

ABSTRACT OF THESIS

CHEMICAL STRUCTURE IN
RELATION TO
INSECTICIDAL ACTIVITY

Submitted by
R. V. Seaman

In partial fulfillment of the requirements
for the Degree of Master of Science
Colorado
Agricultural and Mechanical College
Fort Collins, Colorado

August, 1948

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ABSTRACT

Problem

What correlation exists between chemical structure and insecticidal activity?

Problem analysis.--The mechanism of insecticidal activity is a reciprocal function of the compound and the particular insect under consideration. Consequently, the following factors must be considered in order to establish the presence or absence of specific chemical correlation:

1. What effect does molecular weight exhibit in relation to insecticidal activity?
2. What effect does substituent radical weight exhibit in relation to insecticidal activity?
3. What effect does the chemico-structural nature of the substituent group exhibit in relation to insecticidal activity?
4. What effect does cyclic saturation compared with cyclic unsaturation exhibit in relation to insecticidal activity?

Findings

The question of why one compound exhibits a high degree of insecticidal activity while another closely related compound is completely non-active as an insecticide

was considered with the purpose of determining the role of chemical structure in relation to insecticidal activity.

Mortality data were obtained using *Musca domestica* L. as the test insect in conjunction with a simplified Kearns wind-tunnel apparatus.

Of the 22 chemicals tested, four gave complete kill; the boiling point of each of the active compounds was over 200 degrees, Centigrade, while their molecular weights were all in excess of 160 (Figure 7). Table 2 shows the relation between substituent radical weight and insecticidal activity which further substantiates the dependence on the boiling point of the compound, influenced by the radical, rather than on its chemical composition.

Statistical correlation, based on boiling point, molecular weight, and the degree of insecticidal activity, of a large number of compounds may further establish the dependence of insecticidal activity on the boiling point of a compound which in turn is affected by chemical structure.

Both TEPP (tetraethyl pyrophosphate, the active component of HETP) and the Parathion conform to the boiling point-molecular weight screening curve, Figure 7. It will be noted that dicyclohexyl conforms to the screening curve but was found to be inactive as a contact insecticide. According to the Szent-György (17), 1941, and Seaman (16), 1948, hypotheses, the absence of contact toxicity of dicyclohexyl may be attributed to its particular radiant energy absorp-

tion and electro-magnetic orientation. Its close resemblance to phenylcyclohexane, insecticidally active, would indicate that electromagnetic distribution effected by unsaturation is a contributing factor of contact toxicity.

Although additional exceptions to this generalized screening curve will be found, it should prove useful in indicating those compounds which most probably exhibit insecticidal activity. Application of this screening curve to evaluation investigations will, to a large extent, eliminate fruitless, random testing.

This work is being continued in an effort to also correlate melting point as well as boiling point data with insecticidal activity. In that multiple correlation by statistical methods is dependent to a large extent upon the number of samples, the author 1/ will be very grateful to all who may care to submit information in so far as it may further correlation of insecticidal activity with chemical structure.

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T H E S I S

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COLORADO AGRICULTURAL AND MECHANICAL COLLEGE

July 28 1948

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY
SUPERVISION BY **R. V. SEAMAN**
ENTITLED **CHEMICAL STRUCTURE IN RELATION TO**
INSECTICIDAL ACTIVITY
BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF **SCIENCE**
MAJORING IN **ENTOMOLOGY**
CREDITS **15**

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Permission to publish this thesis or any part of it
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Chapter I

INTRODUCTION

No man can learn what he has not preparation for learning, however near to his eyes is the object. . . . Our eyes are holden that we cannot see things that stare us in the face, until the hour arrives when the mind is ripened; then we behold, and the time when we saw them not is like a dream.

Ralph Waldo Emerson

During the last seven years research laboratories throughout the country have endeavored to develop better organic insecticides. Some compounds were found that have certain advantages over DDT, and also distinct disadvantages. Actually, only five new materials were brought to light and have achieved some degree of economic importance. These compounds, in addition to DDT, are: (1) the gamma isomer of benzene hexachloride (BHC), (2) 1,2,4,5,6,7,8,8a-octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane (Chlordane), (3) chlorinated camphene (Toxaphene), (4) hexaethyl-tetraphosphate (HETP), and (5) o,o-diethyl-o,p-nitrophenyl thiophosphate (Thiophos 3422 Parathion).

Some of these compounds are more effective on certain insects or are lethal to a greater insect variety than is DDT. On the other hand, a greater toxicity to warm-blooded animals and a much shorter residual effect is noted.

While numerous analogs of the above-mentioned insecticidally active compounds have been prepared and studied, there is as yet no agreement, but rather absolute confusion regarding the toxicity mechanism of contact insecticides.

Various schools of thought regarding the problem of chemical structure and insecticidal activity include such specific aspects as chemical composition and electromagnetic orientation, as well as morphology and physiology.

This problem involves many pertinent variables. Contingent upon further knowledge of insect physiology, correlation studies may eventually establish the exact nature of contact toxicity and its relation to chemical structure.

Oftentimes the details of a mosaic thwart our keenest observation because of the closeness from which they are viewed. It may be necessary for us to change our perspective and seek the answer by a grosser survey of the known facts or investigate the complex realm of electromagnetic phenomenon associated with molecular structure.

Out of the morass of apparently contradictory data must evolve the basic mosaic which is necessary before intelligent progress can achieve the enduring keystone to support both the entomological and chemical requirements of insecticidal activity.

