

## SYNERGISM AND SYNERGISTS

# Review of Synergism Among Halogen-Containing Insecticides and Halogen-Containing Synergists

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Combinations of compounds which have a higher biological activity than the sum of the activities of the individual components are said to be synergistic. Numerous synergistic combinations involving a halogenated insecticide and/or a halogenated synergist have been discovered in the laboratory. Such combinations have been used in the field against agricultural pests and insects of importance in disease control. These latter cases of synergism are reviewed by tabulating the various combinations with respect to the chemical constitution of the components, the type of formulation, the method of application, and the degree of enhanced activity. Attempts were made to account for the potentiation in the activity of the mixture on the basis of the physical properties, chemical behavior, or biological activities of one or more of the components. Lastly, the synergists which potentiate DDT and certain related insecticides against resistant houseflies are listed and discussed.

**S**YNERGISM, literally a "working together," is a cooperative action encountered in biologically active combinations in which the combined activity of two like-acting components exceeds the sum of the activity of the components used alone. Hence, synergism is the opposite of antagonism, a phenomenon encountered when an organism is treated with combinations of substances with similar biological activities. Synergism may be operative in combinations involving more than two components.

Synergism has been advantageously used in combinations involving antioxidants (34, 167), drugs (24, 131), virocidcs (117), plant hormones (56, 168, 257), and the economic poisons including fungicides (9, 40, 122, 199), herbicides (49, 110, 121), insect attractants (59, 142, 143), insect repellents (60, 130, 139, 253, 269), fumigants (73, 79, 80, 132, 217), and insecticides. Numerous examples of synergism are found among the insecticides.

### Detection, Measurements, and Definitions of Synergism

In all these fields synergistic combinations have obvious advantages. The higher and/or prolonged activity of the combination permits the use of smaller

amounts of the agents; the activated mixture can overcome a natural or an acquired resistance to chemical control, thus extending its use in areas in which the individual components are less active; and the mechanism of biological activity, usually the most obscure factor, can be elucidated. These applications appear to warrant further investigations of known synergistic combinations and to stimulate searches for new ones. Finally, an exploration for synergists invariably discloses strong antagonists for the biologically active chemical in question and throws additional light on the mechanism of action.

A 500-page volume on economic poisons, published in 1913 (76), makes no direct reference to synergism but mentions soap as a strengthening agent for some six insecticides. The function of soap here can be attributed to a number of factors. Rodda (222) believes that the addition of rotenone to pyrethrum in a kerosine spray is the first example of a synergized insecticidal combination. The industry became aware of the value of synergists for insecticides in the early 1930's. *N*-Isobutylundecylenamide (17), the first important synergist commercialized for pyrethrum, was introduced in 1938. Piperonyl butoxide, of more recent origin, is widely used as a synergist for pyrethrum preparations. Several reviews (19, 100, 176) on pyrethrum synergists have been prepared, usually as a portion of a more comprehensive treatise.

DMC [1,1-bis-(*p*-chlorophenyl)ethanol] was patented in Italy (709) as a synergist for DDT. DDT-synergist combinations have been employed in the field, usually with varying success. Since 1945, numerous publications have reported synergists for the halogenated insecticides and there are earlier reports of the use of halogenated synergists with nonhalogenated insecticides, mainly of botanical origin.

Thus, the commercial developments in the use of synergists are more advanced, and hence more fruitful, with pyrethrum than with the newer halogenated insecticides. Whether this is due to the novelty of the halogenated insecticides or to their failure to lend themselves to useful synergistic combinations remains to be seen.

The existence of synergism is not always clear cut. Synergists have a high degree of specificity depending on the insecticide involved (99), the insect to be controlled (99), the type of formulation used, and the manner in which the contact is made between the insect and the synergized agent. This has led to disagreement as to the prevalence of synergism and in the terms used to describe it (47, 99, 114, 138, 245).

Recognizing the need for clarification in describing and measuring the activity of combinations, Bliss (73) describes the insecticidal activity of discrete agents, used jointly, as follows:

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**Table I. Potentiation of Insecticidal Activity of DDT by Miscellaneous Halogenated Hydrocarbons**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity <sup>a</sup>	Reference
DDT <sup>b</sup> , 25	1,1-Bis-( <i>p</i> -chlorophenyl) ethane, 1	Emulsions	Orchard insects	+	(63)
DDT, —	2,2-Bis( <i>p</i> -ethylphenyl)-1,1,1-trichloroethane, —	...	...	+	(218)
DDT, —	2,2-Bis( <i>p</i> -fluorophenyl)-1,1,1-trichloro- ethane, —	...	...	+	(218)
DDT, —	2,2-Bis(3-fluoro-4-methylphenyl)-1,1,1-tri- chloroethane, —	...	...	+	(218)
DDT, 1	Lindane, 1	Spray, residual	Housefly <sup>c</sup>	+	(197)
DDT, 10	BHC, 1	Dust, field	Mosquito <sup>d</sup>	+	
DDT, 4	BHC <sup>e</sup> , 1	Dust, field	Gladiolus thrips <sup>e</sup>	+	(160)
DDT, 4	BHC, 1	Emul., field	Cabbage moth <sup>g</sup>	+	(103)
DDT, 1	BHC, 0.5-1	Dust, field	Cabbage aphid <sup>h</sup>	+	(103)
DDT, 1	BHC, 1	Dust, field	Bollworm <sup>i</sup>	+	(74)
DDT, 15	BHC, 1	Dust, field	Cotton aphid <sup>j</sup>	+	(74)
DDT, —	M-410 <sup>k</sup> , —	Soln., topical	Grasshopper <sup>k</sup>	+	(267)
DDT, 7	Chlordane, 1	Soln., topical	Grasshopper	++	(267)
DDT, 1	Chlordane, 1	Soln., space spray	Housefly <sup>c</sup>	+	(61)
DDT, 7	Aldrin, 1	Soln., topical	Grasshopper <sup>k</sup>	+	(267)
DDT, —	2,6-Dichlorocamphene, —	...	...	+	(58)
DDT, —	2,6-Dichlorocymene, —	...	...	+	(58)

<sup>a</sup> Increase in activity over that obtained with insecticide alone; +, 1 to 99%; ++, 100 to 299%; +++, 300 to 399%; and +++, 400-499%.

<sup>b</sup> 2,2-Bis(*p*-chlorophenyl)-1,1,1-trichloroethane.

<sup>c</sup> *Musca domestica* L.

<sup>d</sup> Not specified.

<sup>e</sup> *Taeniothrips simplex* (Mor.).

<sup>f</sup> BHC = hexachlorocyclohexane (benzene hexachloride). The proportionate amounts given in this table and subsequent tables refer to the amount of actual gamma-isomer present.

<sup>g</sup> *Pieris rapae* (L.).

<sup>h</sup> *Brevicoryne brassicae* (L.).

<sup>i</sup> *Heliothis armigera* (Hbn.).

<sup>j</sup> *Aphis gossypii* Glov.

<sup>k</sup> *Melanoplus differentialis* (Thos.).

<sup>l</sup> Octachloro-4,7-endomethylenetetrahydrohydrindene.

**1. Independent Joint Action.** Poisons act independently and differently, and susceptibility to them may or may not be correlated. Toxicity of the mixture can be predicted from dosage-mortality curves for each used alone and with the correlation in susceptibility to the two poisons; the observed toxicity can be computed on this basis whatever the relative proportions of the components.

**2. Similar Joint Action.** Poisons provide similar but independent effects, so that one can be substituted in constant proportions for the other. Variations in individual susceptibility to the two components are parallel. The toxicity of a mixture is predictable directly from that of the components if their relative proportions are known.

**3. Synergistic Action.** Toxicity of the mixed components cannot be measured from that of the individual components but depends on a knowledge of their combined toxicity when used in different proportions in which one component may synergize or antagonize the activity of the other.

Other methods of detecting synergism (166, 181), and measuring it (261), in some instances by the application of statistics (77, 208, 260), have been advanced since the appearance of Bliss's paper (13).

As Wadley (261) pointed out, a marked activity over and above that predicted from separate or joint actions must prevail to prove the existence of synergism.

Very few claims of synergism are based on controlled tests and even fewer have been subjected to statistical analyses. In recognition of these inadequacies and in order to report all possible instances of synergism, the statement "the combination had a higher toxicity than either component used alone" is used throughout this review as a minimum requirement for synergism. The term "potentiation" is employed to describe this condition and is used interchangeably with "synergism" in both tables and text.

### Mechanism of Action

The discovery and development of synergists (or antagonists) for insecticides can clarify or reveal their mechanism of action. The manner in which the synergist operates is necessarily based more on speculation than on knowledge (123).

Attempts to explain the action of synergists may be classified as follows:

**1. Physical Properties.** Agents—e.g., surfactants—which increase coverage (65, 89), thereby promoting contact between the poison and the insect, have been credited with synergistic activity. Adjuncts which reduce evaporation (53), prevent crystallization (218), provide adhesiveness (55), and aid in distribution (57) or suspension (4) also increase the toxicity of insecticides. The size (76, 263, 276) and the shape (157, 258) of the particles of solid toxicants have an influence

on their activity both as contact and stomach poisons.

**2. Chemical Action.** By the use of appropriate chemicals, it is possible to release certain insecticides, such as nicotine (129), in an active form, stabilize a number of others, such as pyrethrins (66), DDT (101, 104), and parathion (48), and to bring still others, such as nitroresols (163), to a pH optimum for toxicity.

**3. Permeability of Insect Cuticle.** Increasing the penetration of the insecticide into the cuticle by the simultaneous application of other agents has been cited more than any other mechanism to account for synergism. A study (265) of 20 miscellaneous high-boiling solvents as synergists for diphenylamine against the sheep ked showed that the following properties were critical: rapid penetration of beeswax; high partition coefficient of solvent between beeswax and water; and high solubility of the insecticide in a solution of the solvent in water. Volatility of the solvent and solubility of the insecticide in the solvent were contributing factors. The penetration of ethyl alcohol into blowfly larvae was increased by adding kerosene, an apolar solvent (126). Certain pyrethrum synergists are said to function by forming surface complexes with the insecticide at the peripheral nerve sheath (196). Benzyl alcohol (158) increased the penetration of dodecyl thiocyanate and azobenzene into red spider mite eggs with concomitant increases in mortality. A number of surface active polyethylene glycols (256) increased the toxicity of nico-

tine toward *Aphis crumicis* when applied locally. This increased activity was attributed to greater penetration of the cuticle by the nicotine, since these glycols did not increase the toxicity of nicotine when injected into *Oncopeltus fasciatus*.

**4. Physiological Effects.** Among the simplest applications are the use of auxiliary materials to attract (218), repel (51), or alter the knockdown rate (53) of insects, thereby forcing them into more prolonged contact with the more lethal chemical. In a histological study, two major pyrethrin synergists (112), piperine and sesame oil, were found to augment the attack of the pyrethrins on nerve fibers and cells. A similar mechanism was postulated for the activity of piperonyl cyclonene (146) with the same insecticide. In a less direct application, a pyrethrum-sodium fluoride combination kills the cockroach by a with-

drawal of water by the pyrethrin which dissolves and facilitates absorption of the salt (164). Potassium chloride (145) markedly reduced the paralytic threshold of the cockroach toward nicotine and this must be due to a role of the potassium ion, probably in a transmission of the nerve impulse (102), since sodium chloride used in a similar manner was without effect.

The protective stupefaction induced in red scale by hydrogen cyanide is offset by trichloroacetonitrile, the combination thus providing a degree of control not obtainable with hydrogen cyanide alone (25). Nicotine is not fatal to the poppy weevil, but a combination of nicotine-chloropicrin is, the enhanced activity being credited to the catabolic action of the latter compound (252). The volume of oxygen consumed by the larvae of *Chilo simplex* decreased in direct ratio to their exposure to chloropic-

rin (2). A German patent claims that a combination of two alkaloids, a paralyzant and a stimulant, augment each other in killing insects (87). This claim receives some support from a report (123) that synergism is more likely to result from unlike substances which act on different parts of the body.

**5. Detoxification Mechanisms.** Cases of synergism explainable on this basis are more common in those which operate against resistant insects. Piperonyl butoxide [(3,4-methylenedioxy-6-propylbenzyl)(butyl)diethyleneglycol ether] (37), definitely synergizes the pyrethrins when applied prior to or simultaneously with the insecticide, which may be partly due to the inhibition of lipase, the enzyme capable of inactivating the pyrethrins through hydrolysis (37, 66).

