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Physico-chemical properties of compounds in relation to residual contact toxicity to adult mosquitos *

by

A. B. HADAWAY and F. BARLOW **

Part of the second stage in the World Health Organisation Programme for the evaluation and testing of new insecticides is undertaken by the tropical Pesticides Research Unit at Porton Down in England. Here, under standardised conditions, a measure of the intrinsic toxicity of candidate compounds to adult mosquitos is obtained by topical application of solutions, and the initial and residual contact toxicities of deposits of the compounds, usually from water dispersible powder formulations, on representative building materials are determined by bioassays with laboratory-reared mosquitos, *Anopheles stephensi.* Treated plywood or plaster panels and air-dried bricks of tropical soils are stored at 25 °C and tested at intervals, and the number of weeks that the mortality of mosquitos exposed on the treated surfaces for one hour exceeds 70 % is taken as a measure of residual effectiveness. Observations are also made on mosquito behaviour, and any unusual activity or knockdown recorded.

The total mass of insecticide in residues on building materials decreases with time by two main processes, evaporation and decomposition. Most insecticides are sufficiently stable, and most building materials sufficiently inert for the main cause of loss to be evaporation, although decomposition may occur at extremes of alkalinity or acidity — for example, on limewash of after sorption in some tropical soils. The bioassays are therefore supplemented by chemical determinations of rates of loss by evaporation of compounds from glass-fibre and cellulose filter papers, and of rates of decomposition on standard soils. These biological and chemical properties of candidate insecticides are then taken into account when recommandations are made concerning further evaluation in the next stage in experimental huts against natural populations of mosquitos.

It is well known that both the initial and residual biological activity of deposits are influenced by interaction between the formulation of the active ingredient and the substrate to which it is applied. In the course of evaluating candidate OMS compounds, however, it was observed that even though compounds of equal intrinsic toxicity were formulated in the same way and applied to similar material the contact toxicity of the

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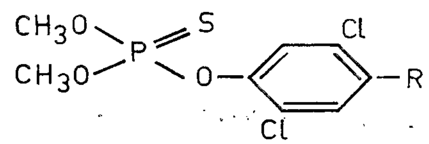
** Ministry of Overseas Development, Tropical Pesticides Research Unit. Porton Dawn, nr. Salisbury, England.

deposits could differ considerably. Possible reasons for such differences were therefore investigated, by studying relationships between physico-chemical properties and biological activity in series of closely related compounds.

The pick-up of insecticide from residues, penetration through the insect cuticle and transfer to the site of action in the insect obviously cannot be related to a single physical property and must depend on a balance of chemical and physical properties. Earlier work published in 1966 (HADAWAY and BARLOW, Bull. ent. Res., 56, 569, 1966) indicated that very low lipoid solubility is a limiting factor in the up-take and penetration into mosquitos of a solid insecticide and is associated with low contact toxicity, and that when solubility is high enough to ensure solution in the wax layer of the cuticle, contact activity is favoured by a low value for the partition coefficient between hexane and water. Since then results obtained with other compounds support this thesis ; those with a series of organophosphorus esters — fenchlorphos, bromophos and the corresponding 4-iodo derivative — are shown in table 1.

TABLE 1.

Toxicity to female *Anopheles stephensi* of fenchlorphos and related esters



R	L.D. 50	Mortality after contact of ... minutes					Solubility
		2	5	15	30	60	
Cl.	24	5	58	100			62
Br.	19		5	78	100		12
I.	11			0	18	77	3

Turning to residual activity, a main cause of loss of insecticide from residues is, as mentioned earlier, evaporation, and thus the likely effective life of a candidate compound can be forecast from volatility measurements. Results obtained with the esters referred to above are given in table 2.

TABLE 2.