Chapter II
REVIEW OF LITERATURE

In the literature on insecticidal activity there were few references concerning the essential requirements of a compound in order that it will possess insecticidal activity. Such data as were available have not yet yielded to statistical correlation. The United States Bureau of Entomology and Plant Quarantine, in a series of articles (1, 2, 3, 18) from 1942 through 1948, evaluated over 7,300 materials and found that about four per cent possessed insecticidal activity. One tabulation of insecticidal evaluation tests (18), published by the Bureau in September, 1947, covering their work from April, 1942, to April, 1947, including 7,076 compounds, did not attempt any correlation whatever.

Up to the present time no one has succeeded in constructing the fundamental ground-work for a hypothesis encompassing the specific chemical requirements of an insecticidal material. It is not possible on the basis of present knowledge to synthesize, at random, a compound which will be an efficient insecticide. The order of magnitude that an insecticidal compound may be discovered by exhaustive tests is about in the probability of one in

10,000. Of course, there are numerous compounds which possess high toxicity, but for certain reasons are not feasible as insecticides. A few common specifications not met by such compounds include phytotoxic effects, toxicity to warm-blooded animals, residual properties, and cost.

With the discovery in 1939 of the insecticidal activity of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT), United States Patent Number 2,329,074, a vast new field of research was opened in entomology and organic chemistry. Intense activity in the investigation of synthetic organic chemicals as insecticides has produced no more than five compounds of commercial insecticidal value.

Chemical correlation

No conclusive data have been published which satisfactorily explain the mechanism of insecticidal toxicity. However, certain correlation studies have been instigated in order that some pattern may be deduced from the great wealth of experimental data already compiled. Frear (7), 1947, has attempted to establish correlation between insecticidal efficiency and chemical structure.

Biological correlation

Another survey, conducted by Friend 1/, may

1/ Letter from Roger B. Friend, Chairman, Entomology subcommittee, Chemical-Biological Coordination Center, National Research Council, to Dr. George M. List, Department of Entomology, Colorado Agricultural and Mechanical College, Fort Collins, Colorado, dated March 29, 1948.

provide the necessary biological correlation required before adequate chemical correlation can succeed.

Morphology

Insect morphology to a large extent may be the determining factor in the efficacy of a particular compound. It cannot be overemphasized that the exoskeletal morphology is an important factor in all insecticidal evaluation tests. While the significance of insect morphology and physiology are generally recognized, there is much dispute regarding the mechanism of contact insecticidal activity. In their work with tsetse flies (Glossina spp.) Potts and Vanderplank (13), 1945, demonstrated that contact activity was a function of the degree of pulvillar development. Contact activity was more rapid on species in which the pulvilli were well developed.

On the other hand, Hickin (9), 1945, vigorously refuted the findings of Potts and Vanderplank. As test insects he used animal lice (Haematopinus suis; Trichodectes latas, and so forth) in which contact with the insecticide is practically entirely through the tarsi, because in these insects the pulvilli are but slightly developed. His results predicated the conclusion that the relative size of the pulvilli had no particular significance in the mode of action of contact insecticides.

Hayes and Liu (8), 1947, established the presence of chemoreceptive sensilla only in the tarsi of houseflies,

and found them to be absent in both the adult German cockroach (Blattella germanica L.), and the adult Mexican bean beetle (Epilachna varivestis Huls.). They also determined the cuticular thickness of the tarsi of these insects--housefly, 12.5 to 25 microns; the Mexican bean beetle, 15 to 40 microns; and the German cockroach, 60 to 90 microns. These data seem to indicate that possibly insecticidal activity is a function of cuticular thickness, since the mortality of the housefly to DDT is very high, while the other two insects exhibit a very low mortality to DDT.

Physiology

Mikalonis and Brown (12), 1941, established the presence of the acetylcholine-cholinesterase system in the ventral nerve cord of the cockroach (Periplaneta americana). The mechanism is essentially the same as that established by Loewi (11), 1945, who indicated that acetylcholine is the chemical transmitter of nerve impulses in vertebrate animals.

Effects of enzyme metabolism are illustrated by Lauser (10), 1945, who showed that a sulfonamide type compound is ineffective on the clothes moth and to the enzyme pancreatin in vitro, but acts as a stomach poison on the Colorado potato beetle. The amylase enzyme of this insect is strongly inhibited. He also demonstrated that a sulfonic ester type compound inhibits the pancreatin enzyme of the clothes moth but apparently has no effect on the

amylase enzyme.

Mechanical

By different techniques Wigglesworth (20), 1942; Roy and Ghosh (15), 1944; and Bredenkamp (4), 1947, arrived at essentially the same conclusion; namely, that the mode of entrance of contact insecticides is mechanical. Wigglesworth found an approximate inverse proportion between the density of an oil and its cuticular penetration speed in the sense that the lighter the oil, the more rapid is its absorption. Roy and Ghosh found that pyrethrum in spray or dust form cannot penetrate insect cuticle rapidly. When oleic acid was included in the mixture, fat globules collected around the tracheal trunks and this would indicate that rapid diffusion of the oil, and the pyrethrins dissolved in it, would take place through the tracheal walls. Bredenkamp concluded that humidity and temperature affected the toxicity time-factor, but that the relationship was complex. He also found concentrated penetration in certain cuticular areas. According to Bredenkamp, cuticular penetration is entirely a mechanical phenomenon.