It is possible that some synergists may

**Table II. Potentiation of Insecticidal Activity of DDT by Some Ethers, Quinones, and Esters**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
<b>Ethers</b>					
DDT, 50	Cyclohexyl diphenyl ether <sup>a</sup> , 25	Emulsion, spray	Greenhouse red spider <sup>b</sup>	+	(62)
DDT, 1	Cyclohexyl diphenyl ether, 1	Dust	Mex. bean beetle lar. <sup>c</sup>	+	(62)
DDT, 1	<i>n</i> -Amyl 2-naphthyl ether <sup>d</sup> , 3	Emulsion, spray	Mex. bean beetle <sup>c</sup>	+++	(137)
DDT, 1	Isobutyl 2-naphthyl ether <sup>d</sup> , 3	Emulsion, spray	Pea aphid <sup>e</sup>	+	(137)
DDT, 1	Allyl 2-naphthyl ether, 3	Emulsion, spray	Potato aphid <sup>f</sup>	+++	(136)
DDT, 1	Methallyl 2-naphthyl ether, 3	Emulsion, spray	Potato aphid <sup>f</sup>	++	(136)
DDT, 8	2'-Hydroxypentamethyl flavan, 10	Dust	Rat flea <sup>g</sup>	+	(183)
DDT, 1	2'-Hydroxypentamethyl flavan, 1.25	Spray	Oriental fruit moth <sup>h</sup>	+	(281)
<b>Quinones</b>					
DDT, —	2-Methyl anthraquinone <sup>i,j</sup> , —	Soln., residual	Mosquito <sup>k</sup>	+	(215)
DDT, 1	Xanthone, 2	Dispersion, spray	Codling moth <sup>l,m</sup>	+	(1)
DDT, —	Xanthone, —	...	Mites <sup>n</sup>	+	(86)
<b>Esters</b>					
DDT, —	Benzoic esters, —	...	...	+	(193)
DDT, 1	Ovatran <sup>o</sup> , 1	Wettable pwd. spray	Two-spotted spider mite <sup>p</sup>	+	(134)
DDT, 1	Ovatran, 8	Emulsion, spray	Mites <sup>q</sup>	++++	(134)
DDT, 1	Ovatran, 1	Emulsion, spray	Mex. bean beetle <sup>c</sup>	+++	(134)
DDT, 1	Ovatran, 1.25	Wettable pwd. spray	Two-spotted mite <sup>p</sup>	++	(134)
DDT, 1	Dimethyl carbate <sup>r</sup> , 1	Soln., space spray	European red mite <sup>r</sup>	++	(134)
DDT, 10	Pyrethrins, 1	Space spray	Housefly <sup>t</sup>	+	(235)
DDT, 1	Piperonyl chrysanthemum carboxylates <sup>v</sup> , 5	Soln., space spray	Mosquito <sup>k</sup>	+	(262)
DDT, —	Pyrethrum, —	Emulsion	Housefly <sup>t</sup>	+	(246)
DDT, —	Pyrethrins, —	Soln., space spray	Mosquito <sup>w</sup>	+	(191)
			Mosquito <sup>z</sup>	+	(51)

<sup>a</sup> This synergist is claimed to activate certain specified insecticides structurally related to DDT.

<sup>b</sup> Not specified.

<sup>c</sup> *Epilachna varivestis* Muls.

<sup>d</sup> Other low weight alkyl 2-naphthyl ethers were somewhat less active in these tests.

<sup>e</sup> *Macrosiphum pisi*. Ketb.

<sup>f</sup> *Macrosiphum solanifolii* (Ashn.).

<sup>g</sup> *Xenopsylla cheopis* Rothschild.

<sup>h</sup> *Grapholitha molesta* (Busck).

<sup>i</sup> *p*-Benzoquinone and benzil are reported to share this activity.

<sup>j</sup> DDT residues (56 mg./square foot) were deposited on glass panels in admixture with 2-methylanthraquinone from 2% solutions of the latter.

<sup>k</sup> *Culex fatigans* Wied.

<sup>l</sup> *Carpocapsa pomonella* (L.).

<sup>m</sup> Oriental fruit moth larvae and European red mite were claimed to be controlled by this combination.

<sup>n</sup> Not specified.

<sup>o</sup> *p*-Chlorophenyl *p*-chlorobenzenesulfonate.

<sup>p</sup> *Tetranychus bimaculatus* Harvey.

<sup>q</sup> *Tetranychus bimaculatus* Harvey, *Bryobia praetiosa* Koch, *Paratetranychus pilosus* (C.F.).

<sup>r</sup> *Paratetranychus pilosus* (C & F).

<sup>s</sup> Dimethyl ester of *cis*-bicyclo[2,2,1]-5-heptene-2,3-dicarboxylic acid.

<sup>t</sup> *Musca domestica* L.

<sup>u</sup> Both kill and knockdown were increased by this combination.

<sup>v</sup> Piperonyl ester of synthetic 2,2-dimethyl-3-isobutenyl cyclopropane-1-carboxylic acid.

<sup>w</sup> *Culex pipiens* var. *pallens*.

<sup>z</sup> *Aedes aegypti* (L.).

Table III. Potentiation of Insecticidal Activity of DDT by Some Nitrogen-Containing Compounds

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
DDT, 10	Cyclohexylamine, 1	Emulsion	Carrot fly <sup>a</sup>	+	(280)
DDT, 1	<i>dl</i> -Threonine, 10,000	Mixture, medium	Mosquito larvae <sup>b</sup>	++++	(125)
DDT, 1	<i>N</i> -Heptylacetamide, 50	Soln., space spray	Housefly <sup>c</sup>	+	(96)
DDT, 1	<i>N,N</i> -Diisopropylacetamide, 50	Soln., space spray	Housefly <sup>c</sup>	+	(96)
DDT, 1	<i>N,N</i> -Diisobutylacetamide, 50	Soln., space spray	Housefly <sup>c</sup>	+	(96)
DDT, 1	<i>N,N</i> -Dipropylcinnamide, 50	Soln., space spray	Housefly <sup>c</sup>	+	(98)
DDT <sup>d</sup> , 1	2,4-Dinitro-6-cyclohexylphenol <sup>e,f</sup> , 1	Wettable pwd.	Peach aphids <sup>g</sup>	++	(151)
			Mex. bean beetle <sup>h</sup>	+++	(151)
			Greenhouse red spider <sup>g</sup>	+	
DDT, 1	<i>N</i> -Butylphthalimide <sup>i</sup> , 50	Soln., space spray	Housefly <sup>c</sup>	+	(97)
DDT, 1	Lethane A-70, 0.5	Powder	German roach <sup>j</sup>	+	(226)
			American roach <sup>k</sup>		
DDT, —	Physostigmine, —				(178)
DDT, 1	Nicotine <sup>l</sup> , 1	Dust	Melonworm <sup>m</sup>	++	(278)
			Southern armyworm <sup>n</sup>	+	
			Housefly <sup>c</sup>	+	
DDT, 1	Sabadilla, 1	Wettable pwd., film	Tarnished plant bug <sup>o</sup>	+	(175)
			Alfalfa plant bug <sup>p</sup>		
DDT, —	Sabadilla, —	Dust, field	Sugarcane froghopper <sup>g</sup>	+	(206)

<sup>a</sup> *Psila rosae* (F.).<sup>b</sup> *Culex quinquefasciatus*.<sup>c</sup> *Musca domestica* L.<sup>d</sup> Certain specified compounds closely related structurally to DDT were activated by 2,4-dinitro-6-cyclohexylphenol.<sup>e</sup> Cyclohexylamine salt of this synergist was used and found active in these tests.<sup>f</sup> A number of other nitrated phenols and substituted phenols were claimed to share the synergistic activity of 2,4-dinitro-6-cyclohexylphenol.<sup>g</sup> Not specified.<sup>h</sup> *Epilachna varivestis* (Muls.).<sup>i</sup> Amyl homolog of this compound is active.<sup>j</sup> *Blattella germanica* (L.).<sup>k</sup> *Periplaneta americana* (L.).<sup>l</sup> Certain nicotine complexes were active here.<sup>m</sup> *Diaphania hyalinata* (L.).<sup>n</sup> *Prodenia eridania* (Cram.).<sup>o</sup> *Lygus oblineatus* (Say).<sup>p</sup> *Adelphocoris lineolatus* (Goeze).

function by more than one mechanism and these mechanisms may not be in the same category. Doubtless, other synergists will be found whose mechanisms of activity are not covered by the foregoing explanations except in a very general way.

An insecticide may be more active in a liquid preparation than in a dust (108). Too, the activity of a dust may depend on a particular solid diluent (117). Synergism may not be involved in any of the cases. Many improvements through formulation changes have been reported, but the combinations listed in the tables were selected on the basis of an enhanced activity, which is believed to depend on synergism.

The various organic compounds found to be active as DDT synergists are classified configurationally into: halogenated hydrocarbons (Table I); ethers, quinones, and esters (Table II); nitrogen-containing compounds (Table III); and miscellaneous agents (Table IV). The use of elemental sulfur with the halogenated insecticides has gained some popularity. On the basis of their increasing chemical complexity the lindane (BHC)-synergist combinations (Table V) and chlordan-, aldrin-, and toxaphene-synergist (Table VI) combinations are reviewed in that order. Table VII is devoted to a group of miscellaneous insecticide-synergist combinations in which

either or both components contain halogen. The botanical insecticides, pyrethrins and nicotine, and their synergists are tabulated in Tables VIII and IX, respectively. Synergized mixtures containing at least three components, one or more of which contain halogen, are listed in Table X. The use of synergistic combinations against resistant insects makes up the data for Tables XI and XII.

In tabulating the numerous insecticide-synergist combinations, it was convenient to select the insecticide of a pair on the basis of relative potency in each individual situation, the weight ratio in those cases where relative potency was questionable, and the chlorinated compounds were given a priority in cases where selections could not be made by the first two criteria. The ratio of the two components, in terms of the technical material, is given where known in place of the dosage used or the amount applied, as it was felt that the proportion of the two components is of particular interest in synergistic mixtures.

The type of formulation and mode of application or dosing were indicated briefly. The species of insect serving as the test objects in the laboratory or being subjected to chemical control in the field were critical in such experiments and special care has been given to their identification in the tables where such information is most useful.

It was often difficult to express even the relative activity of the synergized combinations. Activity was based on percentage mortality or control in most cases and no combinations were included unless they were published values or statements which at least indicated that the combination was more toxic to a given insect than were comparable doses of the two components when used alone.

Some of these values were obtained by interpolations and extrapolations as well as by other methods based on approximations. The existence of enhanced activity in insecticidal combinations can be used as the basis of patent claims, and it is only natural that some of the results from the mixtures have been viewed with charity.

The insecticide-synergist combinations in the several tables are discussed in light of the authors' explanations and/or suggestions for the mechanism of action involved. Attempts are made to account for or to support these action mechanisms by citing collaborative evidence with full knowledge that some of these explanations are speculative.

Any investigation of DDT, particularly one involving synergism, must take into account the fact that technical DDT, while composed of approximately 70% insecticidally active *p,p'*-isomer, is a mixture of some 15 distinct compounds.

**Table IV. Potentiation of Insecticidal Activity of DDT and Methoxychlor by Some Miscellaneous Organic Compounds**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
DDT <sup>a</sup> , —	Petroleum oil, —	Soln., film	Bedbug <sup>b</sup>	++++	(11)
DDT, —	Methylated naphthalenes <sup>c</sup> , —	Dust	Pea aphid <sup>d</sup>	++	(68)
	Velsicol AR-60 <sup>e</sup> , 4	Emulsion, spray	Red spider <sup>f</sup>	++	
DDT, 1	Velsicol AR-50 <sup>g</sup> , 250	Soln., space spray	Housefly <sup>h</sup>	++++ <sup>i</sup>	(127)
DDT, —	Halogenated phenol, —	...		+	(218)
Methoxychlor, <sup>k</sup>	2,2-Bis( <i>p</i> -ethoxyphenyl)-1,1,1-tri- chloroethane, —	...	Mosquito <sup>j</sup>	+	(210)
—			Housefly <sup>h</sup>	+	

<sup>a</sup> Film from oil solution contained 1 mg. DDT/square cm.

<sup>b</sup> *Cimex lectularius* L.

<sup>c</sup> A mixture of di- and trimethylated naphthalenes.

<sup>d</sup> *Macrosiphum pisi* (Kelt.).

<sup>e</sup> Methylated naphthalene (boiling point 500° to 550° F.).

<sup>f</sup> *Tetranychus telarius*.

<sup>g</sup> Methylated naphthalene (boiling point 450° to 500° F.).

<sup>h</sup> *Musca domestica* L.