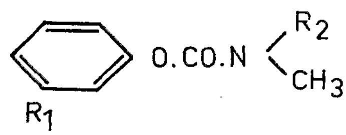
Volatility and residual activity of fenchlorphos and related esters

R	Volatility $g/m^2/day$	Residual life, in weeks
Cl.	0,30	4-8
Br.	0,15	8-12
I.	0,0055	> 24

Data on relationships between chemical structure and volatility are obtained ; for example, in carbamates and organophosphates the introduction of methylthio and nitro groups as substituents on aromatic rings will extend residual action. The relationship between chemical structure and volatility in a series of substituted phényl N-methylcarbamates is shown in table 3.

TABLE 3

Volatility of N-methyl carbamates



Y	Z	X			
		H	CH_3	Cl	SCH_3
H	H	1,0	0,32	0,11	0,011
CH_3 ...	H	0,50	0,10	0,031	0,0040
CH_3 ...	CH_3	0,11	0,0082	0,016	0,0015

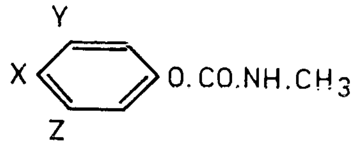
An increase in molecular weight decreases volatility, but the amount of intermolecular interaction is of greater importance. Volatility cannot be altered, however, without changing other physical properties, and it is perhaps unfortunate that increases in the attractive forces between molecules which decrease volatility also usually result in decreased solubility in lipids and alterations in partitioning behaviour which are unfavourable to contact action against insects. This is very noticeable among the carbamate and organophosphorus esters where the compounds which have the greatest persistence are the least effective contact insecticides even though they possess high intrinsic toxicity [e.g. carbaryl, Mobam (4-benzothienyl N-methylcarbamate), and gusathion].

However, when a compound has very low volatility some degree of persistence can be sacrificed on structural modification to increase contact activity. How such a situation could be exploited is illustrated by experiments with N-acyl N-methylcarbamates, a new group of compounds of interest because of the generally more favourable insect/mammal toxicity ratio. N-acylation of substituted phenyl N-methylcarbamates involving short alkyl groups was shown to cause an increase in volatility but because the parent compounds were already relatively volatile the derivatives did not have the required residual action. Data for two such compounds and their N-acetyl derivatives are shown in table 4.

On the other hand, Mobam and carbaryl are so involatile that their N-acetyl derivatives should still be sufficiently persistent despite some increase in volatility, while changes in solubility and other physical properties should improve contact activity. These derivatives, therefore, were synthetized and tested, and as forecast and shown in table 5, their contact activity was superior to that of the parent compounds, although still no as high as that of some other carbamates.

TABLE 4

Volatility and residual activity of two N-methylcarbamates and the N-acetyl derivatives



R_1	R_2	Volatility $g/m^2/day$	Residual life in weeks
Isopropyl ..	H $COCH_3$	0,16 0,90	16-20 2-4
Sec-butyl ..	H $COCH_3$	0,080 0,40	12-16 4,8

Thus, our work in stage II of the WHO programme not only helps in the selection of compounds for potential use in international public health campaigns in the immediate or near future but also provides data on which the design of future insecticides with both high contact activity and persistence may be based.

TABLE 5

Toxicity and properties of Mobam and carbaryl

Compound	L.D. 50	Mortality after contact of ... minutes			Solubility	Volatility
		15	30	60		
Mobam	5	0	0	69	0,046	0,0053
N-acetyl Mobam .	5	0	41	100	0,46	0,0081
Carbaryl	4,6	0	0	0	0,028	0,0016
N-acetylcarbaryl	5,3	0	15	92	0,43	0,0070

NOTES :

LD_{50} : nanogram (ng.) per female mosquito *Anopheles stephensi* by topical application in solution.

Contact toxicity : Percentage mortality of *A. stephensi* after exposure for stated time in minutes on plywood panels sprayed with wettable powder formulation at dosage 1 g. a.i./m².

Residual life : Number of weeks percentage mortality exceeds 70 % after exposure of 60 minutes on w.d.p. deposits at 1 g/m² on plywood panels.

Volatility : Rate of loss from deposits at 1 g/m² on glass-fibre filter papers stored at 25 °C and 50-55 % R.H.

Solubility : % w/v saturated solution in *n*-hexane at 25 °C.