Chemical structure

Some chemico-structural relations were determined by Domenjoz (6), 1946, who found that insecticidal activity is not related to the chlorophenyl radical, nor does the trichloroethyl radical affect the lipoid solu-

bility of the DDT molecule. This is in apparent contradiction to Luger's findings (10), 1945, wherein he stated:

In the DDT group the trichloromethyl group is the component (an aliphatic one) having high lipoid solubility. The remainder of the molecule, namely, the condensed chlorobenzene system, is the toxic component, although the aromatic chlorobenzene system has lipoid solubility as well. (10:4)

In their researches on the arthropod nerve axon Welsh and Gordon (19), 1947, found that those compounds (DDT and its analogs, $p\text{-C}_6\text{H}_4\text{Cl}_2$, naphthalene, and so forth) having a high lipide: H_2O ratio all had a similar action on nerve axons of insects, and because of their diverse chemical structure, their primary action would appear to be physical, not chemical. They concluded that this action is probably due to physical interference at the lipide surface of the axon.

Finally, the most fundamental and most complex interpretation of the correlation between insecticidal activity and chemical structure was presented by Campbell and West (5), 1945, and Seaman (16), 1948. Campbell and West concluded that the evolution of HCl by DDT may be a secondary effect accompanying the fundamental alteration of the electromagnetic pattern of the trichloroethyl radical. They believed that the Cl atoms may be essentially steric, and that the three beta-Cl atoms are required to impart optimal insecticidal activity to DDT, probably due to a certain steric orientation requirement which reaches a maximum when the remaining Cl atoms are in the p-position.

Seaman (16), 1948, forwarded the hypothesis that all insecticidal activity phenomenon may ultimately be resolved on the basis of the distribution and orientation of the electromagnetic fields associated within the insecticide molecule and substituent radicals, superimposed in relation to sympathetic or resonant molecules and substituent radicals existing in insect nerve tissues and enzymes.

Summary

In his correlation studies Frear (7), 1947, has apparently made no differentiation between chemical composition and chemical structure. Further, it is questionable whether his positive mortality index, based on 10 per cent net toxicity, is sufficiently high to warrant a compound containing certain elements and radical groups to be classified without regard to isomerism. To cite one outstanding exception to his correlation based on chemical structure, all the hexachlorocyclohexane isomers should possess a high degree of insecticidal activity, when actually only the gamma isomer complies. Since numerous contributors have supplied much of his data, many different test insects and techniques were employed, and it would be exceedingly difficult to derive any reliable correlation. Of the 6,155 compounds reported, some had as few as 10 tests, while others had as many as 2,467. This classification has little intrinsic value and cannot be considered more than a starting point for more precise correlation.

studies.

For some time the mode of contact intoxication of DDT has been considered as due to the substituent chemical composition of the molecule, Luger, et al., (10), 1945. However, Domenjoz (6), 1946, a year later, concluded that insecticidal power is not related to the chlorobenzene radical, nor does the trichloroethyl radical condition lipoid solubility of the molecule.

Potts and Vanderplank (13), 1945, established the relation between the speed of action of DDT and the degree of pulvillar development. Following this work Hickin (9), 1945, pointed out that pulvillar development had no special significance in the speed of action of DDT. He based his conclusions on results obtained with animal lice as test insects on which the pulvilli are but slightly developed.

In view of the foregoing comments, it should be readily apparent that the problem of insecticidal activity in relation to chemical structure is in a state of continuous turmoil.

Implications

Further correlation studies of both chemical structure and insect morphology and physiology may yield the key to insecticidal activity.

Organized knowledge may eventually enable one to synthesize at will compounds which possess high specific activity to any insect which is desired to be effectively

controlled or eradicated.

A fundamental knowledge of the mechanism of the contact toxicity mechanism would make possible the control of economic insect pests and foster the development of beneficial insects.

This knowledge would benefit all the peoples of the world for it could alleviate and possibly eliminate all diseases of insect origin, and spontaneously materially increase the production potential of all cultivated and natural food resources.

Chapter III

METHODS AND MATERIALS

The test insect

In this work the common housefly (M. domestica L.) was used as the test insect. The flies were reared according to the standard method described by Woodbury (22), 1943. It is of critical importance in comparative evaluation studies, conducted over a period of several months, using bio-assay techniques, that the flies are of the same age and vitality. The larvae population of the culture medium jar (Figure 1) and the adult fly population in the egg-laying cage (Figure 2) must be carefully controlled in order that overcrowding, resulting in subsequent dwarfing, does not occur. The adult fly food, a mixture of equal volumes of skim milk and water, should be changed about every 24 hours to avoid feeding on soured milk as it is questionable whether acceptance of this is as great as for the fresh milk. It has also been observed that egg deposition is significantly reduced in the soured medium.

The test apparatus

The apparatus used (Figures 3 and 4) represents a further simplification of Kearns' modified wind-tunnel apparatus (Figure 6). The particle size of the insecticide

Reduce to $2\frac{1}{2}$ inches
wide.

Tuesday, April 16



Fig. 1.--Housefly larvae feeding in culture medium.



Fig. 2.--Adult houseflies in egg-laying cages.

