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INSECTICIDE RESISTANCE AND VECTOR CONTROL

Seventeenth Report of the WHO Expert Committee on Insecticides

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Geneva, 19-25 November 1968

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INSECTICIDE RESISTANCE AND VECTOR CONTROL

Seventeenth Report of the WHO Expert Committee on Insecticides

The WHO Expert Committee on Insecticides met in Geneva from 19 to 25 November 1968. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General.

1. PRESENT STATUS OF RESISTANCE

1.1 Resistance of arthropods to insecticides

In 1962, the WHO Expert Committee on Insecticides reported that there was clear evidence of developed resistance in 81 arthropod species of medical or veterinary importance, and indications of resistance in about 10 more. In 1968, the number of species which had developed resistance was 102, with isolated indications in 4 more. Many of them have developed 2 or even 3 types of resistance, the comparison over the 6-year period being as follows:

	DDT resistance	*Dieldrin resistance*	*Organophosphorus resistance*
1962	47	65	8
1968	56	84	17

Among the anopheline mosquitos, 38 species have developed resistance to 1 or more insecticide, 36 having developed resistance to dieldrin, 15 to DDT (Table 1), and increased tolerance to malathion developed in 1 species. Among the culicine mosquitos 19 have developed resistance, 16 to DDT, 12 to dieldrin, and 9 to organophosphorus compounds (Table 2), with 4 additional isolated cases which will be mentioned later.

In the housefly, resistance to malathion or to diazinon is now becoming quite widespread in Western Europe, North America and Japan, and diazinon resistance has appeared in Australia (Table 3). Resistance to ronnel is now common in California, with cross-tolerance to fenthion; cross-resistance to dimethoate has been low, but control failures with

TABLE 1.

RESISTANCE OF ANOPHELINE MOSQUITOS TO DDT AND DIELDRIN [a]

Insecticide	Mosquito	Year	Area
DDT	*A. sacharovi*	1951	Greece ; Iran ; Turkey
	A. sundaicus	1954	Java ; Sumatra
	A. stephensi	1955	Saudi Arabia ; Iraq ; Iran ; S. India
	A. subpictus	1956	N. India ; W. Pakistan; Nepal ; Java
	A. albimanus	1958	El Salvador ; Nicaragua ; Guatemala ; Honduras ; Mexico ; Cuba
	A. pharoensis	1959	Egypt ; Sudan
	A. quadrimaculatus	1959	Georgia, USA ; Maryland, USA ; Mexico
	A. annularis	1959	India
	A. culicifacies	1960	W. & S. India ; W. Pakistan ; Nepal
	A. albitarsis	1961	Colombia
	A. nuneztovari	1961	Venezuela
	A. aconitus	1962	Java
	A. fluviatilis	1963	W. India
	A. hyrcanus sinensis	1964	Ryukyus
	A. gambiae	1967	Upper Volta ; Senegal
Dieldrin	*A. sacharovi*	1952	Greece
	A. quadrimaculatus	1953	Mississippi, USA ; Georgia, USA ; Mexico
	A. gambiae	1955	Nigeria ; Liberia ; Ivory Coast ; Dahomey ; Upper Volta ; Cameroon ; Sierra Leone ; Togo ; Ghana ; Mali ; Congo (Brazzaville) ; Sudan ; Mauritania ; Madagascar
	A. subpictus	1957	Java ; Ceylon ; N. India ; W. Pakistan
	A. coustani and *A. pulcherrimus*	1957	Saudi Arabia
	A. albimanus	1958	El Salvador ; Guatemala ; Nicaragua ; Honduras ; Jamaica ; Ecuador ; Mexico ; British Honduras ; Cuba ; Dominican Republic ; Haiti ; Colombia
	A. pseudopunctipennis	1958	Mexico ; Nicaragua ; Peru ; Venezuela ; Ecuador
	A. aquasalis	1958	Trinidad ; Venezuela ; Brazil
	A. culicifacies	1958	W. India ; Nepal
	A. vagus	1958	Java, Philippines
	A. barbirostris and *A. annularis*	1958	Java
	A. sergenti	1958	Jordan
	A. fluviatilis	1958	Saudi Arabia
	A. splendidus	1958	N. India
	A. stephensi	1959	Iran ; Iraq
	A. minimus flavirostris	1959	Philippines ; Java
	A. pharoensis	1959	Egypt ; Sudan ; Israel
	A. albitarsis	1959	Colombia ; Venezuela
	A. labranchiae	1959	Morocco ; Algeria
	A. strodei	1959	Venezuela
	A. triannulatus	1959	Venezuela ; Colombia
	A. sundaicus	1960	Java ; Sumatra ; Sabah
	A. aconitus	1960	Java ; India
	A. neomaculipalpus	1960	Trinidad ; Colombia
	A. crucians	1960	S. Carolina, USA ; Dominican Republic
	A. filipinae	1960	Philippines
	A. maculipennis	1961	Romania
	A. rangeli	1961	Venezuela
	A. maculipennis messeae	1961	Romania
	A. labranchiae atroparvus	1961	Romania ; Bulgaria
	A. philippinensis	1962	Sabah
	A. funestus	1962	Nigeria ; Ghana ; Kenya
	A. nili	1966	Ghana
	A. rufipes	1968	Mali