<sup>i</sup> This activity is based on knockdown instead of per cent mortality, and is, at best, an estimate.

<sup>j</sup> *Culex quinquefasciatus*.

<sup>k</sup> A mixture of methoxychlor, 2,2-bis(*p*-ethoxy)-1,1,1-trichloroethane, 2-(*p*-methoxyphenyl)-2-(*p*-ethoxyphenyl)-1,1,1-trichloroethane, and 2-(4-methoxyphenyl)-2-(3,4-methylenedioxyphenyl)-1,1,1-trichloroethane is said to be better than any one of the compounds used alone.

One of these, *p*-chlorophenyl trichloromethylcarbinol, along with the DDT isomers, paralyzes houseflies (37). Doubtless the other constituents affect the biological properties of the technical material by an influence on its physical properties. Technical and purified DDT have been biologically compared, and the technical was found to have a longer residual action against a variety of insects (203), a higher knockdown against houseflies (190), and an equal toxicity toward cockroaches and bedbugs (124) in spite of its somewhat diluted state. These greater effects have been attributed to the presence of the DDT by-products.

On the chemical side, technical DDT was found to be more resistant to dehydrochlorination by catalyst at an elevated temperature than was purified DDT (78). This might explain the longer residual action of the technical material.

Many of the halogenated hydrocarbons having synergistic activity for DDT are insecticides in their own rights. 1,1-Bis(*p*-chlorophenyl)-ethane (63), an exception to the foregoing generalization, has been patented as a synergist for DDT in controlling a variety of orchard and garden insects. This activity also appeared in the resistant housefly.

Riemschneider (218) cites three DDT analogs, two containing fluorine, and two polychlorinated bicyclic compounds as increasing the knockdown of DDT toward the sheep tick and the fruitfly. These additives are presumed to function by preventing the crystallization of DDT.

The synergism between DDT-hexachlorocyclohexane and DDT-lindane combinations, cited in Table I, is based on percentage mortality (61), life of residual deposits (197), or degree of field control (74). The synergism of these

combinations, weak at best, is further minimized by failing to operate in a different formulation or against other species of insects (103). In fact, DDT was shown to reduce the activity of hexachlorocyclohexane against a grasshopper nymph (84). Another antagonism between DDT and hexachlorocyclohexane is found in warm-blooded animals, two species of which tolerated much larger doses of the combination than of the individual components (174).

A DDT-chlordan mixture, used as a space spray with the housefly (61) and topically applied in an emulsion to the grasshopper (*Melanoplus differentialis*) (267), gave more than an additive effect on contact and as a stomach poison in the latter insect. The ratio of DDT to chlordan was critical in the case of the grasshopper because a mixture richer in chlordan became antagonistic.

Aldrin synergized DDT against a grasshopper (267), but antagonized it against the housefly (61). Dieldrin behaved like aldrin in this respect. Toxaphene, an excellent insecticide *per se*, may or may not synergize DDT (54).

The analogous but lesser chlorinated hydrocarbons, dichlorocamphene and 2,6-dichlorocymene (58), while less potent than toxaphene, are claimed as synergists for DDT. The activity of these latter two compounds is presumed to be due to their ease of dehydrochlorination.

Combinations of DDT, hexachlorocyclohexane, aldrin, toxaphene, etc., are routinely used against cotton insects, but this practice is probably dictated by the need to control a variety of insects rather than attempts to realize synergism.

Most ethers, quinones, and esters are liquids or low melting solids, good solvents or highly eutectic, lipophilic with a corresponding low solubility in water,

and have a high vapor pressure. Chemically, members of this group are usually stable. In addition to providing insecticides and synergists for insecticides, narcotics, anthelmintics, acaricides, and insect repellents are frequently found in these groups.

Ethers, particularly those having a ring oxygen, are frequently insecticidal (83) and this frequency is reflected in the number of synergistic ethers, especially those having activity with pyrethrins (259). The affinity of ethers for nerve tissue is well known and a number of theories have been advanced to explain the biological effects resulting from this affinity, the Meyer-Overton concept of narcosis being the best known (144).

Other ethers, some containing both a chain and a ring oxygen, effectively inhibit the decomposition of DDT (116), which might account for or contribute to their synergistic activity for DDT and other halogenated insecticides.

Flavan (2-hydroxypentamethylflavan) used alone is a weak insecticide, but it is structurally related to some flavones (227) and chromones (188) which are active in this respect. Pentachloroanisole failed to act as a synergist with nicotine but other halogenated ethers (38), especially those containing fluorine (69), appear to be worth a trial, at least on a theoretical basis.

The activity of 2-methylanthraquinone with DDT toward the mosquito was discovered through accident (215). The activity of this general group as a DDT synergist against resistant houseflies was later confirmed. *p*-Benzoquinone, a protein reactant, and benzil, an acaricide and chigger repellent, are said to share the synergistic property of 2-methylanthraquinone with DDT. Xanthone is listed under the quinones but its carbonyl group is extremely inert from a chemical standpoint (184). However,

it has a structural resemblance to anthraquinone and has the benzo- $\gamma$ -pyrone nucleus found in rotenone. Against the California red scale, an extract of derris, the active principle of which is a quinone, was less effective when mixed with DDT than was derris alone (77).

Esters of benzoic acid, especially those with *tert*-aminoalcohols, are strong local anesthetics and, like many insecticides, they paralyze fish. Benzyl benzoate is weakly anesthetic but it is employed as an antispasmodic, an indication of its neuro effect.

In the chemical control of insects, the low molecular weight esters of aliphatic acids, especially dibasic acids, are toxic fumigants, while related esters which are less volatile—e.g., dimethyl carbate—are repellent to insects. Aryl and alkyl benzoates are repellent and toxic to trombiculid mites. Some alkyl esters of halogenated phenoxycetic acid are known to temporarily paralyze houseflies.

Considering repellency a manifestation of toxicity, it is seen that the physiological responses elicited by these esters coupled with their physical properties—e.g., solvency for DDT—render them likely synergists for this insecticide. In

fact, benzyl benzoate favored the absorption of DDT through the skin of the rabbit thereby rendering it toxic, while liquid petrolatum solutions of DDT were nontoxic to this species (749).

The pyrethrins synergized DDT only slightly but it is significant that this was exhibited toward mosquitoes and the housefly, insects susceptible to pyrethrin alone.

The esters of benzenesulfonic acid containing halogen in both moieties are poisonous to spider mites. Mixtures of *p*-chlorophenyl *p*-chlorobenzenesulfonate and DDT gave the most marked synergism recorded in Table II, and this was seen most frequently against mites.

In speculating on the activating mechanism of the nitrogen-containing compounds as synergists, insecticides, or insect repellents, it is interesting to view them as analogs of the corresponding oxygen compounds. Considering ammonia, completely hydrogenated nitrogen (228), as the nitrogen analog of water, which is completely hydrogenated oxygen, this analogy has been extended to yield the ammonia system of organic compounds (87). Thus the *N*-substituted amides (96, 98) and *N*-butyl-

phthalimid (97) would correspond to esters in the oxygen system. Physostigmine (178) and nicotine (278) would correspond to ethers and, in part, to cyclic ethers. The esters and ethers, as was pointed out in Table III, have contributed a number of insecticides and synergists for insecticides. This analogy between oxygen and nitrogen compounds might be responsible for the fact that carbon monoxide (C=O) and the cyano group (C=N) are highly toxic, both forming a stable complex with hemoglobin.

Cyclohexylamine (280), an alcohol in the ammonia system, is quite basic, an emulsifier, a vasopressor pharmacologically, an insect attractant, and toxicant. Almost any one of these properties could account for the slightly enhanced activity which it showed with DDT against the carrot fly.

No explanation was offered for the synergistic effect between DDT and *dl*-threonine (125) against the larval stage of a mosquito. Serine and threonine are antagonistic (279) in bacterial growth, and since this synergism was operative against larvae, one is tempted to look upon *dl*-threonine as serving as

**Table V. Potentiation of Insecticidal Activity of Lindane and BHC<sup>a</sup> by Some Miscellaneous Organic Compounds**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
Lindane, —	Acenaphthene, —	...	Back swimmer <sup>b</sup>	+	(209)
	<i>p</i> -Dichlorobenzene	...	Moths <sup>c,d</sup>		
	1-bromo-4, —	...			
Lindane, —	Chlorobenzene, —	...	Moths <sup>c</sup>	+	(205)
	Chloronaphthalene, —	...	Moths <sup>c</sup>		
Lindane, —	Chlorinated polyphenyls	Spray	...	+	(36)
	Ovatan <sup>e</sup> , 64	Wettable pwd., spray	Southern armyworm <sup>f</sup>	+	(135)
Lindane, 1	Ovatan, 2	Wettable pwd., spray	Mexican bean beetle larvae <sup>g</sup>	+	(135)
Lindane, 3	Ovatan <sup>h</sup> , 2	Wettable pwd., spray	Two-spotted spider mite <sup>i</sup>	+	(135)
Lindane, 1	Ovatan, 0.12	Concentrate spray, wettable pwd.	Two-spotted spider mite <sup>i</sup>	++++	(135)
Lindane, —	Azobenzene, —	...	Back swimmer <sup>b</sup>	+	(209)
Lindane, 1	2,4-Dinitro-6-cyclohexylphenol, 1	Wettable pwd., spray	Mexican bean beetle <sup>g</sup>	+	
			Southern armyworm <sup>f</sup>	+	(150)
BHC	Chloroform, traces	Soln., residual	Hide beetle <sup>j</sup>	+	(189)
BHC, —	BHC by-products, —	Incense	Mosquito <sup>k</sup>	+	(250)
BHC, —	Terpineol, —	Suspension, topical	Granary weevil <sup>l</sup>	++++	(216)
BHC, —	Benzoate esters, —	...	...	+	(193)
BHC, —	Phenylisonitril, —	Soln., residual	...	+	(55)
BHC, —	Thiocyanate <sup>m</sup> , —	...	...	+	(234)
BHC, —	Na thiocyanate, —	...	Cattle tick <sup>n</sup>	+	(182)
			Mite <sup>o</sup>		
BHC, —	2,4-Dinitro-6-cyclohexylphenol <sup>p</sup> , —	Wettable pwd., dust, emulsion, field	Variety <sup>q</sup>	+	(150)

<sup>a</sup> Benzene hexachloride, preferably hexachlorocyclohexane.

<sup>b</sup> *Notonecta* sp.

<sup>c</sup> Not specified.

<sup>d</sup> Combinations were also active against the larva.

<sup>e</sup> *p*-Chlorophenyl *p*-chlorobenzenesulfonate.

<sup>f</sup> *Prodenia eridania* (Cram.).

<sup>g</sup> *Epilachna varivestis* Muls.

<sup>h</sup> A similar formulation gave control of European red mite on Jonathan apples in the field.

<sup>i</sup> *Tetranychus bimaculatus* Harvey.

<sup>j</sup> *Dermestes maculatus* Deg.

<sup>k</sup> Not specified.

<sup>l</sup> *Stiophilus granarius* (L.).

<sup>m</sup> Not specified in abstract.

<sup>n</sup> *Boophilus annulatus* (Say).

<sup>o</sup> Not specified.

<sup>p</sup> Cyclohexylamine salt used in some cases. Other nitrated phenols were active.

<sup>q</sup> Leaf hoppers, aphids, scale, mites, and rusts.

an antimetabolite in this particular activity.

A Swiss patent (88) claims *N,N*-diethyl-*o*-chlorobenzamide as a poison for certain diptera and it is against species of this order that the amides activate DDT.

The synergistic activity of chloropicrin (trichloronitromethane) (252) with nicotine was attributed to its capacity to increase metabolism in the insect. Dinitrophenols, with one nitro group para to the hydroxyl, are known to accelerate oxygen uptake (249) and it may be that the 2,4-dinitrophenols (151) owe their insect toxicity (and synergistic activity) to this biochemical effect. This is further supported by the fact that *o*- and *m*-nitrophenols, while toxic through a different mechanism, are relatively inactive in accelerating metabolism and are apparently without insecticidal activity. Further, the 2,4-dinitrophenols are readily absorbed by insect cuticle and produce symptoms suggestive of nerve poisons.

Physostigmine (178), like the organic phosphorus insecticides, is a powerful cholinesterase inhibitor and has served as the working model for the synthesis of a series of compounds (106), some of which are very poisonous to the housefly. It is not known whether this activity of physostigmine against the housefly explains its synergistic effect with DDT.

Some nitrogen-containing compounds have, in contrast, antagonized DDT in its action on insects. Nicotine-bentonite with DDT at several ratios in a dust formulation was less active in field plots toward the European corn borer

larva (255). Barbiturates were antidotal to DDT in the cockroach (178) and *Drosophila virilis* (14), an antagonism so evident in warm-blooded animals that the barbiturates are the antidotes of choice in DDT poisoning.