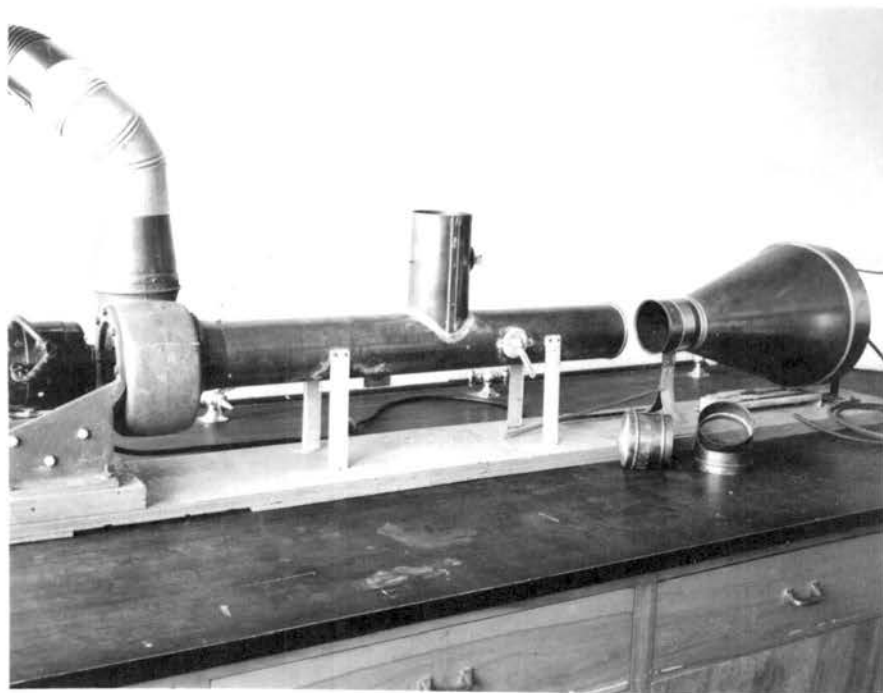


Fig. 3.--Over-all view of wind-tunnel apparatus used to test for contact insecticidal activity.

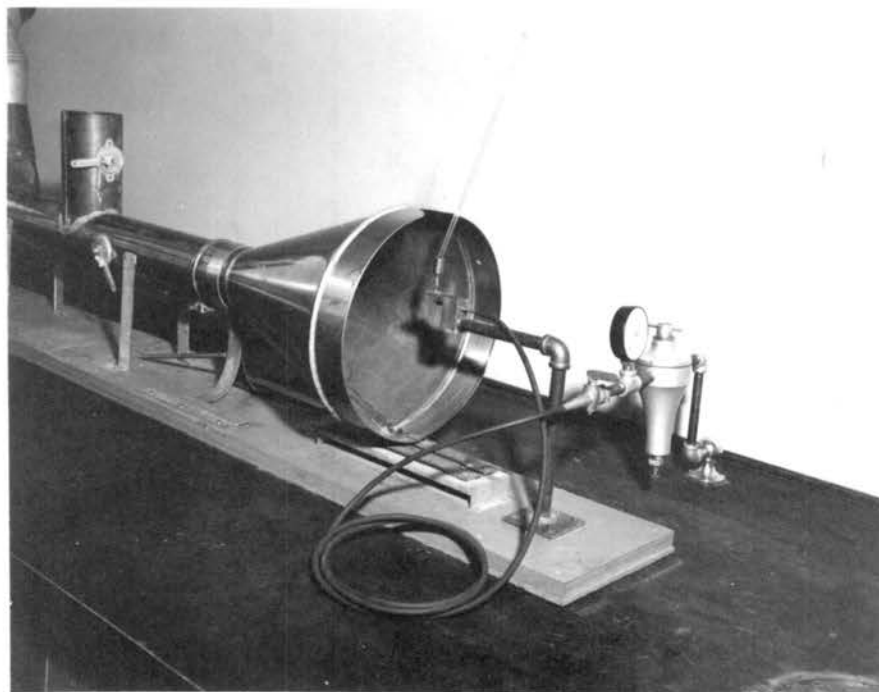


Fig. 4.--Injection-end of wind-tunnel.



Fig. 5.--A group of test chemicals.

