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INSECTICIDE RESISTANCE IN CULICINE MOSQUITOS

Developments since 1975

by

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1. INTRODUCTION

The most recent review of all the problems of insecticide resistance in culicine mosquitos (Mouchet et al., 1975; Mouchet & Quiroga, 1976) was prepared for the twenty-second meeting of the WHO Expert Committee on Insecticides, which was particularly concerned with resistance in vectors and reservoirs of disease (Anon, 1976). Since that time it seems that public health workers and scientists have largely neglected studies in this field. There are few references in the literature, and communications to WHO are not much more frequent. Analysis of the list of tests compiled by the WHO computer in Geneva provides only a few data later than 1975.

Most of the recent information is concerned with the extension and operational consequences of cases of multiple resistance which are already well known. This information comes from the industrialized countries. On the other hand, studies on the species of major epidemiological interest are extremely rare, even in cases where the vectors have been subjected to major control campaigns.

Under these circumstances it is impossible to compile a satisfactory review of resistance in culicine mosquitos throughout the world, and the authors are fully aware of the limitations of the present study. Consequently we suggest some simplifications to the methodology of the tests so as to encourage public health authorities to collect the information which is essential for the success of vector control operations.

2. STATUS OF RESISTANCE IN CULICINE MOSQUITOS

Tables 1 and 2 summarize the information already available in 1975 and add the more recent information in italics.

2.1 Resistance in Culex

2.1.1 Culex of the pipiens group

2.1.1.1 Culex pipiens pipiens

Resistance of this sub-species to organochlorine insecticides, which was already widespread in Europe, North Africa and North America, has been observed in Iran (Lofti et al., 1975)

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TABLE 1. RESISTANCE IN CULICINES (OTHER THAN <u>AEDES</u>)

Species	DDT	Dieldrin	Malathion	Fenitrothion	Fenthion	Chlorpyrifos	Temephos	Propoxur	Pyrethrinoids	Others
Culex *pipiens pipiens*	Europe	Morocco[a]	Egypt		Egypt	Egypt	Egypt			Methoprene (Lab.)
	USA Iran[b] Iraq	Japan	Egypt France USA	France	Israel France USA	Israel France	Israel France			
pipiens pallens	Japan China	Korea	Japan Korea	Japan Korea		Japan	Japan			
pipiens quinquefasciatus	Almost everywhere		Cameroon Sierra Leone	Cameroon				Cameroon		
			Madagascar	Madagascar	Madagascar			Madagascar		Mermis
			Japan Taiwan Vietnam			Japan	Japan			Methoprene (Lab.)
			USA Kenya Guinea	USA Kenya Guinea	USA Kenya	USA Kenya	USA	Kenya	Permethrin (Lab.)	
tritaeniorhynchus	Japan Korea Taiwan Benin Nigeria Bangladesh	Japan Korea Taiwan Nigeria	Japan Korea	Korea	Japan Korea	Japan	Taiwan			
vishnui	Taiwan	Taiwan	Taiwan				Taiwan			
gelidus	Thailand Bangladesh	Thailand								
fuscocephalus	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan			
tarsalis	USA	USA	USA	USA	USA	USA	USA		Pyrethrins (Lab.)	Methoprene (Lab.)
nigripalpus	USA		USA							
peus	USA	USA	USA		USA		USA			
salinarius	USA	USA								
restuans	USA	USA								
erythrothorax	USA									
coronator	Panama									
neblosus	Benin									
poicilipes	Benin									
Psorophora *confinnis*	USA	USA								
discolor		USA								
Culiseta *inornata*	USA	USA	USA		USA	USA	USA			
Armigeres *sulbalbatus*	Japan Malaysia	Japan	Japan		Malaysia					
obturbans	Sri Lanka	Sri Lanka	Sri Lanka		Sri Lanka					
Mansonia *uniformis*		Thailand								
annulifora	Thailand	Thailand								
indiana	Thailand									

[a] Information before 1975

[b] Information after 1975

TABLE 2. RESISTANCE IN AEDES

Species	DDT	Dl.	Malathion	Fenitrothion	Fenthion	Chlorpyrifos	Temephos	Pyrethrinoids and others
Aedes aegypti	Almost all over the world except certain African straits		Antilles[a] Guyana Viet Nam Thailand Puerto Rico[b] Malaysia India	Jamaica	Antilles Suriname Colombia Puerto Rico Venezuela El Salvador Panama Guyana Malaysia ? Congo ?	New Caledonia	Antilles Guatemala Suriname Martinique Puerto Rico Colombia New Caledonia Florida	Decamethrin (Indonesia) Bioresmethrin
albopictus	India, Japan, Thailand, Malaysia, Indonesia, Viet Nam, Philippines, Cambodia		Viet Nam	Madagascar	Malaysia ? Madagascar			
polynesiensis	Tahiti							
vittatus	India							
fijiensis	Fiji							
pseudoscutellaris	Fiji							
togoi	Korea				Korea	Korea		
cantans	Czechoslovakia, Germany							
caspius	Sudan						France	
detritus	France						France	
nigromaculis	USA	USA	USA	USA	USA	USA	USA	Flit Mlo California
taeniorhynchus	USA Antilles	USA Antilles	USA					
sollicitans	USA	USA	USA				USA	
vexans	Canada				USA			
dorsalis			USA ?		USA ?			
canadensis						USA ?		
melanimon	USA		USA		USA			
sierrensis	USA							
triseriatus	USA							
atropalpus	USA							
cantator	Canada	Canada						

[a] Information before 1975.