The combinations listed in Table IV are borderline cases of synergism at best. In addition to the possible synergists listed in Table IV, some pyrethrin synergists (27) and a diaryl sulfide (239) have been advanced as DDT synergists against the body louse and the housefly, respectively.

Glycerol, glycerol dichlorohydrin, phenylbiguanide, and picolinic acid (105) are known to retard the dehydrochlorination of DDT and some of these have been suggested as DDT synergists on this action. Pentaethylene penta-sulfide also has a negative action here and reduced the toxicity of DDT toward the Colorado potato beetle larvae (140).

Lindane, the insecticidally active gamma isomer of hexachlorocyclohexane, and BHC (hexachlorocyclohexane), a complex mixture containing principally the alpha, beta, gamma, delta, and epsilon isomers of this compound, were separated in Table V for convenient reference. They are treated jointly with respect to the discussion of their synergists.

The hydrocarbon acenaphthene (209), was found to be an active synergist for BHC but no mechanism of activity was suggested. Acenaphthene is toxic to codling moth larvae (244) and its eutectic properties may well favor its activity with lindane against the *Notonecta* species.

Two of the synergists for hexachloro-

cyclohexane were halogenated hydrocarbons and their activity has been explained. The enhanced activity of the hexachlorocyclohexane-chloroform mixture (189) was attributed to traces of chloroform which remained in the deposits. The high lipid solubility of chloroform and its selective high solvency for the gamma isomer of hexachlorocyclohexane support this explanation. Chlorinated biphenyls (36) were presumed to act by delaying the crystallization of lindane, to which eutectic mixture the chlorinated biphenyls may lend their own contact toxicity, albeit a weak one. The fumigant, lipid solubility, and nerve-poisoning effect of the dichlorinated benzenes, especially the *p*- isomers, and that of the monochloronaphthalenes contribute to their synergism with lindane.

Terpineol (216), a terpene tertiary alcohol with a lilac odor, is attractive to the oriental fruit moth and it is toxic to *Aphis rumices* (82). Its synergism with hexachlorocyclohexane for the granary weevil is one of the strongest yet encountered, but whether this can be attributed to the physical, chemical, or physiological properties of this alcohol was not specified.

Benzoate esters (193) and *p*-chlorophenyl *p*-chlorobenzenesulfonate (135), both active as DDT synergists, exhibit the same activity with lindane. The latter synergized lindane against a mite, toward which the synergist itself is toxic. However, this same activity was seen with other arthropods for which the synergist has little or no toxicity.

Phenylisonitrile (234) was active with

**Table VI. Potentiation of Insecticidal Activity of Chlordan, Aldrin, and Toxaphene by Some Miscellaneous Organic Compounds**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
Chlordan <sup>a</sup> , 1	DDT, 1	Spray	Argentine ant <sup>b</sup>	+	(198)
Chlordan, 1	DDT, 1	Emulsion, residual	Housefly <sup>c</sup>	+	(192)
Chlordan, —	Chlordan by-products, —	Soln., space spray	Housefly <sup>c</sup>	+	(91)
Chlordan, 20	Rotenone, 1	Dust	Mex. bean beetle larva <sup>d</sup>	+	(243)
Chlordan, 1	Nicotine, 1	Dust	Bean aphid <sup>e</sup>	+	(243)
Chlordan, 40	Parathion, 1	Solution, residual	Weevils <sup>f</sup>	++++ <sup>g</sup>	(48)
Aldrin, 7	DDT, 3	Solution, space spray	Housefly <sup>c</sup>	+	(61)
Aldrin <sup>h</sup> , 1	Ovatan <sup>i</sup> , 8	Wettable pwd., deposit	Southern armyworm <sup>j</sup>	++	
	Ovatan, 1		Spider mites <sup>k</sup>	++	(133)
Toxaphene, 7	DDT, 3	Solution, space spray	Housefly <sup>c</sup>	+	(61)
Toxaphene <sup>l</sup> , 2	Chlordan, 1	Dust	Pea weevil <sup>m</sup>	+	(219)
Toxaphene	Thanite <sup>n</sup>	...	Variety <sup>o</sup>	+	(32)

<sup>a</sup> 1,2,4,5,6,7,8-Octachloro-2,3,3a,4-7,7a-hexahydro-4,7-methanoindene.

<sup>b</sup> *Iridomyrmex humilis* Mayr.

<sup>c</sup> *Musca domestica*.

<sup>d</sup> *Epilachana varivestis* Muls.

<sup>e</sup> *Aphis fabae* Scop.

<sup>f</sup> *Calendra granaria* (Gyll.). *Sitophilus granarius* (L.).

<sup>g</sup> This enhanced activity was seen only in older deposits, 45 days or more.

<sup>h</sup> 1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene.

<sup>i</sup> *p*-Chlorophenyl *p*-chlorobenzenesulfonate.

<sup>j</sup> *Prodenia eridania* (Cram.).

<sup>k</sup> *Tetranychus bimaculatus* Harvey, *Bryobia praetiosa* Koch. and *Paratetranychus pilosus* (C. & F.).

<sup>l</sup> Chlorinated camphene (67–69% chlorine).

<sup>m</sup> *Nezara viridula* (L.), *Euschistus servus* (L.), and *Bruchus pisorum* (L.).

<sup>n</sup> Isobornyl thiocyanacetate.

<sup>o</sup> Mexican bean beetles, tobacco horn worm, flies, clothes moths, roaches, and cotton insects.

**Table VII. Potentiated Insecticidal Combinations with a Halogenated Insecticide and/or a Halogenated Synergist**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
Hexachloroethane, 49	Acetone-chloroform <sup>a</sup> , 1	...	Moths (butterflies) <sup>b</sup>	++++ <sup>c</sup>	(204)
Hexachloroethane, —	1-Bromo-4-chlorobenzene,	...	Moths (butterflies) <sup>b</sup>	+	(205)
Hexachloroethane, 4	Chloronaphthalene, 1	...	Moth larvae <sup>b</sup>	+	(205)
<i>p</i> -Dichlorobenzene, 19	Hexachloroethane, 1	...	Moth worms <sup>b</sup>	++++	(204)
<i>p</i> -Dichlorobenzene, 99	1-Bromo-4-chlorobenzene, 1	...	Moth worms <sup>b</sup>	+++	(204)
<i>p</i> -Dichlorobenzene, 9	Acetone-chloroform <sup>a</sup> , 1	...	Moth worms <sup>b</sup>	++++ <sup>c</sup>	(204)
2-Chloroacrylonitrile, 1	2,2,3-Trichlorobutyronitrile, 1	Soln., fumigant	Stored grain insects <sup>d</sup>	+	(45)
<i>p</i> -Dichlorobenzene	Thymol <sup>e</sup> , 1	...	Moth worms <sup>b</sup>	+++	(204)
Carbon disulfide, —	<i>p</i> -Dichlorobenzene <sup>f</sup> , —	Soln., fumigant	Cane grub <sup>g</sup>	+	(186)
HCN, —	Trichloroacetoneitrile, —	Fumigant	Calif. red scale <sup>g</sup>	+	(25)
Phenothioxin, 2	Di-(4-chlorophenoxy) methane, 1	Variety	Variety <sup>h</sup>	+	(64)

<sup>a</sup> 1,1,1-Trichloro-2-methyl-2-propanol.

<sup>b</sup> Not specified.

<sup>c</sup> This mixture in slightly different proportions was equally as active against moths (butterflies).

<sup>d</sup> Six species.

<sup>e</sup> This mixture in slightly different proportions was equally as active against moth worms. Isothymol is also active.

<sup>f</sup> *p*-Dichlorobenzene was reported earlier to activate carbon disulfide toward the beet weevil larva (224).

<sup>g</sup> *Anididella aurantii* (Mask.).

<sup>h</sup> Mites, thrips, scale, aphids, moths, etc.

hexachlorocyclohexane in a residual deposit in which the synergist was said to produce adhesiveness. The synergist, with a nauseous odor and a high mammalian toxicity, was found to be only slightly toxic to the codling moth (153), while its isomer is not a contact poison because of poor absorption. The low toxicity of phenylisocyanide toward insects thus supports an explanation of this synergism which is based on adhesiveness or some other favorable physical property of the hexachlorocyclohexane-phenylisocyanide mixture.

Azobenzene (209), an acaricide, increases oxygen consumption in insects and apparently produces decomposition products,—e.g., smokes—which have an insect toxicity.

The two dinitrophenols (150), both easily absorbed by insects which are poisoned through a nerve effect, are thought to act as synergists by accelerating metabolism, which may account, at least in part, for their toxicity when used alone.

The knockdown and contact activity of the organic thiocyanates, especially those with ether and ester functions, might account for the unexpected activity of the hexachlorocyclohexane-thiocyanate (234), but there is even less on which to base use of sodium thiocyanate (182) for this purpose. Potassium thiocyanate and thiourea (18), both with a potential —S—C≡N linkage (270), are two compounds, out of a number tested, capable of breaking the diapause of the walnut fruit fly. At the moment, any relationship between this action of potassium thiocyanate and its action in accelerating the effect of hexachlorocyclohexane against ticks and lice is a matter of conjecture.

Hexachlorocyclohexane by-products (250), presumably lesser chlorinated molecules, when mixed with hexachlorocyclohexane gave an incense more poisonous than that obtainable with ordinary hexachlorocyclohexane toward mosquitoes. The increased toxicity of the incense from hexachlorocyclohexane-hexachlorocyclohexane by-products could, of course, be due to a single compound from the by-products mixture which, on volatilization with partial decomposition, yields a vapor highly toxic to mosquitoes. Octachlorocyclohexane (209), a more highly chlorinated compound than hexachlorocyclohexane, was found to increase the lethal effects of hexachlorocyclohexane toward *Daphnia*, a water flea.

These instances of synergism between hexachlorocyclohexane and closely related compounds are not accompanied by reports of antagonisms, at least as far as insects are concerned. It is known, however, that the several isomers of hexachlorocyclohexane are antagonistic in warm-blooded animals.  $\gamma$ -Hexachlorocyclohexane, which stimulates the central nervous system, was found to be antagonized by the beta and delta isomers when given to the dog (159). Pretreating white rats with the alpha or beta isomers markedly reduces  $\gamma$ -hexachlorocyclohexane toxicity but leaves intact the protective action of the gamma form for metrazole-induced convulsions (45).  $\beta$ -Hexachlorocyclohexane protects rats against Lethane (organic thiocyanates) (44).

Table VI is concerned with the polychlorinated bicyclic hydrocarbon insecticides. Of the 12 synergists listed in Table VI, 10 are definitely insecticidal when used alone, but not necessarily

against the particular insect susceptible to the listed combinations.

DDT-chlordan combinations were listed in Table I as being synergistic toward a grasshopper (267) and the housefly (67). The chlordan-DDT pairs in Table VI, active against the Argentine ant (198) and the housefly (192), are reversed and placed in Table VI on strength of the author's conclusions that the chlordan synergized the DDT. The basis of these conclusions was not given but it is known that chlordan is active against both the ant and the housefly and provides a fumigant action which DDT lacks. DDT has entered into synergistic combinations with lindane, hexachlorocyclohexane, chlordan, aldrin, and toxaphene in 15 instances, involving the housefly five times, a grasshopper three times, and aphids twice. None of these synergisms reached a potency greater than (+), and probably reflect the widespread use of these insecticides, particularly DDT, rather than a tendency for them to enter into strong synergistic combinations.

The chlordan-chlordan by-products (97) mixture was included on the author's statement that technical chlordan was more toxic than crystalline chlordan was to houseflies. The composition of the reference crystalline chlordan was not given but chlordan yields several crystalline analogs, especially heptachlor, which show marked but wide differences in their toxicity to insects (128, 155).

Two quinones (1, 86, 215), were found to be active with DDT, but this is the first time that rotenone (243) has been found among the synergists for halogenated hydrocarbon insecticides.

The marked synergism obtained from the chlordan-parathion deposits (48) was not evidenced until after some aging.