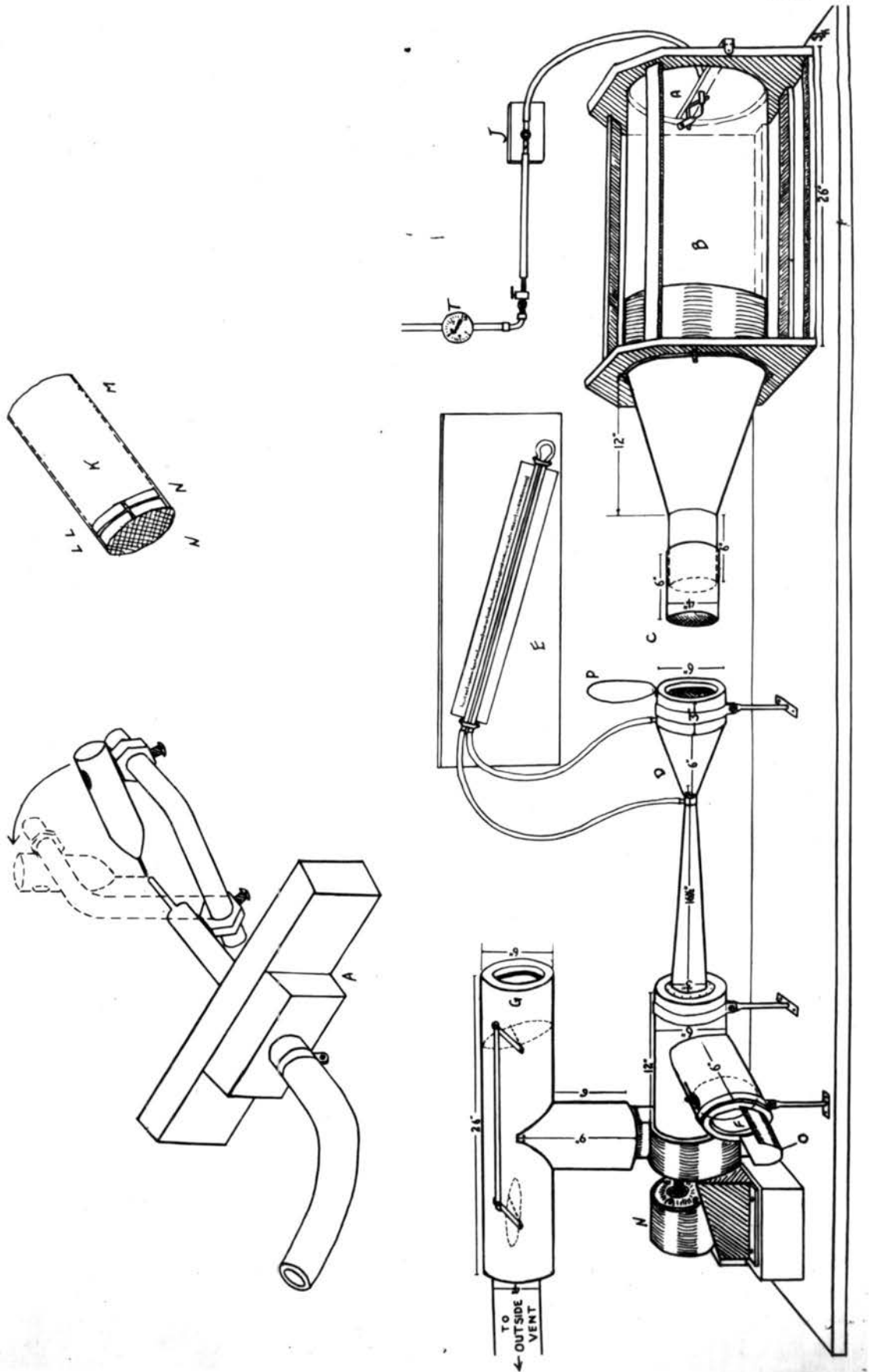


Fig. 6.--Kearns' modified wind-tunnel apparatus.

is automatically maintained by the specially constructed injection nozzles and by careful regulation of the atomizing air-pressure. The apparatus is so designed that at an air-pressure of eight pounds per square inch the insecticide velocity through the test cage is approximately five miles per hour. Thus, by exact pressure regulation alone, uniform reproduction of dispersion and distribution of the test compounds is easily attained.

The test chemicals

All of the chemicals tested (Figure 5) were either of the C. P. grade or a chemical analysis was provided by the manufacturer. The physical constants of the test compounds were obtained from standard reference sources. Of the 22 compounds tested, all were liquids at room temperature with the single exception of diphenylamine which was tested as a 50 per cent solution in benzene.

Procedure

Four-day-old flies were transferred from the egg-laying cages to the test cage and anesthetized in carbon dioxide gas for 30 seconds. Thirty flies, taken at random and not separated as to sex, were used for all tests. For each test, replicated three times in succession, 0.6 ml. of the test chemical was used. As a check for comparative net toxicity and also on the fly strain tested two control tests were included with each compound; these consisted of

an untreated check and a standard check using 0.6 ml. of a standard Chlordane solution (0.025 mg./100 ml. Deobase).

Immediately after an injection period of 60 seconds, which was found to be adequate for complete injection of 0.6 ml. of each of the test chemicals, the flies were again anesthetized for 30 seconds and transferred to a recovery cage containing a lump of cellucotton moistened with the skim-milk-water mixture. Mortality counts, not including moribund flies, were made 24 hours later after allowing the live flies to escape.

All tests were made at a temperature of 75 to 85 degrees, Fahrenheit, a relative humidity of 30 to 40 per cent, and an atmospheric pressure of 630 to 640 mm.

Chapter IV
ANALYSIS OF DATA

Correlation between chemical structure and insecticidal activity is indirectly indicated on the basis of the molecular weight and boiling point of the compounds tested.

In Table 1 are listed the chemicals tested together with certain physical constants. Six of the compounds were found to possess insecticidal activity. Nitrobenzene gave complete knockdown in less than 15 seconds, while nitrocyclohexane required about two minutes. In both cases, however, recovery was complete within 10 minutes. Complete knockdown in less than 10 seconds with no recovery (death occurred in less than five minutes) was effected by dicyclohexylamine, diphenylamine, phenylcyclohexane, and benzotrichloride.

1. Molecular weight -
insecticidal activity

It is apparent that those compounds which gave complete kill have a molecular weight of 160 or greater, Figure 7, line M.W., and all lie above the arbitrary line S. All the compounds which possess insecticidal activity have a boiling point over 200 degrees, Centigrade, Figure

Table 1.--PHYSICAL CONSTANTS OF COMPOUNDS TESTED FOR CONTACT INSECTICIDAL ACTIVITY.