[a] This table covers only the first reported instance of resistance in any area.

TABLE 2. RESISTANCE OF CULICINE MOSQUITOS TO THREE INSECTICIDE GROUPS [a]

Mosquito	DDT group		HCH-dieldrin group		Organophosphorus group [b]	
	Year	Area	Year	Area	Year	Area
Culex fatigans (quinquefasciatus)	1952	India	1951	California, USA	1959	Cameroon (O)
	1953	Reunion	1953	Malaya ; India	1960	California, USA (M)
	1956	Venezuela ; Taiwan	1954	E. Asia	1963	Sierra Leone (O)
	1957	Puerto Rico	1956	S. America	1967	Ryukyus (M)
	1958	W. Africa ; S. Australia ; Panama	1957	W. Africa		
	1959	Tanganyika ; Hawaii ; Congo	1958	Panama		
	1961	Madagascar ; Cuba ; Georgia, USA	1959	Zanzibar ; Congo		
			1960	Texas, USA		
	1964	China (mainland)	1961	Mali ; Madagascar ; Brazil		
	1966	Ryukyus ; Queensland, Australia	1964	Tanganyika ; China (mainland)		
			1966	Togo ; Ivory Coast ; Queensland, Australia		
C. pipiens	1947	Italy	1950	Italy		
	1955	Massachusetts, USA ; New Jersey, USA	1955	Israel		
	1959	Israel ; Japan ; California, USA	1959	France ; Japan		
	1961	New York, USA ; Maryland, USA ; Illinois, USA ; Utah, USA	1965	Korea		
			1966	Morocco		
	1965	France ; Korea ; Turkey				
C. tarsalis	1951	California, USA	1951	California, USA	1956	California, USA (M)
	1956	Oregon, USA	1961	Oregon, USA	1961	Oregon, USA (M)
	1961	Washington, USA ; Utah, USA				
C. coronator	1958	Panama				
C. tritaeniorhynchus	1958	Ryukyus	1959	Dahomey ; Ryukyus	1967	Ryukyus (M)
			1965	Korea		
C. peus	1961	Oregon, USA				California, USA (M)
Aedes aegypti	1954	Trinidad ; Dominican Republic	1959	Puerto Rico	1965	Jamaica, Venezuela (M)
	1955	Venezuela	1962	Jamaica ; Haiti ; Curaçao	1966	Thailand ; S. Viet-Nam (M) ; Congo (Brazzaville)
	1956	Haiti	1963	Virgin Islands		
	1957	Antigua, Colombia	1964	Surinam ; Guyana ; Cambodia ; S. Viet-Nam		
	1958	S. Viet-Nam				
	1959	Puerto Rico ; Jamaica ; Guadeloupe ; French Guinea	1965	Texas, USA		
			1966	Cameroon ; Tahiti ; Thailand ; Congo ; Senegal ; Ivory Coast		

TABLE 2. RESISTANCE OF CULICINE MOSQUITOS TO THREE INSECTICIDE GROUPS [a] (concluded)