**Table VIII. Potentiation of Insecticidal Activity of Pyrethrins by Some Halogenated Organic Compounds**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
Pyrethrum, —	Pentachloroethane, —	...	Bedbugs <sup>a</sup>	+	(225)
Pyrethrins, 1	<i>x</i> -Diethyl- <i>x</i> -chloronaphthalene <sup>b</sup> , 178	Soln., space spray	Housefly <sup>c</sup>	++	(67)
Pyrethrins, 1	2,2'-Dichlorodiethyl ether, 20	Soln., deposit	Corn earworm <sup>d</sup>	+	(10)
Pyrethrins, —	Di-( <i>p</i> -bromophenyl)-ether, —	Space spray	Housefly <sup>c</sup>	+	(90)
Pyrethrins	K-383 <sup>e</sup> , —	...	...	+	(3)
Pyrethrum, 1	2-Methoxy-3,5, <i>X</i> -trichlorodiphenyl <sup>f</sup> , 50	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(43)
Pyrethrins, 1	1-Ethoxy-2-bromodihydroisosafrate <sup>g</sup> , 80	Soln., Peet-Grady	Housefly <sup>c</sup>	++	(211)
Pyrethrins, 1	Isosafrole dibromide, 80	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(211)
Pyrethrins, 1	2-(3,4-Methylenedioxyphenyl)-4-chloromethyl-1,3-dioxane <sup>h</sup> , 20	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(213)
Pyrethrum, —	Terpene esters with halogen <sup>i</sup> , —	...	...	+	(15)
Pyrethrins, —	Bis(2-chloroethyl)-1,2,3,4-tetrahydro-3-methyl-6,7-methylenedioxy-1,2-naphthalenedicarboxylate, —	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(247)
Pyrethrins, 1	3-(3,4-Methylenedioxyphenyl)-propyl- <i>o</i> -chlorobenzylsulfide <sup>j</sup> , 16	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(212)
Pyrethrins, 1	1-Methyl-2-(3,4-methylenedioxyphenyl)-ethyl 2-( <i>p</i> -chlorobenzyl) ether, 16	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(212)
Pyrethrins, 1	1-Methyl-2-(3,4-methylenedioxyphenyl)ethyl 2-( <i>p</i> -chlorophenoxy)-ethyl sulfide, 16	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(212)
Pyrethrins, 1	3-(3,4-Methylene-dioxyphenyl)-propyl <i>o</i> -chlorobenzyl sulfone <sup>k</sup> , 16	Soln., Peet-Grady	Housefly <sup>c</sup>	++++	(248)
Pyrethrins, 1	1-Methyl-2-(3,4-methylenedioxyphenyl)ethyl <i>p</i> -chlorophenyl sulfone, 16	Soln., Peet-Grady	Housefly <sup>c</sup>	++++	(248)
Pyrethrum, —	<i>N</i> -3,3,5-Trimethylcyclohexylchloralimine, —	Soln., Peet-Grady	Housefly <sup>c</sup>	+	(50)
Pyrethrins, 1	<i>N</i> -( <i>o</i> -Chlorophenyl)piperonylamide <sup>l</sup> , (less than 2)	Soln., turntable	Housefly <sup>c</sup>	+	(94)
Allethrin, 1	<i>N</i> -( <i>o</i> -Bromophenyl)piperonylamide <sup>m</sup> , 10	Soln., turntable	Housefly <sup>c</sup>	+++	(93)
Pyrethrins, 1	2'-Bromobenzanilide <sup>n</sup> , 20	Soln., turntable	Housefly <sup>c</sup>	+	(179)
Pyrethrins, 1	<i>p</i> -Chloroacetophenone semicarbazone, —	...	...	+	(95)
Pyrethrins, 1	<i>N</i> -Amyl- <i>p</i> -bromobenzenesulfonamide, 20	Soln., turntable	Housefly <sup>c</sup>	++	(92)
Pyrethrins, 1	<i>N</i> -Propyl- <i>p</i> -bromobenzenesulfonamide <sup>o</sup> , 20	Soln., turntable	Housefly <sup>c</sup>	+	(92)
Pyrethrins, —	1,2-Dibromo-2-nitroethylbenzene, —	Soln., turntable	Housefly <sup>c</sup>	+	(156)
Pyrethrum, —	1-(2-Thiocyanoethyl)-1-(2'-chloroethoxy)-2-methylpropane, —	Powder, space	Flies <sup>p</sup> Mosquitoes <sup>p</sup> Roaches <sup>p</sup>	++ + +	(187)

<sup>a</sup> *Cimex lectularius* L.

<sup>b</sup> A different mixture of isomers and an *x*-isopropyl-*x*-monochloronaphthalene were even more active in comparable but separate tests.

<sup>c</sup> *Musca domestica* L.

<sup>d</sup> *Heliothis armigera* (Hbn.).

<sup>e</sup> 2-Chloro-2<sup>b</sup>-(2,4,6-trichlorophenoxy) diethyl ether.

<sup>f</sup> Certain other ethers of this phenol were active.

<sup>g</sup> The *N*-butyl homolog was as active.

<sup>h</sup> Probable structure. An analogous compound, 2-(2-bromo-3,4-methylenedioxyphenyl)-4-dimethyl-6-dimethyl-1,3-dioxane, was slightly more active.

<sup>i</sup> RCOOR'—X, R = reduced allo-ocimene crotonaldehyde condensate, R' = aralkyl, X = halogen.

<sup>j</sup> The *p*-chloro isomer of this compound was equally as active.

<sup>k</sup> The 2,4- and the 3,4-dichlorobenzyl analogs were slightly less and more active, respectively.

<sup>l</sup> The bromo analog at 10 parts was definitely synergistic.

<sup>m</sup> The *m*-isomer, *o*-chloro-, and *m*-chloro analogs had (++) activities. The *p*-bromo and *p*-chloro analogs at 2.5 parts had (+) activities.

<sup>n</sup> The 2'-chloro and 2',5'-dichloro analogs were less synergistic.

<sup>o</sup> The *N*-propyl and *N*-butyl homologs had (++) and (+) activities, respectively.

<sup>p</sup> Not specified.

This led the author to the belief that the chlordan preserved the parathion against decomposition or that a decomposition product of the parathion synergized the chlordan. The potential acidity of chlordan would retard the hydrolysis of parathion (72), and at least one of its decomposition products, *p*-nitrophenol, is known to synergize DDT and hexachlorocyclohexane against a variety of insects. Obviously, these mechanisms are mutually excluding.

The toxaphene-thaנית pair (32) was recommended on the basis of the residual

activity of the former and the knockdown capacity of the latter.

The 20 synergistic combinations in Table VII include principally contact poisons and fumigants. Sixteen of these combinations are cited in support of patent claims. The various combinations (204, 205) prepared from hexachloroethane, dichlorobenzene, 1-bromo-4-chlorobenzene, chloronaphthalene, 1,1,1-trichloro-2-methyl-2-propanol, and thymol contain relatively small amounts of the synergists. The increased efficacy of these combinations was based on the

greater speed with which they killed the insect used in the tests. This would indicate a more rapid penetration by the mixture and possibly an increased toxicity as well. The high vapor pressure, mutual solubility, and lipophilic nature of these compounds, with the attending potential for narcosis is well known. *p*-Dichlorobenzene is an established insecticide and hexachloroethane is sometimes substituted for it, particularly against the clothes moth, itch mites, certain weevils, and flies. Mixed halogenation of benzene has generally led to

compounds with increased activity toward insects (39), but contrary to expectation 1-bromo-4-chlorobenzene (165) proved to be an exception in that it is less toxic.

Acetone-chloroform (1,1,1-trichloro-2-methyl-2-propanol) is a solid halogenated alcohol having a camphoraceous odor like that of hexachloroethane. Acetone-chloroform has a trichloromethyl group which is frequently found in powerful insecticides. Acetone-chloroform readily volatilizes to vapors which produce excitation, ataxia, spasms, and eventually death in the housefly (120).

Thymol, 2-isopropyl-5-methylphenol, while unhalogenated, is soluble in or eutectic with the halogenated compounds listed above. Thymol is a general anthelmintic and has been found toxic to blowflies, mosquitoes, and moths (82).

The alkenyl and alkyl nitriles, with or without halogens, are very toxic to all forms of life and are widely used as insect fumigants and occasionally as sprays, depending on their volatility. Synergism is easily demonstrated among the fumigants and mixtures are more commonly used than individual compounds in the insect control by fumigation. The adjuncts serve as diluents and control fire hazard, etc., but it is very likely that they favorably alter the evaporation rate and provide synergism through an alteration in physiological action. The mixture of 2-chloroacrylonitrile and 2,2,3-trichlorobutyronitrile (46) might be expected to provide synergism as both cyanides and halogenated hydrocarbons contain toxophoric groups. Halogenated nitriles can activate other insecticides and trichloroacetonitrile is said to increase kills of scale insects by hydrocyanic acid through a reduction of a protective stupefaction (25) which occurs when cyanide is used alone.

Phenothioxin, its oxide, dioxide, and nuclear-substituted derivatives of these, were employed with the di(*p*-chlorophenoxy)-methane (64), but no explanation was given for their high activity against household and agricultural pests.

#### **Halogenated Hydrocarbon Insecticides And Inorganic Synergists**

A number of insecticide-synergist combinations consisting of a halogenated organic insecticide and an inorganic synergist (163, 229) have been discovered. The most prevalent combination in this series are the insecticide-sulfur pairs and DDT is the insecticide most frequently encountered. Based on insect mortality, lowered insect population, or increases in crop yields, DDT-sulfur combinations are claimed to be superior to either agent alone against bees (148), suckflies (268), caterpillars (5), Mexican bean beetles (264), milkweed bugs (264), pea aphids (257), thrips (70, 141, 273), pea leaf

miners (233), tomato russet mites (274), chiggers (27), and rat mites (183).

Addition of 2 parts of sulfur to 1 part of lindane extended the infestation-free period of red ants from less than 4 weeks to 12 weeks (254). Mixtures of chlorinated camphene and sulfur were more active against red spiders than were mixtures of chlorinated camphene with other diluents (85). The insolubility of sulfur and its activity, either mechanically or through its conversion to sulfur dioxide or hydrogen sulfide, probably explains why the more powerful insecticides were applied frequently with sulfur rather than as a substitute for it. No mechanisms for this synergism have been postulated. Most of the insects and related organisms listed are those against which sulfur was used, often alone, before the availability of the modern halogenated insecticides. This, linked with sulfur's abundance, its useful physical properties—e.g., solid state, water insolubility, etc.—has led to the practice of using sulfur-clay diluents as a vehicle for the modern halogenated insecticides.

The use of synergists with the pyrethrins is the rule rather than the exception in the application of this insecticide. Although a number of outstanding pyrethrin synergists are used routinely, the halogenated synergists are generally inferior with this insecticide. Carson and Eddy (29) tested several hundred compounds as synergists for pyrethrum against the body louse, but among the best 23 found none contained halogen. A comprehensive and recently published list of allethrin synergists (227) contained no halogenated compounds. Two halogenated sulfones (248) proved to be strongly synergistic with the pyrethrins and hence constitute exceptions to the general rule that the best pyrethrin synergists are found among nonhalogenated compounds.

Groupwise, the best synergists for the pyrethrins are certain alcohols, ethers, and esters derived from terpene, compounds with the methylenedioxyphenyl grouping, and some *N*-substituted amides as well as certain compounds containing both of the latter functions.

The synergism of the terpene alcohols is attributed to properties other than physiological ones and it is possible that other synergists for pyrethrins may function in this way (52). However, some halogenated counterparts of the more active pyrethrin synergists are available and these, along with other halogenated compounds, are listed in Table VIII.

Three DDT-pyrethrin combinations, listed in Table II, were found synergistic toward two common diptera. Pentachloroethane (225) with pyrethrum exterminated bedbugs, against which pyrethrum alone is not a persistent insecticide. The dialkylchloronaphthalene (67) did not increase the knockdown of pyrethrin toward the housefly but the kills were

definitely higher. This is the expected action from pyrethrins and aryl halides possessing neurotoxic effects. The relative effectiveness of the alkyl and aryl halide cannot be compared because different insects were used in those cases where comparisons could have been made.

Except for dichlorodiethyl ether (10), itself a fair substitute for the pyrethrins, all the pyrethrin-haloether pairs in Table VIII were tested as space sprays against the housefly.

Among the halogenated ethers, one simple ether (90), two mixed ethers (3, 43), and three methylenedioxyphenyl ethers (211, 213), the last of varying complexity, showed synergism with the pyrethrins. The most active of the short series was an ether with an alkyl-*O*-aryl linkage plus a methylenedioxyphenyl group (217). Significantly enough, the introduction of a second 1,3-dioxo linkage in a methylenedioxyphenyl ether failed to increase activity in the one trial reported (213). The brominated isosafroles were more active than the corresponding safroles. The halogenated isosafroles in Table VIII (217) were outstanding among some 17 related materials, some of which even reduced fly mortalities by the pyrethrins. Two additional ethers, 1-chloro-2-[2-(2,3,4,6-tetrachlorophenoxy)ethoxy]ethane and 2-(*p*-chlorophenoxy)-2'-(2-iodoethoxy) diethyl ether, (220) are active pyrethrin synergists, at least by implication.