Compound	Formula	Molecular weight	Substituent Radical	Weight
1. Benzene	C_6H_6	78.05	----	----
2. Benzaldehyde	C_6H_5CHO	106.05	-CHO	29
3. Toluene	$C_6H_5CH_3$	92.06	-CH ₃	15
4. m-Xylene	$C_6H_4(CH_3)_2$	106.08	-(CH ₃) ₂	30
5. Nitrobenzene	$C_6H_5NO_2$	123.05	-C ₆ H ₅	77
6. Nitrocyclohexane	$C_6H_{11}NO_2$	129.10	-C ₆ H ₁₁	83
7. Chlorobenzene	C_6H_5Cl	112.50	-Cl	35.5
8. o-Dichlorobenzene	$C_6H_4Cl_2$	146.95	-Cl ₂	70
9. Aminobenzene	$C_6H_5NH_2$	93.06	-C ₆ H ₅	77
10. Cyclohexylamine	$C_6H_{11}NH_2$	99.11	-C ₆ H ₁₁	83
11. Dicyclohexylamine	$(C_6H_{11})_2NH$	181.12	-(C ₆ H ₁₁) ₂	166
12. Diphenylamine	$(C_6H_5)_2NH$	169.09	-(C ₆ H ₅) ₂	154
13. Phenylcyclohexane	$C_6H_5C_6H_{11}$	160.12	-C ₆ H ₅	77
14. Dicyclohexyl	$C_6H_{11}C_6H_{11}$	166.18	-C ₆ H ₁₁	83
15. Benzotrichloride	$C_6H_5CCl_3$	195.41	-CCl ₃	118
16. Chloroform	CHCl ₃	119.38	-H	1.008
17. Carbon tetrachloride	CCl ₄	153.83	-Cl	35.5

Table 1.--PHYSICAL CONSTANTS OF COMPOUNDS TESTED FOR
CONTACT INSECTICIDAL ACTIVITY--Continued.

Compound	Formula	Molecular weight	Substituent Radical	Weight
18. Chloral	CCl_3CHO	147.38	-CHO	29
19. Trichloroacetyl- chloride	CCl_3COCl	181.83	-COCl	63.5
20. Acetone	CH_3COCH_3	58.05	----	----
21. 2-Chlorothio- phene	$\text{C}_3\text{H}_4\text{SCl}$	118.50	----	----
22. Paraldehyde	$(\text{CH}_3\text{CHO})_3$	132.09	----	----

Table 1.--PHYSICAL CONSTANTS OF COMPOUNDS TESTED FOR CONTACT INSECTICIDAL ACTIVITY--Continued.

Compound	Density (20/4)	Boiling point	Solubility in water (20°)
1. Benzene	0.8941	80.1	0.082
2. Benzaldehyde	1.0504	179.5	0.330
3. Toluene	0.8660	110.8	0.047
4. m-Xylene	0.8641	138.8	Insoluble
5. Nitrobenzene	1.1987	210.9	0.190
6. Nitrocyclo- hexane	1.0630	203.0	0.002
7. Chlorobenzene	1.1066	132.0	0.049
8. o-Dichloroben- zene	1.3048	180.0	0.015
9. Aminobenzene	1.0220	184.0	3.400
10. Cyclohexyl- amine	0.8191	134.5	Miscible
11. Dicyclohexyl- amine	0.9104	255.8	Slightly soluble
12. Diphenylamine	1.1590	302.0	0.030
13. Phenylcyclo- hexane	0.9440	237.5	Insoluble
14. Dicyclohexyl	0.8906	214.0	Insoluble
15. Benzotrichlo- ride	1.3800	214.0	Insoluble
16. Chloroform	1.4985	61.3	1.000
17. Carbon tetra- chloride	1.5950	76.0	0.080

Table 1.--PHYSICAL CONSTANTS OF COMPOUNDS TESTED FOR CONTACT INSECTICIDAL ACTIVITY--Continued.

Compound	Density (20/4)	Boiling point	Solubility in water (20°)
18. Chloral	1.5120	98.0	Miscible
19. Trichloroacetyl- chloride	1.6290	118.0	Decomposes
20. Acetone	0.7920	56.5	0.082
21. 2-Chlorothio- phene	1.2900	126.0	Insoluble
22. Paraldehyde	0.9943	124.0	12.000