[b] Information after 1975.

and in Iraq (Bakry et al., 1976); in the latter country there also appears to be tolerance to Gardêna.

In Egypt, Moustapha et al. (1977) have confirmed multiple resistance, or rather "multiple tolerance" of this mosquito to the organochlorines, particularly to malathion, dichlorvos, methyl parathion, bromophos, leptophos and also to a carbamate, carbaryl.

In France, resistance to chlorpyrifos observed in 1973 (Sinegre et al., 1976) in the vicinity of Montpellier has extended along the whole of the Languedoc coastline (Sinegre, 1978). In some places the LC_{95} has increased 73-fold. Resistance to chlorpyrifos produces cross-resistance to most of the organophosphorus compounds except for dimethoate, in respect of which the drop in susceptibility is only about threefold. On the other hand, there is no cross-resistance with propoxur or with the pyrethroids (Sinegre et al., 1977). The resistance phenomenon associated with esterase-20.64 is unrelated to autogenesis (Pasteur & Sinegre, 1978). It is therefore not suprising to observe it both in the anautogenous rural strains and in the autogenous urban strains. In the latter case the selection pressure probably comes not from the treatment of trees but from the use of chlorpyrifos for Culex control in enclosed spaces.

In the United States it is often difficult to know whether the resistance concerns Culex pipiens pipiens or Culex pipiens quinquefasciatus, which have an extensive sympatric zone, especially in California. In this State Cx. p. pipiens displays resistance of the order of eight times to fenthion (Georghiou et al., 1975a). In Utah both Hart & Womeldorf (1977) and Merell & Wagstaff (1977) regard this mosquito as resistant to fenthion and parathion by comparison with a particularly susceptible laboratory strain. The criteria used by these authors to identify the resistant strains are still very low (cf. section 3.2.2.1). It should be pointed out that resistance to malathion was reported in Missouri as long ago as 1965 (In: Mouchet et al., 1975).

By laboratory selection Brown et al. (1978) achieved about 100-fold resistance to methoprene in the fortieth generation. By selecting the same strain with diflubenzuron they achieved only a fivefold drop in susceptibility in 11 generations. However, susceptibility to growth inhibitors seems to fluctuate to some extent, with reversals to an earlier situation (Hsieh et al., 1974; Hsieh & Steelman, 1974).

2.1.1.2 Culex pipiens quinquefasciatus Say (= fatigans Wied)

This pantropical mosquito has undergone considerable expansion in recent decades and has become a pest in most tropical and subtropical cities. It was already well known that it was resistant to the organochlorine insecticides practically throughout the whole of its distribution area.

Resistance to malathion, detected in 1960 in Cameroon (In: Mouchet et al., 1975), was reconfirmed in the same country in 1975 by Colussa (WHO communication); it was accompanied by resistance to fenitrothion and to a carbamate, propoxur.

In 1980 the same author (WHO communication) observed a strain resistant to malathion, fenitrothion, chlorpyrifos and propoxur at Mombasa, Kenya.

In the United States multiple resistance to organophosphorus compounds, already reported in California by Georghiou et al. (1975b), has spread (Gutierrez et al., 1977). It now extends to Texas (Micks & Rougeau, 1977), to Louisiana (Steelman & Dewitt, 1976) and to Tennessee (Moseley et al., 1977), where, however, the tests were not performed by the method recommended by WHO.

In California multiple resistance extends to the hybrids Cx. pipiens x Cx. p. quinquefasciatus, the limit of which is difficult to establish. It is thought to be induced by agricultural spraying (Georghiou et al., 1975a).

The resistance is thought to be due to the esterase B 2 which catalyses the hydrolysis of β-naphthylacetate and may be suppressed by DEF (S,S,S-tributyl phosphorotrithioate) (Georghiou & Pasteur, 1978). This product, generally used as a defoliant, when used as a synergist restores to chlorpyrifos an activity compatible with its operational use. The effect is less marked with fenthion and parathion (Stewart, 1977).

There is no new information on the multiple resistance to organophosphorus compounds observed in Japan (In: Mouchet et al., 1975).

By selection of a multiple-resistant strain in the laboratory, Priester & Georghiou (1978) managed to achieve 400-fold resistance to perlethrin, of multifactorial origin (Priester & Georghiou, 1979). This strain was resistant to DDT, a finding which is not surprising: Plapp & Hoyer (1968) had already shown the existence of DDT/pyrethroid cross-resistance in Cx. tarsalis and houseflies which was linked to the gene kdr-O.