The halogenated terpene ester (15) was patented as a synergist for the pyrethrins and rotenone. The claim with respect to the pyrethrins agrees with the observations that terpenes even with several different types of functional groups are active with the pyrethrins. The bis(2-chloroethyl)-1,2,3,4-tetrahydro-3-methyl-6,7-methylenedioxy-1,2-naphthalene dicarboxylate (247) has ether and ester groups which are frequently found in insectotropic compounds. The corresponding ethyl ester was more active in its effects with pyrethrins but the 2-chloroethyl ester was more active than the corresponding tetrahydrofurfuryl compound. Thus the halogenated compound is intermediate in activity. Di-(2-chloroallyl) succinate (220) is a simpler ester with a 2-chloroalkenyl radical which has been mentioned also in connection with pyrethrin synergists.

The mixed thioethers with methylenedioxyphenyl substituents (212) were toxic to the housefly both as knockdown and lethal agents. They were also synergistic with the pyrethrins in that they permitted the use of less pyrethrins without reduction in mortality rates. The oxidation of the sulfide to the corresponding sulfone further increased the effectiveness of this class of compounds. The presence of halogen in these molecules had no marked effect in either increasing or decreasing their synergistic activity.

The sulfo esters have exhibited synergistic activity with DDT, lindane, and aldrin. The activity of the sulfones, which may be regarded as representing an intermediate stage between the sulfides and the sulfo esters, suggest the testing of the sulfones with halogenated insecticides and the sulfo esters with the pyrethrins. The high activity of the sulf-oxides (248) with the pyrethrins has a bearing on the relationship between the structure and biological effect of this group of compounds. Chloromethyl *p*-chlorophenyl sulfone is said to be more toxic than DDT to body lice and bed-bugs.

*N*-3,3,5-trimethylcyclohexylchloralimine may be considered the Schiff base of chloral. This compound has an azomethine linkage which is found in some insect toxicants (26). This synergist is easily hydrolyzed to yield a primary amine and trichloroacetaldehyde, both of which are narcotic toward some insects.

The amides without *N*-substitutions are nerve sedatives in humans but appear to be generally devoid of contact activity in insects. Perhaps this is due to poor absorption. Substitution on the nitrogen atom of amides increases

their local effects on insects and some of these are excellent lousicides (20). The best pyrethrin synergists are the *N,N*-disubstituted amides. Apparently this effect is carried over into amides with a chlorinated *N*-aryl substituent (93, 94). The contribution of the methylenedioxyphenyl radical is also in evidence here.

2'-Bromobenzanilide (179), an analog of the halogenated *N*-substituted amides, was nontoxic to houseflies. As a synergist for the pyrethrins, this compound was slightly less effective than the 2'-chloro and the 2',5'-dichloro analogs. Other isomeric halogenated benzanilides were even less active.

**Table IX. Potentiation of Insecticidal Activity of Nicotine by Some Halogenated Organic Compounds**

Insecticide, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
Nicotine, —	Pentachloroethane, —	Dust, foliage	Melon worm <sup>a</sup>	+	(169)
Nicotine, —	<i>p</i> -Dichlorobenzene, —	Dust, foliage	Southern armyworm <sup>b</sup>	+	(169)
Nicotine, —	Pentachlorocumene, —	...	Southern armyworm <sup>b</sup>	+	(170)
Nicotine, 1	Aroclor 1232, 2.5	Dust, foliage	Beet armyworm <sup>c</sup>	+	(172)
Nicotine, —	Pentachlorophenol, —	Dust, foliage	Diamond-back moth <sup>d</sup>	+	(172)
			Melon worm <sup>a</sup>	+	(169)
			Southern armyworm <sup>b</sup>	+	(169)
Nicotine, 1	2,2'-Dichloroethyl ether <sup>e</sup> , 1	Dust <sup>f</sup>	Cucumber beetle <sup>g</sup>	+++	(42)
			Harlequin bug <sup>h</sup>	+++	(42)
Nicotine, —	Pentachlorophenyl methyl ether, —	...	Elm beetle <sup>i</sup>	+	(170)
			Southern armyworm <sup>b</sup>	+	(170)
Nicotine, —	<i>p</i> -Chlorophenyl dodecyl ether, —	...	Pea aphid <sup>j</sup>	+	(170)
Nicotine, —	Pentachlorophenyl octadecyl ether, —	...	Melon worm <sup>a</sup>	+	(170)
			Southern armyworm <sup>b</sup>	+	(170)
Nicotine, —	Pentachlorophenyl dodecyl ether, —	...	Southern armyworm <sup>b</sup>	+	(170)
Nicotine, —	Pentachlorophenyl 2,4-dinitro- phenyl ether, —	...	Southern armyworm <sup>b</sup>	+	(170)
Nicotine, —	2-Chlorallyl lactate, —	Dust, foliage	Melon worm <sup>a</sup>	+	(169)
			Southern armyworm <sup>b</sup>	+	(169)
			Diamond-back moth <sup>d</sup>	++	(169)
Nicotine, —	Di-( <i>p</i> -chlorophenyl) sulfide, —	Dust, foliage	Pea aphid <sup>j</sup>	++	(171)
			Calif. oakworm <sup>k</sup>	+	(171)
			Dock beetle <sup>l</sup>	+	(171)
			Armyworm <sup>m</sup>	+	(171)
			Bean aphid <sup>n</sup>	+	(171)
Nicotine, —	Di-( <i>p</i> -chlorophenyl)sulfide, —	...	Southern armyworm <sup>b</sup>	+	(170)
Nicotine, 1-2.5	Di-( <i>p</i> -chlorophenyl)sulfide, 1	Dust	Variety <sup>o</sup>	+	(277)
Nicotine, 1	Di-( <i>p</i> -bromophenyl)sulfide, 2.5	Dust, foliage	Pea aphid <sup>j</sup>	+	(172)
Nicotine, 1	Di-( <i>p</i> -chlorophenyl)disulfide, 4	Dust, foliage	Armyworm <sup>b</sup>	+	(173)
			Diamond-back moth <sup>d</sup>	+	(172)
Nicotine, 1	2-Chlorodibenzothiophene, 2.5	Dust, foliage	Diamond-back moth <sup>d</sup>	+	(172)
Nicotine, 1	4-Chlorovaleronitrile, 2.5	Dust, foliage	Pea aphid <sup>j</sup>	+	(172)
Nicotine, —	<i>p</i> -Chloroacetophenone semicar- bazone, —	...	...	+	(92)
Nicotine, —	<i>p</i> -Bromobenzenesulfonamide, —	...	Southern armyworm <sup>b</sup>	+	(170)
			Variegated cutworm <sup>p</sup>	+	(170)
Nicotine, —	<i>N</i> -butyl- <i>p</i> -bromobenzenesulfon- amide, —	...	Southern armyworm <sup>b</sup>	+	(170)
Nicotine, —	Chloropicrin, —	Dust	Poppy weevil <sup>q</sup>	+	(173)

<sup>a</sup> *Diaphania hyalinata* (L.).

<sup>b</sup> *Prodenia eridania* (Cram.) (B.).

<sup>c</sup> *Laphygma exigua* (Hbn.).

<sup>d</sup> *Plutella maculipennis* (Curt.).

<sup>e</sup> A ratio of 2 parts nicotine to 1 part synergist gave comparable results.

<sup>f</sup> Liquid formulations were active also.

<sup>g</sup> *Diabrotica Soror*.

<sup>h</sup> *Murpentina histrionica* (Hahn).

<sup>i</sup> *Halicta bimarginata*.

<sup>j</sup> *Macrosiphum pisi* (Keth.).

<sup>k</sup> *Phryganidia californica* (Pack).

<sup>l</sup> *Gastrophysa cyanea* (Melsh.).

<sup>m</sup> *Cirphis unipuncta* (Haw.).

<sup>n</sup> *Aphis fabae* (Scop.).

<sup>o</sup> Diamond back moth, alder flea beetle, armyworm, pea aphid, greendock beetle and California oakworm.

<sup>p</sup> *Peridroma margaritosa* (Haw.).

<sup>q</sup> *Ceuthorrhynchus macula-alba* Hbst.

**Table X. Potentiated Insecticidal Combinations with Three Active or Activating Components, One or More of Which Contain Halogen**

Insecticide, Parts	Insecticide or Synergist, Parts	Synergist, Parts	Formulation and Application	Insect	Activity	Reference
<i>p</i> -Dichlorobenzene, 98	<i>p</i> -Dibromobenzene, 1	Acetonechloroform, 1	...	Moths <sup>a</sup>	+++	(204)
<i>p</i> -Dichlorobenzene, 98.5	Acetonechloroform, 0.75	Thymol, 0.75	...	Moths, butterflies <sup>a</sup>	++	(204)
DDT, 40-50	BHC, 10-15	Camphor, 40-50	...	...	+	(195)
Toxaphene, 3	DDT, 1	Sulfur, 8	...	Salt marsh caterpillars <sup>b</sup>	+	(33)
DDT, —	Pyrethrins, —	Piperonyl butoxide, —	Wettable pwd., dusting pwd., soln.	...	+	(152)
DDT, 10	Pyrethrins, 1	1-(3,4-Methylenedioxyphenyl)-2-methyl-1,3-epoxypropane <sup>c</sup> , 100	Soln., space spray	Housefly <sup>d</sup> Mosquito <sup>e</sup>	++++ ++++	(147)
DDT, 10	Pyrethrins, 1	Ethyl 6-iso-propyl-2-methyl-4-oxo-2-cyclohexene-1-carboxylate <sup>c</sup> , 100	Soln., space spray	Housefly <sup>d</sup> Mosquito <sup>e</sup>	++++ ++++	(147)
DDT, —	Pyrethrins	Piperonyl butoxide, —	Wettable pwd.	Hornflies <sup>f</sup> Stable flies <sup>g</sup>	+++	(154)
DDT, 25	Pyrethrins, 6	Benzal 3-5-xyldine <sup>h</sup> , 50	Soln., NAIDM <sup>a</sup>	Housefly <sup>d</sup>	+	(230)
DDT, 10	Pyrethrins, 1	<i>N,N</i> -Diisopropyl-3-hydroxy-3-methylvaleramide <sup>c</sup> , 100	Soln., space spray	Housefly <sup>d</sup> Mosquito <sup>e</sup>	++++ ++++	(147)
DDT, 10	Pyrethrins, 1	<i>N,N</i> -Diethyl-1-cyclohexoxyacetamide <sup>c</sup> , 100	Soln., space spray	Housefly <sup>d</sup> Mosquito <sup>e</sup>	++++ ++++	(147)
DDT, 10	Pyrethrins, 1	Allyl <i>N,N</i> -diisopropylsuccinamate <sup>c</sup> , 100	Soln., space spray	Housefly <sup>d</sup> Mosquito <sup>e</sup>	++++ ++++	(147)
DDT, —	Pyrethrins, —	Ca- <i>N</i> -dodecyl- <i>N</i> -(2-hydroxypropyl)phthalamate <sup>i</sup>	Soln., space spray	Housefly <sup>d,j</sup>	++	(231)
DDT, 80	Pyrethrins, 1	<i>N</i> -(2-Ethylhexyl)bicyclo-(2,2,1)-5-heptane-2,3-carboximide <sup>k</sup> , 40	...	Housefly <sup>d</sup>	+	(113)
DDT, 1	Turpentine, 2.5	Malhaute NNE <sup>l</sup> , 5	Soln.	Anopheline larva <sup>a</sup>	+	(28)
Derris, —	Pyrethrum	Chloropicrin, —	Dust	Greenhouse white fly <sup>m</sup>	+	(252)

<sup>a</sup> Not specified.

<sup>b</sup> *Estigmene acrea* (Drury).

<sup>c</sup> This synergist is one of the five most active compounds found among some 3800 tested for synergistic activity toward the housefly and mosquito. In general, the most active compounds were found among the thiocyanate esters, glutaric acid derivatives, amides, cinnamic acid derivatives, and compounds containing the methylene-1,2-dioxyphenyl group. The mosquito showed susceptibility to more of these combinations than did the housefly.

<sup>d</sup> *Musca domestica* L.

<sup>e</sup> *Anopheles quadrimaculatus* (Say).

<sup>f</sup> *Siphona irritans* (L.).

<sup>g</sup> *Stomoxys calcitrans* (L.).