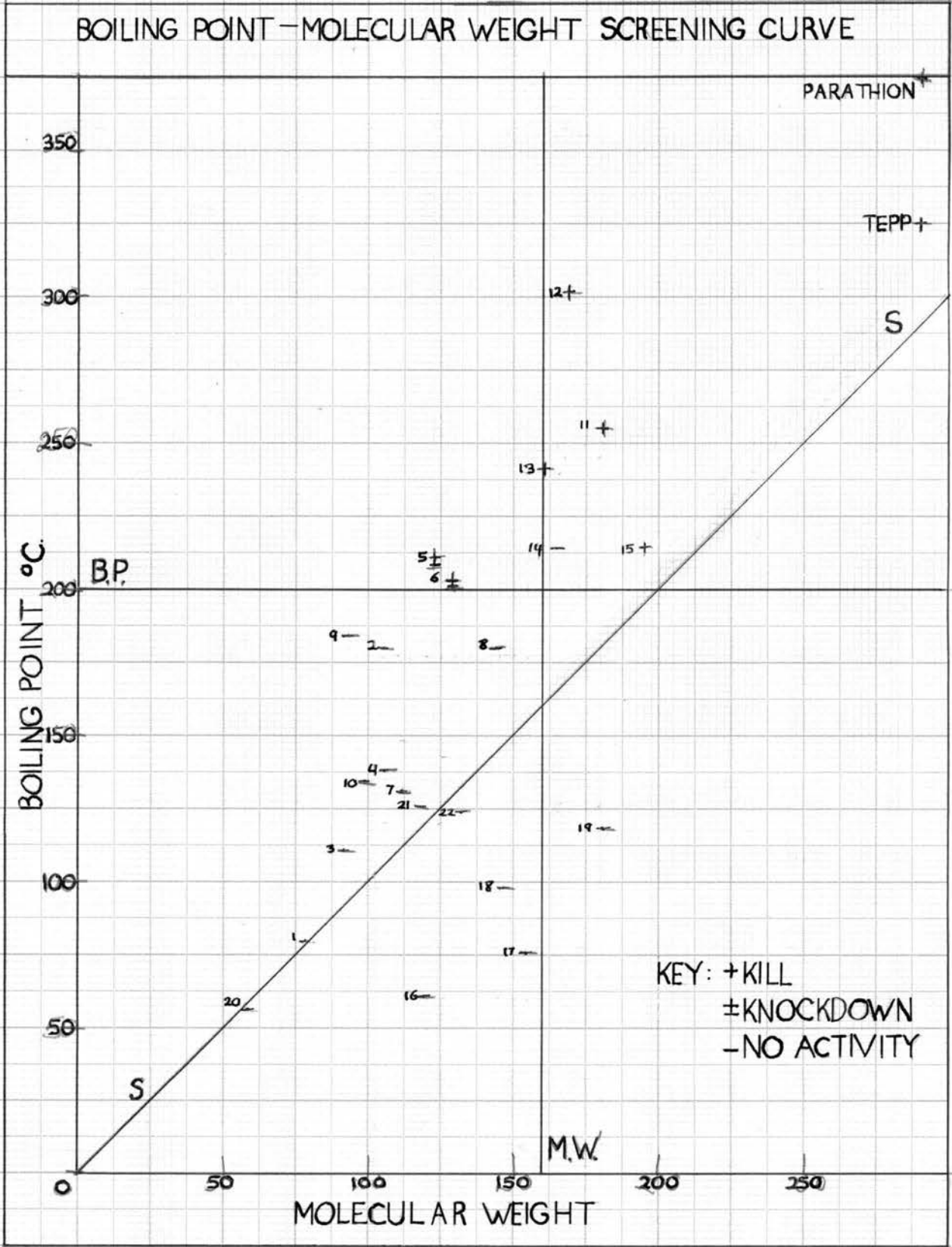


FIGURE 7

7, line B. P.

2. Substituent radical weight - insecticidal activity

In the substituted benzene as well as the substituted trichloromethyl series (Table 2) there seems to be a relation between radical weight and insecticidal activity. Only those compounds containing a radical of high weight were active. An exception to this is nitrobenzene, but its knockdown activity may be accounted for by the resonance of the nitro radical. The effect of the substituted radical on the boiling point must also be considered.

3. Chemico-structural nature of substituent radical - insecticidal activity

Comparison of toluene with benzotrichloride would indicate that chemical composition as well as structure have some bearing on insecticidal activity.

A high chlorine content is not essential for insecticidal activity: trichloroacetylchloride, % Cl = 78; benzotrichloride, % Cl = 54.5; dicyclohexylamine, diphenylamine, and phenylcyclohexane contain no chlorine.

These differences in toxicity may again be contributed to the influence which these factors have on boiling point.

Table 2.--SUBSTITUENT RADICAL WEIGHT AND INSECTICIDAL ACTIVITY.

Compound	Radical	Weight	Boiling point	Activity
1. C_6H_6	-----	---	80.1	---
2. $C_6H_5CH_3$	-CH ₃	15	110.8	-
3. $C_6H_5NH_2$	-NH ₂	16	184.0	-
4. C_6H_5CHO	-CHO	29	179.5	-
5. $C_6H_4(CH_3)_2$	-(CH ₃) ₂	30	138.8	-
6. C_6H_5Cl	-Cl	35.5	132.0	-
7. $C_6H_5NO_2$	-NO ₂	46	210.9	±
8. $C_6H_4Cl_2$	-Cl ₂	71	160.0	-
9. $C_6H_5C_6H_{11}$	-C _{6H₁₁}	83	237.5	+
10. $C_6H_5NHC_6H_5$	-NHC _{6H₅}	92	302.0	+
11. $C_6H_5CCl_3$	-CCl ₃	118.5	214.0	+
12. $CCl_3C_6H_5$	-C _{6H₅}	77	214.0	+
13. CCl_3COCl	-COCl	63.5	118.0	-
14. CCl_3Cl	-Cl	35.5	76.0	-
15. CCl_3CHO	-CHO	29	98.0	-
16. CCl_3H	-H	1	61.3	-

Key: - NO KILL

± KNOCKDOWN

+ KILL

4. Cyclic saturation and unsaturation - insecticidal activity

The more rapid knockdown action of nitrobenzene in comparison with nitrocyclohexane may be due to the unsaturated phenyl radical. Although unsaturation may be an essential requirement for insecticidal activity, dicyclohexylamine would contraindicate this. It is interesting to note that phenylcyclohexane gives rapid knockdown and kill but that dicyclohexyl causes no observable toxicity. Phenylcyclohexane is identical to dicyclohexyl except that the latter compound is saturated while phenylcyclohexane is only half saturated. In all cases of analogous test chemicals studied, the unsaturated compounds have a significantly higher boiling point.