Finally, there was a 30-40% drop in parasite infestation by Romanomermis culicivorax in a strain of Cx. p. quinquefasciatus selected in the laboratory for 300 generations. This drop in parasite activity does not seem to be associated with a humoral mechanism (Petersen, 1978).

2.1.1.3 Culex pipiens pallens

There is no recent information on this subspecies from the Far East, in which resistance to DDT and dieldrin was reported in Korea (Self et al., 1974) and resistance to organophosphorus compounds was reported in Japan (Mukai et al., 1974).

2.1.2 Culex tritaeniorhynchus

No new information has been received on this mosquito since 1975, apart from the demonstration of its resistance to DDT in Bangladesh (Joshi, WHO communication, 1977), a phenomenon which had earlier been detected in Korea, Japan and Taiwan. The suspicions of resistance to the organophosphorus compounds in Korea (Self et al., 1974), Taiwan (Mitchell & Chen, 1974) and Japan (Moriya et al., 1969; Buei & Ito, 1974) have not been confirmed (or proved groundless).

2.1.3 Other Asiatic Culex species

Nothing has been published since the study by Mitchell & Chen (1974) in Taiwan on Cx. vishnui (formerly Cx. annulus) and Cx. fuscocephalus, two species which apart from their resistance to the organochlorines displayed some tolerance for the organophosphorus compounds.

The resistance of Cx. gelidus to DDT, already noted in Thailand, has been observed in Bangladesh (Joshi, WHO communication, 1977).

2.1.4 Culex tarsalis

Multiple resistance to the organophosphorus compounds has become widespread in California (Apperson, 1974; Gutierrez et al., 1976a). The tolerance to fenthion and parathion reported from Utah by Hart & Womeldorf (1976) seems slight.

Each organophosphorus compound selects a resistance to all substances in this group. Nevertheless, if selection at the larval stage produces resistance in adults, this resistance is slight (Apperson & Georghiou, 1975).

2.1.5 Other American Culex species

Gutierrez et al. (1976b) confirmed the resistance to organophosphorus compounds of Cx. peus in California and Boike et al. (1978) confirmed the resistance of Cx. nigripalpus to malathion in Florida.

No new information on the other American Culex species has been received since the 1975 review.

2.2 Resistance in Aedes

2.2.1 Aedes aegypti

Resistance of this mosquito to DDT and dieldrin is constant throughout its distribution area, except in Africa. In Africa and Madagascar there are many strains susceptible to the organochlorine compounds. These are generally forms with black integuments, i.e. forms specific to tropical Africa, found in localities which have not been subjected to insecticide pressure by vector control operations. Agricultural spraying does not generally seem to induce any very strong selection pressure on account of the ecology of this mosquito.

Since 1975 little information has been received about the resistance of this mosquito to the organophosphorus compounds, which occurred mainly in the Caribbean and South-East Asia. In India, however, Kaul et al. (1976) confirmed resistance to malathion. The drops in susceptibility observed were generally limited, which made it difficult to conclude that resistance was present. We accordingly defined thresholds of tolerance and resistance (Mouchet et al., 1972; Cossemans et al., 1978) which made it possible to "classify" the strains.

In Martinique in 1979 Yebakima et al. obtained an LC_{50} of 0.005 and an LC_{95} of 0.02 ppm, which were precisely within the "tolerance" zone. In the town of Fort de France the susceptibility of Ae. aegypti to temephos has only halved in 10 years. Admittedly the selection pressure was not very strong.

In Puerto Rico, Fox (1977) managed to increase resistance to fenthion 10-fold by selection in the laboratory over nine generations of an already "tolerant" strain. The LC_{50} rose from 0.013 to 0.015 ppm.

There has been no confirmation of the resistance to bioresmethrin reported in Bangkok by Wickhan (In: Mouchet, 1975). The laboratory study which followed showed, as was to be expected, that the strains resistant to DDT were three to five times less susceptible to bioresmethrin than the strains susceptible to DDT (Mouchet et al., 1975). In 1977, Prasittisuk & Busvine reported cross-resistance to permethrin of the order of 70 times in a DDT-resistant strain from Guyana.

Recently Shaw (WHO report, 1980) found at Semarang in Indonesia that a local DDT-resistant strain of Ae. aegypti gave only 50% mortality after one hour's exposure to paper impregnated with 0.025% decamethrin, which induced 100% mortality in anopheline mosquitos.

DDT-pyrethroid cross-resistance seems to be a fairly general phenomenon in South-East Asia (Chadwick et al., 1977).

2.2.2 Other Aedes species of South-East Asia and the Pacific

There has been no further information since 1975 on Ae. albopictus, Ae. polynesiensis, Ae. vittatus, Ae. fijiensis, or Ae. pseudoscutellaris.

Ae. togoï, suspected of resistance to fenthion and chlorpyrifos in Korea, is resistant to DDT in that country, particularly on the island of Jegu-do where it is a vector of Brugia malayi (Lee et al., 1977).