<sup>h</sup> Furfural-aniline, benzal-aniline, and cinnamyl-aniline were slightly less active.

<sup>i</sup> Data indicate synergism with DDT alone.

<sup>j</sup> Claimed to be active against "silver fish, ants, bedbugs, and the like."

<sup>k</sup> Substituting chlordan for DDT gave an active combination.

<sup>l</sup> Presumably an emulsifier. Sodium sulforicinate is said to give the same results (28).

<sup>m</sup> *Triallurodes vaporariorum*.

<sup>n</sup> National Association Insecticide and Disinfectant Manufacturers.

The semicarbazones of aldehydes and ketones have been tested against numerous insects, but generally with disappointing results. Probably, the most toxic of those tested is the semicarbazone of *p*-chloro-benzaldehyde (95). This superiority is reflected in its activity as a synergist in which capacity it serves pyrethrum, derris nicotine, and the arsenical insecticides.

Esters of benzenesulfonic acid were found to synergize both halogenated insecticides and the pyrethrins against certain insects. Sulfides, sulfoxides, and sulfones, especially the sulfones, gave even more effective combinations with the pyrethrins.

A series of halogenated benzenesulfonamides has been tested directly against the housefly, and only one, *N,N*-

diethyl - *p* - chloro-benzenesulfonamide, was found to be toxic when used alone. At least four members of the series (92), and possibly more, proved quite active as synergists for pyrethrins against the same insect. In these compounds having sulfur at several levels of oxidation, halogenation appears to add activity to the esters and amides of the arylsulfonic acids. Halogenation did not detract from the activity of the compounds in the other series.

The 1,2-dibromo-2-nitroethylbenzene (156) is structurally related to both trichloronitromethane and 1,2-dihaloalkanes. Like these latter compounds, 1,2-dibromo-2-nitroethylbenzene is a highly toxic fumigant for insects. The 2-nitroalkylbenzene portion of this synergist re-

lates it to 2-nitro-1,1-bis(*p*-chlorophenyl)-propane and 2-nitro-1,1-bis(*p*-chlorophenyl)-butane, both of which have a high contact toxicity toward the housefly. The 2-bromoalkylbenzene portion is suggestive of 2,2-bis-(*p*-bromomethyl)-1,1,1-trichloroethane whose structural and insecticidal similarity to DDT is well known. Thus, the synergistic activity of this bromonitrobenzene is not entirely unexpected.

1-(2-Thiocanoethyl)-1-(2'-chloroethoxy)-2-methylpropane (187) has a thiocano linkage and a 2-chloroethoxy group, both of which are found in commercially important insecticides. This hybrid molecule was cited as accelerating the action, increasing the killing power of, and stabilizing several botanical insecticides, including pyrethrum.

**Table XI. Potentiation of Insecticidal Activity of DDT Against Resistant Housefly by Organic Compounds, Classified According to Chemical Structure**

Insecticide, Parts	Synergist, Parts	Formulation and Applications	Activity	Reference
Halogenated Hydrocarbons				
DDT, 10	2,2-Diphenyl-1,1,1-trichloroethane, 1	Soln., residual deposit	++	(242)
DDT, 10	2,2-Bis( <i>p,p'</i> -ethylphenyl)-1,1,1-trichloroethane, 1	Soln., residual deposit	+	(242)
DDT, 5	Bis( <i>p</i> -chlorophenyl)-methane, 1	Soln., topical	++++	(161)
DDT, 5	1-( <i>p</i> -Chlorophenyl)-1-( <i>m</i> -chlorophenyl)-ethane, 1	Soln., topical	++++	(161)
DDT, 10	1,1-Bis( <i>p</i> -chlorophenyl)-ethane, 1	Soln., residual deposit	++++	(241)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-ethane, 1	Soln., topical	++++	(161)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-ethylene, 1	Soln., topical	++++	(161)
DDT, 5	Bis( <i>p</i> -chlorophenyl)-chloromethane, 1	Soln., topical	++++	(161)
DDT, 5	Bis( <i>p</i> -chlorophenyl)-bromomethane, 1	Soln., topical	++++	(161)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-1-chloroethane, 1	Soln., topical	++++	(161)
DDT, 10	2,2-Bis( <i>p</i> -fluorophenyl)-1,1,1-trichloroethane, 1	Soln., residual deposit	+++	(242)
DDT, 10	2,2-Bis( <i>p</i> -chlorophenyl)-1,1,1-tribromoethane, 1	Soln., residual deposit	+++	(242)
DDT <sup>a</sup> , 1	DDT by-products <sup>b</sup> , 10 <sup>c</sup>	Soln., residual deposit	++++ <sup>d</sup>	(6)
DDT, —	Lindane, —	Field formulations	+	(107)
Halogenated Alcohols				
DDT, 10	1-( <i>p</i> -Chlorophenyl)-2,2,2-trichloroethanol	Soln., residual deposit	++	(242)
DDT, 10	1,1-Bis( <i>p</i> -chlorophenyl)-ethanol <sup>e</sup> , 1	Soln., residual deposit	++++	(242)
DDT, —	1,1-Bis( <i>p</i> -chlorophenyl)-ethanol <sup>f</sup> , —	...	+	(22)
DDT, 7.5	1,1-Bis( <i>p</i> -chlorophenyl)-ethanol, 1	Spray, deposit	+	(41)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-ethanol, 1	Soln., topical	++++	(161)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-2-propen-1-ol, 1	Soln., topical	++++	(161)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-2-propyn-1-ol <sup>g</sup> , 1	Soln., topical	++++	(161)
DDT, 5	1,1-Bis(2,4-dichlorophenyl)-2-propyn-1-ol, 1	Soln., topical	++++	(161)
DDT, 10	1,1-Bis( <i>p</i> -fluorophenyl)-ethanol, 1	Soln., residual deposit	++++	(242)
Ethers				
DDT, 1	Methylallyl 2-naphthyl ether, 20	Soln., topical	+	(200)
DDT, 1	<i>n</i> -Amyl 2-naphthyl ether, 20	Soln., topical	+	(200)
DDT, 10	Flavan <sup>h</sup> , 1	Soln., residual deposit	++++	(241)
DDT, 5	1,1-Bis( <i>p</i> -chlorophenyl)-ethyl methyl ether, 1	Soln., topical	++++	(161)
DDT, 5	Di[1,1-bis( <i>p</i> -chlorophenyl)ethyl] ether, 1	Soln., topical	++++	(161)
DDT, 1	2,2-Bis( <i>p</i> -methoxy)-1,1,1-trichloroethane <sup>i</sup> , 1 <sup>j</sup>	Emulsion <sup>k</sup> , residual	+ <sup>l</sup>	(240)
DDT, 10	2,2-Bis( <i>p</i> -ethoxyphenyl)-1,1,1-trichloroethane, 1	Soln., residual	++	(242)
Sulfur Compounds				
DDT, 5	Dibenzyl sulfide, 1	Soln., topical	+++	(161)
DDT, 5	Di( <i>p</i> -chlorophenyl) sulfide, 1	Soln., topical	++++	(161)
DDT, 5	Bis( <i>p</i> -chlorophenylmercapto) methane, 1	Soln., topical	++++	(161)
Carbonyl Compounds				
DDT, 10	<i>l</i> -Xylose, 1	Soln., residual	++++	(241)
DDT, 10	<i>p</i> -Chlorophenyl 1,2-dichloro-2-( <i>p</i> -chlorophenyl)ethyl ketone, 1	Soln., residual	++++	(241)
DDT, 10	Dihydroxyanthraquinone <sup>m</sup> , 1	Soln., residual	++++	(241)
DDT, 10	Quinhydrone, 1	Soln., residual	++++	(241)
Acids and Esters				
DDT, 10	3-Hydroxy-2-naphthoic acid, 1	Soln., residual	++++	(241)
DDT, 10	3-Bromo-2-nitrobenzoic acid, 1	Soln., residual	++++	(241)
DDT, 10	2,4-Dichlorophenoxyfumaric acid, 1	Soln., residual	++++	(241)
DDT <sup>a</sup> , 1	Benzyl benzoate, 2.5	Soln. <sup>n</sup> , residual	++++ <sup>o</sup>	(6)
DDT, 1	Benzyl benzoate, 2.5	Soln., residual	++++	(6)
DDT, 1	Benzyl <i>p</i> -chlorobenzoate, 5	Soln., residual	+ <sup>p</sup>	(6)
DDT, 10	Isopropyl 2-naphthoxyacetate, 1	Soln., residual	++++	(241)
DDT, 10	Di- <i>p</i> -nitrobenzyl terephthalate, 1	Soln., residual	++++	(241)
DDT, 1	Piperonyl cyclonene <sup>q</sup> , 10	Soln., topical	++++	(162)
DDT, 1	Piperonyl cyclonene, 20	Soln., topical	++++	(202)
DDT, 1	Piperonyl cyclonene, 20	Soln., topical	++++	(200)
DDT, 1	Lanolin <sup>r</sup> , 1	Soln., topical	++	(6)
DDT, 10	Na 2,6-dichloroindophenol, 1	Soln., residual	++++	(241)
DDT, 10	<i>p</i> -Chlorobenzaldehyde semicarbazone, 1	Soln., residual	++++	(241)
DDT, 1	Isobutylundecylenamide, 20	Soln., topical	+	(200)
DDT, 10	Malachite green G, 1	Soln., residual	++++	(241)
DDT, 10	Phenylmercuric salt of 2,4-pentanedione, 1	Soln., residual	++++	(241)
DDT, 10	2-Hydroxy-1,3,2-benzodioxastibiole, 1	Soln., residual	++++	(241)

<sup>a</sup> *p,p'*-DDT. <sup>b</sup> Oily fraction of technical DDT. <sup>c</sup> A ratio of DDT to DDT by-products of 1 to 20 was equally as effective. <sup>d</sup> This degree of activity, based on knockdown could not be approached by simply using technical DDT. <sup>e</sup> DMC, Di-(*p*-chlorophenyl)-methylcarbinol. <sup>f</sup> Activates insecticides related to DDT. <sup>g</sup> This compound, melting point 72.5° to 74° C., was slightly less active at lower but comparable doses than another sample melting at 61° to 73° C. <sup>h</sup> 2'-Hydroxypentamethylflavan. <sup>i</sup> Methoxychlor. <sup>j</sup> Combinations with smaller proportions were active. <sup>k</sup> Suspensions and solutions were also active. <sup>l</sup> As active toward resistant flies as toward normal strains. <sup>m</sup> Mixture of the 1,5-isomer (65%) and the 1,8-isomer (35%). <sup>n</sup> The emulsion is also active. <sup>o</sup> Activity is based on knockdown. <sup>p</sup> Gave satisfactory control for 2 weeks. <sup>q</sup> 3-Alkyl-6-carbethoxy-5-(3,4-methylenedioxypheyl)-2-cyclohexen-1-one and 3-alkyl-5-(3,4-methylenedioxypheyl)-2-cyclohexen-1-one. <sup>r</sup> Chiefly cholesteryl and isocholesteryl esters of fatty acids.

Nicotine, *l*-1-methyl-2-(3'-pyridyl)-pyrrolidine, is a naturally occurring alkaloid found in several species of tobacco. Nicotine, having several sites of activity in the nervous system with both a stimulant and depressant phase, is highly toxic in mammals and to lower forms, including insects. Nicotine has been widely used as a fumigating, contact, and stomach poison, especially against small, soft-bodied insects. This activity of nicotine is shared, at least in insects, by nornicotine and anabasine, both structural analogs of nicotine.

Activating nicotine by releasing the volatile alkaloid from its salts and increasing its coverage, as by soap, was mentioned earlier in this paper.

In an effort to conserve this relatively expensive insecticide by extending its action, Mayer and his associates carefully screened a large number of compounds for synergistic action with nicotine. The early discovery of the activity of phthalonitrile and di(*p*-chlorophenyl) sulfide with nicotine warranted the use of these as patterns for later selections. Compounds listed in Table IX (169, 170-173, 277) were taken from their reports.

Mayer *et al.* (173) offered no explanation for activity of the synergists which they found. It is known that compounds used in conjunction with nicotine, such as mineral oil and ethyl ether, can retard and promote, respectively, its penetration into and, hence, its toxicity toward insects (271, 272). It has been found repeatedly that two neurotoxic compounds when used jointly can provide more or less than the sum of their effects in insects. Thus, the following halogenated individual compounds or series: hydrocarbons, ethers, esters, thioethers, nitriles, semicarbazones, and amides possess properties which make them act in either or both of these capacities. The nitrated halocompounds have the added interest of being catabolic agents in insects just as is nicotine.