Mosquito	DDT group		HCH-dieldrin group		Organophosphorus group [b]	
	Year	Area	Year	Area	Year	Area
Aedes aegypti (cont.)	1961 1963 1965 1966 1968	Florida, USA Guyana ; Thailand E. India ; Japan ; Texas, USA W. India ; St Vincent Liberia ; Ivory Coast ; Dahomey ; Cameroon	1968	Liberia ; Togo ; Nigeria ; Upper Volta		
A. sollicitans	1947 1951	Florida, USA Delaware, USA	1951 1958	Florida, USA Delaware, USA		
A. taeniorhynchus	1949 1959	Florida, USA Georgia, USA	1951 1959	Florida, USA Georgia, USA		
A. nigromaculis	1949	California, USA	1951	California, USA	1958 1960	California, USA (P) California, USA (M)
A. melanimon [c]	1951	California, USA	1951	California, USA	1962	California, USA (P)
A. dorsalis					1966	New Mexico, USA (O
A. cantator	1960	New Brunswick, Canada	1960	New Brunswick, Canada		
A. cantans	1958	Germany				
A. detritus	1959	France				
A. albopictus	1964	S. Viet-Nam, S. India				
A. vittatus	1964	W. India				
Psorophora confinnis			1954	Mississippi, USA		
P. discolor			1954	Mississippi, USA		

[a] This table covers only the first reported instance of resistance in any area.
[b] M = malathion resistance ; P = parathion resistance ; O = general organophosphorus resistance.
[c] Formerly called *A. dorsalis*.

TABLE 3. RESISTANCE TO THREE INSECTICIDE GROUPS BY NOXIOUS DIPTERA [a]

Species	DDT group		HCH-dieldrin group		Organophosphorus group	
	Year	Area	Year	Area	Year	Area
Musca domestica	1946	Sweden ; Denmark	1949	California, USA ; Sardinia ; Egypt	1955	Denmark ; Florida, USA
	1947	USA ; Mediterranean	1950	USA ; Scandinavia	1956	Switzerland ; Italy ; Georgia, USA
	1948	New Zealand ; S. America	1951	S. America	1957	New Jersey, USA
	1949	W. Europe ; Canada	1952	Africa	1958	California, USA ; Arizona, USA ; Louisiana, USA
	1950	USSR ; Africa	1953	USSR	1960	Japan
	1953	Japan	1954	Japan	1961	Germany ; France
	1956	China	1957	India	1962	Australia
	1958	Czechoslovakia ; Poland	1961	Caribbean	1967	USSR
	1960	India	1962	Romania		
Stomoxys calcitrans	1948	Sweden	1958	Norway		
	1958	Norway	1965	Florida, USA		
	1966	Germany ; Italy	1966	Germany		
Phaenica cuprina			1957	Australia	1966	Australia
Phaenica sericata			1959	New Zealand ; S. Africa		
Chrysomyia putoria			1949	Congo (Kinshasa)	1954	Congo (Kinshasa)
			1960	Madagascar		
			1961	Zanzibar		
Protophormia terraenovae	1964	European Russia				
Haematobia irritans			1959	Texas, USA	1962	Louisiana, USA
Fannia canicularis	1953	Spain	1967	California, USA		
	1962	Japan				
	1967	England ; California, USA				

TABLE 3. RESISTANCE TO THREE INSECTICIDE GROUPS BY NOXIOUS DIPTERA [a] (concluded)

Species	DDT group		HCH-dieldrin group		Organophosphorus group	
	Year	Area	Year	Area	Year	Area
F. femoralis	1967	California, USA	1967	California, USA		
Simulium aokii	1963	Japan				
S. ornatum	1966	Japan				
S. venustum	1967	Quebec, Canada				
Chironomus zealandicus			1966	New Zealand		
Glyptotendipes paripes			1953	Florida, USA	1955	Florida, USA
Chaoborus astictopus	1961	California, USA				
Psychoda alternata	1949	Illinois, USA	1953	England		
Leptoconops kerteszii	1961	California, USA				
Culicoides furens			1958 1959	Florida, USA Panama		
Hippelates collusor			1957	California, USA		
Leptocera hirtula	1955	Malaya	1955	Malaya		
Drosophila virilis [b]	1952	Japan				

[a] This table covers only the first reported instance of resistance in any area.
[b] Also *D. melanogaster*, both field strains.

dimethoate started to appear in Denmark and New Jersey in 1966. Resistance to trichlorfon in baits and sprays has been encountered first in Florida, then in Denmark, and very recently in the USSR. The use of dichlorvos vapour can induce resistance, but very slowly. Resistance to coumithioate has developed in Italy; fenitrothion and Gardona [1] have not yet been used long enough for their liability to resistance to be determined.