2.2.3 Palaearctic Aedes species

The cold-climate species which occur in only one or two generations each year do not always display resistance. This is the case with Ae. vexans, Ae. excrucians, Ae. communis, Ae. sticticus, and Ae. punctor in Czechoslovakia (Rettich, 1977). Only Ae. cantans seems to have developed resistance to DDT.

In France, in the Bas-Languedoc, the halophilic Aedes species Ae. caspius and Ae. detritus have been subjected to strong selection pressure by the organophosphorus insecticides which have been used for over 10 years by the mosquito control services; their susceptibility to these compounds has been gradually reduced in recent years.

By comparison with the results of the 1968 tests, the susceptibility to temephos of Ae. detritus has dropped 6.8-fold (Sinegre, 1978) when tested at 25°C. However, temephos is less active in cold water and when the tests are carried out at 10°C the resistance is of the order of 16-20-fold: the physiological resistance and the drop in activity due to the temperature have a cumulative effect (Sinegre, personal communication, in press). The operational implications of this phenomenon will be discussed later.

In the same regions the LC_{50} of temephos for Ae. caspius populations rose between 1968 and 1978 from 0.0008 to 0.0055 ppm, i.e. a 6.9-fold drop in susceptibility which Sinegre (1978) interprets as incipient resistance, the operational consequences of which can already be felt.

There is no resistance to fenitrothion in these two species.

2.2.4 Aedes nigromaculis

The multiple resistance to organophosphorus compounds in this mosquito of the irrigated fields in California has long been known. The phenomenon now extends to Utah, where resistance to parathion, fenthion and malathion has been reported (Hart & Womeldorf, 1976; Merell & Wagstaff, 1977).

In California the pyrethroids, particularly Pydrin®, still provide good control of the resistant strains when applied at 60 g per hectare. At a dose five times higher this product does not control Cx. quinquefasciatus (Lewallen & Stewart, 1977).

Trials with diflubenzuron have proved promising (Schaeffer et al., 1977). On the other hand, Ae. nigromaculis displays some "resistance" to Flit MLO. The dosage of this oil needs to be increased to control the resistant strains (Darwazeh, 1978).

2.2.5 Aedes taeniorhynchus

This species provides one of the rare examples of resistance to malathion; the resistance is limited to this compound only, and there is no cross-resistance with other organophosphorus compounds. This resistance to malathion has spread along the whole West Coast of the United States (Mount et al., 1974; Boike & Rathburn, 1975).

Initially this mosquito was highly susceptible to malathion, with an LC_{50} of 0.019 and an LC_{95} of 0.038. The larvae have developed 30-35-fold resistance and the LC_{95} is as high as 1.3 ppm, a value which would scarcely be regarded as indicating resistance in Ae. aegypti. The adults have developed much more pronounced resistance, roughly 500-fold, perhaps because it is mainly at this stage that selection pressure is exerted (Boike et al., 1978).

Resistance to malathion is believed to be inherited primarily as a single dominant gene (Seawright & Mount, 1975).

2.2.6 Other American Aedes species

Ae. sollicitans, which is already resistant to DDT, dieldrin and malathion, seems to be developing tolerance for temephos on the East Coast of the United States, with an LC_{50} exceeding 0.0025 ppm (Sutherland & Evans, 1976).

In Utah both Hart & Womeldorf (1976) and Merell & Wagstaff (1978) have reported resistance of Ae. dorsalis to fenthion, parathion and malathion and resistance of Ae. vexans to fenthion and parathion. To describe these strains displaying some degree of tolerance they used the term "borderline". It must be emphasized that Ae. vexans was already resistant to DDT in Canada, whereas in Europe this mosquito has up to now never displayed any reduction in susceptibility.

Sutherland & Evans (1976) suspected tolerance to chlorpyrifos in Ae. canadensis in the United States, with an LC95 of 0.22 ppm.

In California Gutierrez et al. (1976) mentioned resistance in Ae. melanimon to malathion and fenthion. This species had already been resistant to DDT, parathion and temephos since 1971 (Gillies et al., 1971).

There is no recent information on Ae. sierrensis, Ae. triseriatus, Ae. atropalpus and Ae. cantator.

2.3 Other culicine genera

No recent reports have been found on resistance in Culiseta, Psorophora and Armigeres.

It has been well known since the studies by Yap et al. (1968) in the United States, by Sinegre et al. (1971) in France, and by Yap & Hanapi (1976) in South-East Asia that Mansonia larvae by virtue of their specific biological characteristics are less susceptible to insecticides than the larvae of other mosquito genera. For example, Ma. richiardii larvae are 50 times less susceptible to fenthion and fenitrothion than Ae. caspius larvae. On the other hand, the susceptibility of the adults approaches that of Anopheles, according to the studies by Hamon & Sales (1963) on Ma. uniformis in Upper Volta. This species is susceptible to DDT and malathion in the Philippines (Galand & Wenceslao, 1973) and Thailand (Yasuno et al., 1967). On the other hand, it is resistant in that country to DDT and dieldrin and shows little susceptibility to malathion; Ma. indiana is resistant to DDT in Thailand.

