCJENA EKSPOZICIJE PESTICIDIMA I NJIHOVE OPASNOSTI ZA LJUDE

Premda su u ocjeni opasnosti svakog novog pesticida toksikološka proučavanja na pokusnim životinjama od bitne važnosti, konačna ocjena njegove sigurnosti za predstojeću široku upotrebu zasniva se na rezultatima proučavanja njegovih mogućih učinaka na eksponiranim ljudima. Spojevi što se uvode u upotrebu u javnom zdravstvu podliježu veoma temeljitom toksikološkom proučavanju i njihova sigurnost pri upotrebi ocjenjuje se uporedo s njihovim usavršavanjem za određenu primjenu. Postoji očita potreba da se sličan postupak ocjene moguće opasnosti uvede i za one pesticide što se upotrebljavaju u poljoprivredi a napose za one što se primjenjuju u tropskim klimatskim uvjetima.

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