The synergistic activity of 2,2'-dichlorodiethyl ether (42) for nicotine and its sulfate was more specifically attributed to the insect-feeding inhibition of the combination. This inhibition was specified for cucumber beetles on squash and aphids on cabbage, but may have been seen with other species. Crude 2,2'-dichlorodiethyl ether could be employed for this purpose but other homologs and isomers of this ether were less active.

The natural resistance of tobacco-infesting insects to nicotine has been attributed to a nicotine immunity of the synapse of an insect which has recovered from an exposure to nicotine (12). Many tobacco insects are susceptible to certain halogenated hydrocarbon insecticides. An investigation of the reaction of the tobacco insects to nicotine-halo-synergist combinations might be helpful in understanding the mechanism of the

synergism exhibited by these compounds.

The insecticidal mixtures listed in Table X are composed of three components, usually two insecticides and one synergist. Among the 19 mixtures, one contains halogen in all three components, three mixtures contain halogen in two components, and 15 mixtures contain halogen in only one component.

Lindquist and coworkers (147) screened some 3800 compounds for their potential in increasing the knockdown rate and lethal properties of a DDT-pyrethrum spray against the housefly and mosquito (*Anopheles quadrimaculatus*). As expected, some test compounds reduced the effectiveness of the combination while others were inactive, only moderately toxic, or strongly toxic. The mosquito was more vulnerable than the fly to the various combinations. More compounds were synergistic with respect to knockdown than to mortality. Only five compounds were outstanding in both categories against these species. These five compounds are listed in Table X under reference (147). None of these contained halogen but they are close structural relatives of compounds known to synergize both DDT and pyrethrins, especially against the dipterous insects.

### Discussion

Since negative results are seldom reported, it is statistically unsound to emphasize the type of compound most frequently encountered among the more active synergists. By the same token, it is difficult to say which of the entomological characteristics predispose an insect to attack by an activated combination.

The 200 synergists, listed in Tables I to X, are distributed among the chemical classes as follows: halogenated hydrocarbons 60, esters 17, hydrocarbons 13, halogenated ethers 13, ethers 10, esters of benzenesulfonic acids 10, and amides 10. The remainder are scattered among some 25 chemical classes.

About one fourth of the 200 synergists were found to be active with DDT. There were enough halogenated hydrocarbons, ethers, quinones, and esters, (probably hydrocarbons and possibly amides) to warrant setting up separate tables or sections of tables for these groups. The halogenated ethers and halogenated thioethers were more active with pyrethrins and nicotine than with DDT, lindane, chlordan, aldrin, and toxaphene.

An attempt was made to find some correlation between synergistic activity and other biological effects of the listed synergists. The synergists for DDT, lindane, chlordan, aldrin, and toxaphene, as listed, contain a much larger proportion of compounds with acaricidal activity than would be expected from random distribution.

There are 229 cases of synergism listed in Tables I to X. Of these 205 involve insects, 22 involve arachnids (principally plant mites), 1 involves a nematode, and 1 involves a fungus. The distribution of the 205 insects as to orders was diptera 84, lepidoptera 48, hemiptera 39, coleoptera 21, and orthoptera 9, with the remaining 4 insects falling into 3 separate orders (185). The distribution frequency of these species of insects probably reflects the amount of effort which has been devoted to their control, especially by chemical means. The species of insects found in the tables are about equally divided between those which are known to be important in disease transmission and those which cause economic loss by destruction of food and clothing.

### Use of Insecticide-Synergist Combinations Against Insecticide-Resistant Insects

The marked difference in the capacity of different species and of individual subjects in the same species to withstand challenging doses of active substances are termed species tolerance and individual tolerance, respectively, and account for much of the difficulty in making biological determinations and translating results obtained therefrom.

The phenomena of acquired susceptibility or especially acquired resistance is being met more frequently with the increasing exposure of high and low forms of life to specific chemical agents—frequently chemical agents with powerful biological effects. The development of germicide-fast microorganisms, insecticide-resistant insects, and morphine tolerance in humans can be cited as examples of acquired resistance.

A number of insect species, some in both the immature and adult stages, have been found to have a resistance to insecticides; this can be acquired under laboratory conditions or in the field. From the standpoint of chemical control, the development of resistance in muscoid flies has presented the greatest problem. Resistance of this species is most common with DDT, but this may reflect its almost universal use against the housefly.

Smith (232), Quayle (214), Monro (180), Babers (7), Babers and Pratt (8), Metcalf (177), and Hess *et al.* (118, 119) have reviewed insecticide resistance.

The development of resistance in harmful insects has necessitated changes in control measures. Chemical control, the origin of the problem, has been strengthened by the use of larger doses of the insecticide (23), application of insecticide combinations, or substitution of other insecticides, preferably of a different type (266).

The combinations of insecticides or insecticide-synergists, at least one of

which is halogenated, which have shown activity against resistant insects are listed in Tables XI and XII.

Of the 55 synergists for DDT listed in Table XI, 24 were reported by this author and coworkers (241, 242), 16 by March and Metcalf (161), 5 by Reuter and Levinson (6), and 5 by Hoskins *et al.* (200, 202).

The testing procedure used by Sumerford *et al.* (241, 242) and by Reuter and Levinson (6) consisted of exposing resistant flies for stated periods to weighed deposits of the insecticide-synergist on posterboard and glass plates, respectively. In sharp contrast to this procedure, March and Metcalf (161) and Hoskins *et al.* (200, 202) tested for synergism by applying measured amounts of the combinations in solution to the body of the fly. Sumerford *et al.*, March and Metcalf, and Hoskins *et al.* based activity on mortality of the female flies. Reuter and Levinson used interval and rate of knockdown in terms of the age of the deposit as criteria of activity.

Reuter and Levinson (6) believe that the DDT synergists which they reported are dependent for their activity through the formation of eutectic mixtures with the insecticide. Others have found that the physical state of DDT is a strong factor in its toxicity to normal insects. The use of camphor (795) and polychlorinated biphenyls (36) were cited as examples of compounds which increase the toxicity of DDT and lindane by preventing its crystallization. Fats and oils added to DDT solutions (30) were said to make it as toxic to resistant houseflies as it formerly was to normal strains.

Hoskins *et al.* (200, 202) concluded that

piperonyl cyclonene synergized DDT in resistant houseflies by inhibiting its detoxification to DDE [2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene], a reaction which they (207) and others (238) have shown to be readily carried out by resistant flies. Piperonyl cyclonene consists of two molecules, 1,2-methylene-*o*-dioxycyclohex-4-en-3-one or (2-carbethoxy-5-alkyl-cyclohex-4-en-3-one) groupings. Thus, these molecules taken together possess three chemical linkages associated with insecticidal activity: methylenedioxybenzene, cyclohexenone, and a carbethoxy group. Exclusive of piperonyl cyclonene, there are 16 synergists listed in Table XI which contain either an ether linkage or an ester linkage without the methylene-*o*-dioxycyclohexenone group. This conspicuous absence is in accord with March's (161) failure to obtain synergistic activity with several compounds having the methylene-*o*-dioxycyclohexenone nucleus.

This author and his associates screened a large number of chemicals selected at random and uncovered activity in compounds for which no explanation is available at this time. These workers selected as possible DDT synergists a number of compounds structurally related to the insecticide (242). This selection was based on the possibility that the compound would be absorbed along with the insecticide, after which the resistant insect would preferentially detoxify (probably by dehydrohalogenation) the synergist and leave some or all of the insecticide to exert its toxicity. The list of halogenated hydrocarbons (particularly the DDT analogs) indicates that this was based on something

more than wishful thinking. The most active compound of the group, 1,1-bis(*p*-chlorophenyl)-ethanol, also bears a relationship to DDT, and its dehydration, which proceeds readily, resembles dehydrohalogenation to the extent that both reactions consist of removing a negative and a positive unit from separate carbons of an alkane chain containing identical substituents (the chlorine atom) on one of the carbon atoms. This explanation does not apply to cover the activity of the ether (161) of this alcohol unless it undergoes a prior hydrolysis, which would appear unlikely. Another very active synergist, *p*-chlorophenyl 1,2-dichloro-2-(*p*-chlorophenyl)ethyl ketone (247), while neither a halogenated hydrocarbon nor a halogenated alcohol, is subject to a dehydrochlorination and its tendency to undergo such a reaction may be optimum for its activity with DDT. Neither this ketone nor the 1,1-bis(*p*-chlorophenyl) ethanol were insecticidal to the housefly when used alone.

At 275 mg. per kg. doses, DDT and 1,1-bis(*p*-chlorophenyl)ethanol gave 60 and 6% kill, respectively, in white rats. A combination of DDT at 250 mg. per kg. and 1,1-bis(*p*-chlorophenyl)ethanol at 25 mg. per kg. gave an 80% kill (115). Thus it would appear that this compound blocks the rat's detoxification mechanism, the initial step of which may be identical with that used by the insect.

DDT and many other insecticides are thought to owe their activity to the toxicity of their aryl halide radicals. Of the two known detoxification mechanisms of the monohalobenzenes in animals, one is dependent on the synthesis of a mercapturic acid by this general reaction (275):

**Table XII. Insecticidal Combinations with a Halogenated Insecticide and/or a Halogenated Synergist Having a Potentiated Activity Against Insecticide-Resistant Insects**

Insecticide, Parts	Synergist, Parts	Formulation and Applications	Insect	Activity	Reference
DDD <sup>a</sup> , 1	Piperonyl cyclonene, 20	Soln., topical	Housefly <sup>b</sup>	++++	(200)
DFDT, 10	1,1-Bis( <i>p</i> -fluorophenyl)ethanol, 1	Soln., residual deposit	Housefly <sup>b</sup>	++++	(242)
DFDT, 10	1,1-Bis( <i>p</i> -chlorophenyl)ethanol, 1	Soln., residual deposit	Housefly <sup>b</sup>	++++	(242)
DDT, 10	1,1-Bis( <i>p</i> -chlorophenyl)ethanol, 1	...	Cockroach <sup>c,d</sup>	+	(223)
Methoxy- chlor, 5	Bis( <i>p</i> -chlorophenyl) chloro- methane, 1	Soln., topical	Housefly <sup>b</sup> XXXX	+++	(161)
Methoxy- chlor, —	Lindane, —	Wettable powder, resid- ual deposit	Housefly <sup>b</sup>	+	(35)
Methoxy- chlor, 5	Bis( <i>p</i> -chlorophenyl)-2-propyn-1- ol, 1 <sup>e</sup>	Soln., topical	Housefly <sup>b</sup>	++	(161)
Methoxy- chlor, 1	Piperonyl cyclonene, 20	Soln., topical	Housefly <sup>b</sup>	++++	(200)
Chlordan, 2	DDT, 1	Emulsion-suspension, residual deposit	Housefly <sup>b</sup>	+	(207)
Parathion, 1	1,1-Bis( <i>p</i> -chlorophenyl)ethanol, 1	Wettable powder + concentrate <sup>f</sup>	Mite <sup>g</sup>	++++	(194)
Chloro- phenol, —	Alkyl sulfate, —	...	Potato root eel worm <sup>h</sup>	+	(237)

<sup>a</sup> 2,2-Bis(*p*-chlorophenyl)-1,1-dichloroethane.

<sup>b</sup> *Musca domestica* (L.).

<sup>c</sup> Organisms with natural rather than acquired resistance.

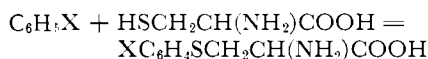
<sup>d</sup> *Periplaneta americana* (L.).

<sup>e</sup> Lower melting form was about 2/3 as active.

<sup>f</sup> Water-wettable powder mixed with an emulsion.

<sup>g</sup> *Paratetranychus pilosus* (C. & F.).

<sup>h</sup> *Heterodera rostochiensis*.



This detoxification mechanism, while known only in animals, is worth considering in light of an observation that thiourea completely protected resistant strains of male and female houseflies from any observed symptoms of DDT poisoning, although DDT alone on forced contact is still lethal to the former and temporarily paralyzes the latter (75).

March and Metcalf tested almost 100 candidate synergists of which many were active. No mechanism of activity was suggested. However, the compounds were grouped according to their functional groups, and the compounds within classes were discussed from the standpoint of molecular configurations which confer synergistic activity. The bis(*p*-chlorophenyl) structure is frequently associated with this activity, especially when it is linked through an aliphatic group.

The synergists active with DDT against resistant houseflies were also found active with close analogs of DDT against the same insect in the few cases in which trials were made.

A recent and pertinent paper lists the synergistic activity of some 115 compounds, including bis(*p*-chlorophenyl) sulfonamide, for DDT against resistant houseflies (236).

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