Finally, Focks et al. (1979) showed that the adults of the predator mosquito Toxorhynchites rutilus were more susceptible to the organophosphorus insecticides and less susceptible to resmethrin than the species that would be their probable prey in biological control: Ae. aegypti and Cx. quinquefasciatus.

3. METHODOLOGY FOR THE STUDY OF RESISTANCE

3.1 Evaluation tests

Since the description of the tests on larvae and adults given in the seventeenth report of the Expert Committee on Insecticides (Anon, 1970) no substantial changes have been made in the methodology for evaluating susceptibility to insecticides.

3.1.1 Tests on adult insects

3.1.1.1 Exposure to a single concentration

One of the recommendations of the last Expert Committee (1975) concerned the measurement of susceptibility by exposure to a single concentration for variable periods of time, in view of the fact that concentration x contact time is constant, at any rate for DDT, the carbamates, and the organophosphorus compounds (Hamon & Sales, 1970; Sales & Mouchet, 1975). Since the cost of papers impregnated with organophosphorus compounds and carbamates is relatively high and their period of efficacy is fairly limited (hardly exceeding three months), this method could produce substantial savings. This method does not seem to have been used very much in recent years or to have been subjected to specific research.

3.1.1.2 Tests with aerosols

Mount et al. (1976) described apparatus for testing the efficacy of insecticides. The mosquito or fly is placed in a tunnel in which air is circulating at 6.4 km/h. An aerosol of insecticide is introduced into the tunnel and the insect thus receives a genuine topical application. Although this method is not specifically intended for measuring susceptibility, it enabled both Boike & Rathburn (1975) and Mount et al. (1974) to compare the lethal doses of different strains of Ae. taeniorhynchus and to determine their resistance by reference to a susceptible laboratory strain.

This technique avoids the difficulties inherent in the manufacture of high-concentration impregnated papers. However, the fairly complicated equipment makes the technique difficult to use on a large scale, particularly in the developing countries.

3.1.1.3 Evaluation of susceptibility to pyrethroids

The growing danger of cross-resistance between DDT and pyrethroids calls for increased surveillance.

At present no papers are available which are impregnated with the products most widely used, in particular bioresmethrin, permethrin and decamethrin. There is an urgent need to identify the best solvents for manufacturing these papers and to determine the effective concentrations for each product. Later on the stability of these papers should be studied so as to decide whether they should be manufactured extemporaneously or whether they keep long enough to permit semi-industrial manufacture and distribution by WHO.

Evaluation of susceptibility over time to a single dose is a possibility which ought to be explored. Nevertheless, in view of the knock-down effect of the pyrethroids it still has to be proved that concentration x contact time remains constant.

3.1.2 Larval tests

3.1.2.1 Quality of water

The drinking-water supplied by the official distribution services is often sterilized with calcium hypochlorite in doses of around 2 ppm. This substance induces rapid oxidation of some insecticides, bringing about a reduction in their activity which could give a false impression of resistance.

This phenomenon was reported for fenthion (Mouchet et al., 1972), in which it produces about 100-fold reduction in activity. It led the authors to cast serious doubt on certain cases of resistance to fenthion reported from practically all parts of the world, including some reported by themselves.

Recently (Sinegre, personal communication, 1980) has observed similar effects on temephos.

In laboratories which have no distilled water, this drawback can be overcome simply by leaving tap water in the fresh air for 24 hours. The hypochlorite decomposes and loses its activity; the tap water can then be used to perform the tests.

3.1.2.2 Conditions for performing the tests

We repeat our 1975 proposal to reduce the exposure time from 24 hours to six or even three hours. The tests could then be carried out and read on the same day, which would represent a great advantage for travelling investigators. The constancy of time x concentration has in fact been verified for the larvae (Brengues, 1964) and could easily be checked again.

Sinegre (personal communication, 1980) observed that the susceptibility of Ae. detritus to organophosphorus compounds varied from one to four, depending on whether the tests were carried out at 10°C or at 25°C. Under laboratory conditions it is unusual for the temperature to drop below 18°C, which limits the variations. It should be noted that the activity of some pyrethroids such as decamethrin increases when the temperature decreases.

The concentrated solutions of insecticides should be changed as frequently as possible and should in any case be kept in the refrigerator away from light. The same goes for impregnated papers.

In view of the growing difficulties presented by the cleaning of glass receptacles in laboratories in the industrialized countries, it would be useful to look into the possibility of using disposable cardboard or plastic receptacles.

3.1.3 Susceptibility of field and laboratory strains

It is often necessary to get an insect strain to reproduce in the laboratory for two or three generations so as to obtain a large enough number of specimens to carry out a series of tests. As Silberstein (personal communication) has shown, however, breeding in the laboratory induces a genetic drift involving the loss of certain alleles. These alleles could affect the susceptibility to insecticides, although this has never been proved.