The stable fly, *Stomoxys*, has developed DDT resistance in Western Europe and dieldrin resistance in Florida. The latrine fly, *Fannia canicularis*, has become resistant to DDT in England and Japan, and in addition is resistant to dieldrin in California where *F. femoralis* has also developed resistance to both insecticides. The blowfly, *Protophormia terraenovae*, has developed DDT resistance in European Russia. The horn fly, *Haematobia*, first developed resistance to toxaphene in Texas, and then to ronnel in Louisiana. The sheep blowfly, *Phaenicia cuprina*, is gradually developing resistance to diazinon in New South Wales, Australia. Whether the same change has occurred in the dieldrin-resistant species *P. sericata* in South Africa (wrongly listed as *P. cuprina* in the Committee's thirteenth report) has yet to be established. Increased tolerance to DDT and dieldrin in *Leucophyra leucostoma* in California is not yet high enough to be listed. Resistance has not yet been recorded in *Phlebotomus*, or in *Glossina*.

One of the most serious developments has been the recent appearance of populations of *Simulium* blackflies resistant to the larvicides which have been used against them, DDT resistance and some HCH tolerance has been reported in a population of *S. aokii* near Tokyo, and DDT resistance coupled with tolerance to fenthion in *S. ornatum* at Chino, Japan. A third species, *S. venustum*, has developed a population 10 times as resistant to DDT as normal in an area of Quebec Province, Canada, which had been treated with this insecticide for the preceding 10 years. A recent control failure with DDT against *S. damnosum* on the lower Volta River in Ghana may have been caused by an increased tolerance to DDT in this important vector of onchocerciasis. Among the midges, the only addition since 1962 is *Chironomus zealandicus*, which has developed resistance to HCH and cyclodiene insecticides in New Zealand.

Among body lice, new records of DDT-resistant populations have come from Hungary and Romania, and strong HCH resistance has recently been found in Turkey (Table 4). There have been a number of new reports of resistance among lice of veterinary importance and these are listed in Table 4.

New records of chlordane resistance in the German cockroach, *Blattella*, have come from Germany, Denmark, Hawaii, New South Wales (Australia) and New Guinea. Diazinon resistance has been found in Texas as well as in Kentucky and Indiana, and malathion resistance in Louisiana, Texas

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[1] Dimethyl 2,4,5-trichloro-alpha-(chloromethylene)benzyl phosphate.

TABLE 4. RESISTANCE OF CERTAIN ARTHROPODS OF PUBLIC HEALTH AND VETERINARY IMPORTANCE [a]

Species	DDT group		HCH-dieldrin group		Organophosphorus group	
	Year	Area	Year	Area	Year	Area
Pediculus corporis	1951 1952 1955 1956 1958 1959 1961 1964	Korea ; Japan Egypt ; E. Mediterranean (UNRWA camps) Iran ; Turkey ; Ethiopia ; W. Africa ; Peru ; Chile France Yugoslavia ; Libya ; Afghanistan ; India Mexico ; Uganda Sudan Romania	1955 1956 1957 1958 1959 1961	France ; Japan W. Africa ; S. Africa Iran India ; Korea Tanganyika Sudan		
Linognathus vituli	1957 1966	Virginia, USA Alberta, Canada				
L. africanus and *L. stenopsis*			1967	S. Africa		
Haematopinus eurysternus	1964	Alberta, Canada	1964	Alberta, Canada	1966	Alberta, Canada
Boophilus limbata and *B. caprae*			1957	Texas, USA		
Blatta orientalis	1964	Czechoslovakia	1958 1964	Germany Czechoslovakia		
Blattella germanica	1958 1959 1961	France ; Germany ; Cuba ; Bahamas ; Puerto Rico Trinidad ; Poland England	1951 1955 1956 1958 1959 1961 1963	Texas, USA S. E. USA N. E. USA California, USA ; Panama ; Cuba ; Puerto Rico Canada ; Trinidad ; Japan ; Poland England ; Germany Denmark ; Hawaii ; Australia ; New Guinea	1960 1964 1966	Kentucky, USA ; Indiana, USA Texas, USA Louisiana, USA