However, in the Ae. aegypti strains from the Caribbean tested in the laboratory we have always observed lower LC_{50}s and LC_{95}s than those reported by Tinker in extemporaneous tests on natural populations (in VBC/IRG).

This point deserves to be clarified because it could be important to detect resistance to organophosphorus insecticides in its early stages. Later on, when resistance is well established, there is little or no risk of failing to detect it.

3.2 Determination of resistance

3.2.1 Classification of strains

The initial studies on resistance concerned the organochlorine compounds, DDT and dieldrin. In most cases the resistance is monofactorial and rapidly becomes widespread as soon as the population carrying the resistance gene is submitted to selection pressure. In the laboratory it has generally been possible to isolate the susceptible and resistant genotypes and to evaluate their susceptibility together with that of the hybrids in terms of the LC_{50} or LC_{95}. It is then easy to determine whether the strain is susceptible, resistant or heterozygous and to establish diagnostic criteria.

On the other hand, resistance to the organophosphorus compounds generally develops slowly and continuously; no criteria have been put forward for distinguishing between the SS and RR homozygotes and the hybrids.

Sinegre et al. (1976) proposed classifying the strains according to the ratio:

$$\frac{LC_{50} \text{ of tested strain}}{LC_{50} \text{ of susceptible reference strain}}$$

and the ratio: $\frac{LC_{95}}{LC_{50}}$

If the first ratio is lower than 2.5 the strain is susceptible, if it is between 2.5 and five the strain is tolerant, if it is above five the strain is resistant. Moreover, if the ratio

$$\frac{LC_{95}}{LC_{50}}$$

is below 2.5, the strain is homogeneous, susceptible or resistant; if it is higher the strain is heterogeneous. This latter situation is encountered when a drop in susceptibility starts to appear. Coosemans et al. (1978) did not make allowance for the heterogeneousness of the response within one strain, but did take the increase in LC_{95} into consideration. After determining the natural variability of 250 strains of Ae. aegypti they calculated the P_1 and P_2 values of the LC_{95}s, which correspond to probabilities of 10^{-3} and 10^{-4} of having a normal strain. Between these two values they regard the strains as tolerant; above the second value they regard them as resistant.

The term "tolerance" was rejected by the last Expert Committee. It is very useful, however, especially at the operational level, for classifying strains which have undergone a drop in susceptibility but which have not developed a high level of resistance. These strains ought after all to be kept under very special surveillance, but it has not been proved that they develop high resistance liable to endanger control operations. This is the situation which has existed for more than 10 years with Ae. aegypti in the Caribbean.

Moreover, Sinegre also uses the term tolerance and WHO in its computer programme uses the term "intermediate", which has a similar meaning. Here attention must be drawn to the inconsistency of the diagnoses provided by the computer, which needs reprogramming.

More recently, in Utah in the United States, Merell & Wagstaff (1977) introduced the term "borderline" to describe the intermediate strains.

It is essential to adopt a term (intermediate, tolerant, borderline) to describe the strains whose status is not easy to define. This is not a terminology dispute but reflects the need to provide clear information for the agencies responsible for vector surveillance, one of the essential duties of WHO.

3.2.2 Diagnostic doses

In order to simplify the procedures for evaluating susceptibility, the last Expert Committee in 1975 proposed performing a single test with one diagnostic dose. If more than 5% survive this dose, the strain should be regarded as resistant.

3.2.2.1 Larvae

The report of the Expert Committee (page 82) presents two series of diagnostic doses for the larvae of Ae. aegypti and Cx. fatigans (Table 3). In the same year, after the meeting of the Committee but before publication of its report, a mimeographed WHO document (Anon, 1975b, WHO/VBC/75.583) proposed diagnostic doses which differ substantially, especially for malathion and temephos (Table 3).

Finally, in 1978 Coosemans et al. proposed diagnostic doses for Ae. aegypti which are fairly close to those proposed by the Expert Committee (Table 3). Nevertheless these authors provide two values, the former for distinguishing the "tolerant" strains and the latter for distinguishing the resistant strains. The last Expert Committee rejected the idea of two discriminating doses. In practice, however, it is found that the use of a single dose leads to confusion. If the dose is too high it does not reveal resistance in its early stages when it is only slight. If the dose is too low there is a danger that it will mislead the authorities responsible for mosquito control and result in unjustified measures. Accordingly we believe that two doses should be used even if this calls for extra work by the investigators.

The diagnostic doses for Cx. quinquefasciatus proposed by the Expert Committee are identical to those for Ae. aegypti. Rapid analysis of the results stored in the computer leads us to the same conclusions.

The differences appearing in document WHO/VBC/75.583 probably arise from the fact that the doses proposed for Anopheles were also recommended for the culicine mosquitos, which is not a legitimate procedure.

TABLE 3. DIFFERENT DIAGNOSTIC DOSAGES RECOMMENDED FOR CULICINE MOSQUITOS

	DDT	Dieldrin	Malathion		Fenitrothion		Fenthion		Temephos		Chlorpyrifos	
Coosemans, 1978			1.0	2.0	0.06	0.1	0.05	0.1	0.02	0.03	0.01	0.015
WHO/VBC 75.583			3.125		0.125		0.05		0.125		0.025	
Expert Committee report												
Aedes aegypti	0.05	0.02	0.25*		0.05		0.05		0.02		0.01	
Culex fatigans			1.25		0.05		0.05		0.02		0.01	

* Probably this is a typographical error and should read 1.25.

Susceptibility may in fact vary considerably from one species to another. In Utah, Hart & Womeldorf (1976) and Merell & Wagstaff (1977) proposed discriminating doses for Ae. vexans, Ae. dorsalis and Cx. pipiens related to the LC50s (Table 4); these doses were much lower than those proposed in 1975 for Ae. aegypti by Mouchet et al.

TABLE 4. DISCRIMINATING DOSAGES FOR AEDES DORSALIS

LC_{50}		0.0025	0.005
Parathion Fenthion	susceptible	borderline	resistant
LC_{50}		0.05	0.01
Malathion	susceptible	borderline	resistant

It would be a good idea to propose diagnostic dosages for all the major vectors.

3.2.2.2 Adults

Comparatively few data are available on the susceptibility of adult culicine mosquitos to the organophosphorus insecticides and the carbamates. The data were collated for the previous Expert Committee (Mouchet et al., 1975). The findings on the two species on which most information is available, Cx. quinquefasciatus and Ae. aegypti, can be summarized as follows (Table 5) for the African strains (Hamon & Sales, 1963, 1970; Sales & Mouchet, 1973).

TABLE 5. SUSCEPTIBILITY OF ADULT CULICINE MOSQUITOS

(One hour's exposure)

Species	Malathion		Fenitrothion		Fenthion		Propoxur	
	LC_{50}	LC_{95}	LC_{50}	LC_{95}	LC_{50}	LC_{95}	LC_{50}	LC_{95}
Aedes aegypti	0.84 to 1.2	1.5 to 2.5	0.2	0.45	0.23 to 0.35	0.4 to 0.65	0.092	0.22
Culex fatigans	1.06 to 1.15	2.2	0.65	1.2 to 1.3	0.21 to 0.38	0.43 to 0.75	0.068	0.19

There are therefore few differences between the two species, except in respect of fenitrothion.

In document WHO/VBC/75.582 (Anon, 1975a), the diagnostic doses proposed for Cx. quinquefasciatus were as follows:

Malathion : 5% for 30 minutes

Fenitrothion : 1% for 1 hour

Fenthion : 2.5% for 30 minutes

Propoxur : 0.1% for 2 hours

These diagnostic doses are close to the LC_{95}s, except for fenthion. For this insecticide the dose seems to be too high.

For convenience in the tests and to simplify the work of the investigators, it would be a good idea to reduce the contact time to one hour by adopting the appropriate concentration.

4. DYNAMICS OF RESISTANCE

The problems relating to the dynamics of resistance were explained very clearly in the report of the 1975 Expert Committee (Anon, 1976, pp. 53-57) and by Georghiou & Taylor (1976).

The information obtained in recent years provides a basis for specific observations in support of certain concepts.

The pace at which resistance develops varies according to the insecticide pressure. In Louisiana Steelman & Dewitt (1976) noted a pronounced development of resistance by Cx. quinquefasciatus to chlorpyrifos (X 42), to malathion (X 47) and to naled (X 60) in rural areas subjected to intense pressure from agricultural spraying, whereas the peri-urban strains remained susceptible.

In the south of France, Sinegre et al. (1977) observed regularly developing resistance in Cx. pipiens to chlorpyrifos, increasing from 13-fold to 73-fold in five years following continuous insecticide applications by the mosquito control services and farmers.

1972	R X 13	(by comparison	with a	susceptible	strain)
1973	R X 15	"	"	"	"
1974	R X 33	"	"	"	"
1975	R X 47	"	"	"	"
1976	R X 73	"	"	"	"

At Fort de France in Martinique, the susceptibility of Ae. aegypti to temephos was only halved between 1968 and 1978 (Yebakima et al., 1979). The temephos applications were undoubtedly somewhat lax, but the ecology of this species safeguards it from insecticide pressure associated with agricultural activities. Moreover, it is quite conceivable that there is some intrinsic genetic factor which limits the extent of resistance in this species to the organophosphorus compounds: although resistance to organophosphorus insecticides in Ae. aegypti has been reported in the Caribbean for more than 10 years, it has never reached a very high level, even though Fox (1977) managed to achieve 50-fold resistance to fenthion by selection.

The extent of resistance is less marked for the organophosphorus compounds, where it rarely reaches 100-fold, than for DDT, where it may be as high as 1000-fold in Ae. aegypti for example.