Periplaneta brunnea			1968	Florida, USA	1968	Florida, USA
Cimex lectularius	1947	Hawaii	1954	Italy	1964	Israel
	1952	Ohio, USA; Illinois, USA; Indiana, USA; Utah, USA; Congo; Israel; Korea; Greece	1956	Israel		
	1953	Japan; Italy	1960	Indonesia; Zambia; Rhodesia; Borneo		
	1955	Iran; Colorado, USA; Pennsylvania, USA; Texas, USA	1961	S. India		
	1956	French Guiana	1962	S. Africa		
	1957	Trinidad; Turkey	1965	N. India		
	1959	Hungary; Poland; Rhodesia	1967	Egypt		
	1960	Borneo; Indonesia; Colombia				
	1961	S. India				
	1962	S. Africa				
	1967	Egypt				
C. hemipterus	1952	Taiwan	1956	W. India		
	1954	Hong Kong; Singapore	1957	Tanzania; Kenya; Upper Volta		
	1955	W. India	1959	Dahomeh; Zanzibar		
	1957	Somalia; Kenya	1960	Malaya; Gambia		
	1960	Malaya; Gambia; Thailand	1961	Madagascar; S. India		
	1961	Madagascar; S. India				
Pulex irritans	1949	Peru	1959	Tanzania		
	1950	Ecuador	1965	Turkey		
	1951	Greece	1967	Egypt		
	1952	Brazil; Palestine				
	1965	Turkey				
	1967	Egypt				
Ctenocephalides canis and/or *C. felis*	1952	Georgia, USA	1956	USA		
	1953	French & British Guiana; Colombia	1957	Hong Kong		
	1956	Scattered areas of USA	1958	Hawaii; Japan		
	1958	Hawaii				
Xenopsylla cheopis	1959	W. India	1962	W. India; S.E. India		
	1960	S. India	1966	Thailand		
	1961	N. India				
	1964	S. Viet-Nam				
	1966	Thailand				
	1967	Egypt				
X. astia	1961	N. India	1962	S. India		
	1962	S. India				

TABLE 4. RESISTANCE OF CERTAIN ARTHROPODS OF PUBLIC HEALTH AND VETERINARY IMPORTANCE [a] (concluded)

Species	DDT group		HCH-dieldrin group		Organophosphorus group	
	Year	Area	Year	Area	Year	Area
Boophilus decoloratus	1956	Cape Province, S. Africa	1948 1952 1956	Cape Province, S. Africa Transvaal N. Rhodesia		
B. microplus	1954 1956	Queensland, Australia Brazil	1950 1952 1960	Queensland, Australia Brazil N. India ; Guadeloupe	1964	Queensland, Australia
Amblyomma americanum			1954 1963	Oklahoma, USA Madagascar		
Rhipicephalus sanguineus			1954 1958 1961	New Jersey, USA Panama ; Texas, USA Puerto Rico		
R. evertsi			1960	S. Africa		
R. appendiculatus			1965	S. Africa		
Dermacentor variabilis	1959	Massachusetts, USA	1959	Massachusetts, USA		

[a] This table covers only the first reported instance of resistance in any area.

and Colorado. The cross-resistance to fenthion ranged up to 5-fold in Texas and 11-fold in Louisiana, and in the latter State cross-resistances ranged up to 14-fold to the carbamate insecticide OMS-33.[1] The oriental cockroach, *Blatta*, is reported to have developed resistance to DDT and dieldrin in Czechoslovakia.

Populations resistant to DDT or the cyclodiene insecticides or both are now frequent among bedbugs, *Cimex hemipterus* and *C. lectularius*, in most regions of the world. Moreover, a most serious development has appeared in Israel, where *C. lectularius* has become resistant to malathion and fenthion. By contrast, reduviid bugs such as *Rhodnius* and *Triatoma* have not provided any proven instance of resistance to HCH or the cyclodiene compounds despite their long history of use against these vectors of Chagas' disease.