One of the rare exceptions is resistance to malathion in Ae. taeniorhynchus, which can be as high as 500-fold in adults (Boike et al., 1978). Laboratory selection indicates that resistance to the pyrethroids can reach a high level in Cx. quinquefasciatus (Priester & Georghiou, 1978).

The number of generations per year conditions the speed at which resistance develops. In Czechoslovakia the univoltine or bivoltine Aedes species display no resistance, even though DDT has been used for many years against them (Rettich, 1977).

The development of resistance is encouraged if the population is isolated and slowed down when there is a high degree of immigration. Conversely emigration may carry the resistance genes into untreated regions. In the south of France Ae. detritus has developed 6.8-fold resistance to temephos after more than 10 years of intensive use of this compound for Aedes control. However, the area subjected to insect control is next to the Camargue National Park where no insecticides are used except in agriculture. Ae. detritus has a long flight range and there are substantial movements between the two areas, which explains the low degree of resistance; on the other hand, however, susceptibility has dropped almost fourfold in the untreated Camargue region (Sinegre, 1978, and personal communication, 1980).

Susceptibility to insecticides varies with the seasons and, in the case of larvae, with the water temperature in the breeding place. As stated above for Ae. detritus, it drops almost fourfold between 25°C and 10°C. Resistance varies in the same proportion, reaching 20-fold in the spring whereas it is only sixfold in the summer.

5. RELATIONSHIPS BETWEEN RESISTANCE IN LARVAE AND IN ADULTS

It has often been noted that some species display strong resistance in the adult state, whereas their larvae are almost susceptible. This was particularly the case with Cx. quinquefasciatus in Africa (Hamon & Mouchet, 1967). In Korea adult Cx. tritaeniorhynchus displayed tolerance to the organophosphorus compounds whereas the larvae were susceptible (Self et al., 1974).

Margham & Wood (1976) showed that in Ae. aegypti there were two types of resistance to DDT governed by different genes. One type occurred mainly in the larvae, the other mainly in adults. Selection pressure at the larval stage increased the resistance of the pre-imaginal stages, but not necessarily that of the adults.

Similarly, Apperson and Georghiou (1975) observed that the selection of Cx. tarsalis at the larval stage by organophosphorus compounds produced only a slight increase in resistance in adults. In Florida adulticide treatments with malathion produced 500-fold resistance in adult Ae. taeniorhynchus, whereas the resistance was not more than 10-fold in the larvae (Boike et al., 1978).

It is therefore important to carry out the susceptibility tests on the stage which is subjected to control operations, otherwise major operational problems may occur.

6. OPERATIONAL CONSEQUENCES AND REPLACEMENT PRODUCTS

We shall not go into detail on this point as it is dealt with elsewhere.

However, it should be pointed out that the consequences of resistance take very different forms depending on:

- the extent of resistance;

- the ecology of the insects concerned.

In the Lower Languedoc in France, for example, where the breeding sites of Aedes detritus and Aedes caspius have been treated mechanically with carefully judged doses, a sixfold reduction of suceptibility to temephos in these two species produced operational repercussions, particularly for the former; the treatments are in fact carried out in the spring in cold water, which heightens the manifestations of resistance.

An increase in the dose, apart from its financial implications, may have repercussions on non-target fauna which are not readily acceptable to the ecologists.

On the other hand, a 10-fold drop in the susceptibility to temephos of Ae. aegypti in the Caribbean had no operational consequences because applications to small breeding places in the vicinity of homes are almost always characterized by an "overdose".

Among the replacement products, the pyrethroids have aroused great hopes. It is important therefore to keep a watch on the development of resistance to these products, something that is unfortunately quite feasible in view of the possibilities of cross-resistance with DDT.

The operational aspect of resistance to oils, growth inhibitors and to Mermis has not been assessed.

It should be noted that in the laboratory Harvey & Howell (1965) achieved a 10-50-fold reduction in the susceptibility of flies to Bacillus thuringiensis after selection over 27 generations. At a time when the use of this biological insecticide against culicine mosquitos is being seriously considered it would be advisable to carry out similar studies on mosquitos.

7. CONCLUSIONS

This review reveals a lack of interest on the part of research workers in the problems of resistance; this is probably connected with the poor image of insecticides in the academic world, which is largely characterized by "ecological" ideologies.

This is a deplorable situation because insecticides, after all, remain the basis for most vector control campaigns. In the absence of competent scientists there is a danger that responsibility for these campaigns will fall into the hands of non-specialist technicians. It is then that there would be a risk of the operations becoming ineffective and causing pollution.

Little is in fact known about the resistance situation in culicine mosquitos. There are only a few countries where investigators are carrying out high-quality studies, often in a climate of general indifference.

Many developing countries carry out few vector control operations unless these operations are included in major, often international, programmes which benefit the countries at no cost to themselves. The achievements reported at international meetings often take on more modest proportions when they are objectively evaluated, for the integration of vector control into public health planning is difficult to achieve. In the context of growing decentralization there is reason to fear that the technical problems, including resistance to insecticides, are not always taken fully into account.

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