When DDT resistance was discovered in the oriental rat fleas, *Xenopsylla cheopis* and *X. astia*, in Maharashtra, Mysore and Uttar Pradesh, in India in 1960, it was accompanied by increased tolerance to HCH and dieldrin. The situation was the same in flea populations in Andhra Pradesh, India, where plague broke out in 1964. Nevertheless, these Indian populations are still reported to be amenable to control with HCH formulations. More recently, DDT resistance has been found in *X. cheopis* in Thailand and Vietnam; at certain places in Thailand dieldrin resistance was also found. In areas of Vietnam open to the hazard of plague, diazinon has proved effective against flea populations resistant to organochlorines. Application of the WHO standard test has discovered strong DDT resistance and some dieldrin resistance in *Pulex irritans* at several places in Turkey.

The brown ear tick, *Rhipicephalus appendiculatus*, has now joined *R. evertsi* and *Boophilus decoloratus* in showing resistance to cattle-dips containing toxaphene or gamma-HCH in the East London area of South Africa. The Australian cattle tick, *B. microplus*, was found to have developed resistance to the organophosphorus compound dioxathion at Rockhampton, Queensland in 1964. Cross-resistance was shown to carbophenothion but not to most of the other organophosphorus compounds, although elsewhere in Queensland a more universal type of organophosphorus resistance is developing.

Among culicine mosquitos, the number of species which have developed organophosphorus resistance has increased from 5 to 9, consequent on the increasing use of organophosphorus compounds as larcivides. *Culex pipiens fatigans* has developed malathion resistance at Douala, Cameroon; Freetown, Sierra Leone; and Okinawa among the Ryukyu islands. *Culex*

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[1] This compound has also been known as Bayer 39007, Baygon, IMPC, UNDEN and propoxur; the name " arprocarb" has been used but this name has also been applied to another carbamate.

tritaeniorhynchus has also developed malathion resistance on Okinawa. In California, malathion resistance has developed in *C. peus* but has largely disappeared in *C. tarsalis*.

Whereas resistance to organochlorines in *C. fatigans* is a general occurrence, new records of such resistance in *C. pipiens* have come from France, Morocco, Turkey, and Korea. Isolated cases of DDT resistance have been found in *C. salinarius* in New Jersey, but not elsewhere in eastern North America, and in *C. erythrothorax* in California; dieldrin resistance was evident in a larval sample of *C. restuans* in New York.

In *Aedes aegypti*, DDT resistance has now been recorded from India, Thailand, Japan, the Americas and West Africa. Dieldrin resistance accompanies DDT resistance throughout the Caribbean area, and has developed in parts of West Africa (e.g., Upper Volta) in the absence of DDT resistance; it is also present in the large cities in Cambodia and Vietnam, and on the island of Tahiti. Populations of *Ae. aegypti* with increased tolerance to malathion have been found in Jamaica, Venezuela, Congo (Brazzaville), Thailand, and Vietnam.

It has become evident that the salt-marsh mosquito, *Ae. taeniorhynchus*, has developed malathion tolerance in several parts of Florida where organophosphorus compounds have been consistently applied as adulticides. The irrigation-water mosquito *Ae. nigromaculis* in the south-central part of the San Joaquin valley of California has developed, in succession, resistance to parathion, methyl parathion, fenthion, and even to Dursban,[1] although remaining controllable by OMS-33.[2] Organophosphorus resistance is also intensifying in *Ae. melanimon*, but more slowly. Fenthion resistance has recently been encountered in *Ae. dorsalis* in New Mexico, USA.

Ae. albopictus has developed DDT resistance in Saigon, Vietnam and Bangalore, India, while *Ae. vittatus* has been found to be DDT-resistant at Baroda, India. An isolated case of increased DDT tolerance was found in *Ae. vexans* in, British Columbia, but elsewhere this species has remained susceptible. *Ae. atropalpus* was found to be DDT-tolerant in every sample tested in North America except one, and *Ae. fijiensis* proved to be DDT-resistant in every sample tested in Fiji; whether these were developed or pre-existing tolerances is not clear.

In the anopheline vectors of malaria, DDT resistance has now developed in *Anopheles gambiae*, appearing first in the A form in Upper Volta and then in the B form in Senegal. Records of dieldrin resistance from outside West Africa have now come from the Sudan, Kenya, Rhodesia and Madagascar; both A and B forms have been involved.

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[1] *O,O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate.

[2] This compound has also been known as Bayer 39007, Baygon, IMPC, UNDEN and propoxur; the name " arprocarb " has been used but this name has also been applied to another carbamate.