Summary

Molecular weight, substituent radical weight, chemico-structural nature of the substituent radical, and cyclic unsaturation are all related to insecticidal activity through one basic, physical constant; namely, the boiling point of the compound.

Chapter V

DISCUSSION

It is probable that some fundamental correlation exists between insecticidal activity and the boiling point of a compound. Those compounds which have a molecular weight greater than 160 and a boiling point over 200 degrees, Centigrade, were all insecticidally active and gave complete kill in less than one minute.

The results here reported are in agreement with the findings of Welsh and Gordon (19), 1947, who have indicated that a high lipid:H₂O ratio is a characteristic of all insecticidally active compounds. They suggest, in view of the similar action of various insecticides of such diverse chemical structure, that their primary action is probably a physical interference at the lipid surface of the axon.

Since the only difference between toluene and benzotrichloride is the replacement of the hydrogen atoms of the methyl radical by three chlorine atoms, the activity of benzotrichloride may be due to the alteration of the basic electromagnetic nature of the benzyl group. Campbell and West (5), 1945, discussed the mode of action of DDT on the basis of the steric orientation and electromagnetic

phenomena associated with the three beta-Cl atoms of the molecule.

The effect of substituent radical composition on insecticidal activity was studied on the basis of chloral, trichloroacetylchloride, and chlorobenzene. None of these compounds produced any observable contact toxicity. This may be due to the low lipide:H₂O ratio of the first two compounds, but does not account for chlorobenzene. It is obvious, therefore, that in addition to a high lipide:H₂O ratio, some other factor is also necessary to impart contact insecticidal activity. If the oxygen atom of chloral is replaced by two p-chlorophenyl groups, DDT is the resultant compound. Based on the foregoing data, these conclusions are in accord with Domenjoz (6), 1946, in that neither the chlorophenyl nor the trichloroethyl radicals effect insecticidal activity. Domenjoz found that the toxicity of a compound was, in some cases, related to its ability to liberate HCl. Trichloroacetylchloride, easily hydrolyzed to liberate HCl, was found to be non-toxic, which is an additional exception to Domenjoz's findings.

Suggestions for further study

Correlation between boiling point and insecticidal activity is indicated on the basis of the foregoing data. To effect a more comprehensive study of the various factors contributing to insecticidal activity, it is sug-

gested that numerous studies of different series of organic compounds be made similar to the work of Prill, et al.(14), 1947. In this work an investigation was made of some cyclic acetals containing the 3,4-methylenedioxyphenyl radical and their effects on the housefly.

Another important phase of this work includes the concurrent changes in insects subjected to various insecticides. According to Wilson (21), 1948, the housefly is capable of developing, within several generations, a marked resistance to DDT. It seems necessary therefore that coordinated investigations be made so that biological changes may be studied in the light of chemical mechanisms.

A purely statistical approach, based on boiling points of compounds tested for insecticidal activity, would obviate a great deal of fruitless, systematic testing. Since boiling point alone may be the underlying effect of the various factors studied, it is suggested that other researchers in this field contribute boiling point data not only of those compounds which were tested and exhibited a high degree of insecticidal activity, but also boiling point data on those compounds which exhibited little or none.

Chapter VI

SUMMARY

The question of why one compound exhibits a high degree of insecticidal activity while another closely related compound is completely non-active as an insecticide was considered with the purpose of determining the role of chemical structure in relation to insecticidal activity.

Mortality data were obtained using *Musca domestica* L. as the test insect in conjunction with a simplified Kearns wind-tunnel apparatus.

Of the 22 chemicals tested, four gave complete kill; the boiling point of each of the active compounds was over 200 degrees, Centigrade, while their molecular weights were all in excess of 160 (Figure 7). Table 2 shows the relation between substituent radical weight and insecticidal activity which further substantiates the dependence on the boiling point of the compound, influenced by the radical, rather than on its chemical composition.

Statistical correlation, based on boiling point, molecular weight, and the degree of insecticidal activity, of a large number of compounds may further establish the dependence of insecticidal activity on the boiling point of a compound which in turn is affected by chemical structure.

Both TEPP (tetraethyl pyrophosphate, the active component of HETP) and Parathion conform to the boiling point-molecular weight screening curve, Figure 7. It will be noted that dicyclohexyl conforms to the screening curve but was found to be inactive as a contact insecticide. According to the Szent-György (17), 1941, and Seaman (16), 1948, hypotheses, the absence of contact toxicity of dicyclohexyl may be attributed to its particular radiant energy absorption and electro-magnetic orientation. Its close resemblance to phenylcyclohexane, insecticidally active, would indicate that electromagnetic distribution effected by unsaturation is a contributing factor of contact toxicity.

Although additional exceptions to this generalized screening curve will be found, it should prove useful in indicating those compounds which most probably exhibit insecticidal activity. Application of this screening curve to evaluation investigations will, to a large extent, eliminate fruitless, random testing.

This work is being continued in an effort to also correlate melting point as well as boiling point data with insecticidal activity. In that multiple correlation by statistical methods is dependent to a large extent upon the number of samples, the author 1/ will be very grateful to all who may care to submit any information in so far as it may further correlation of insecticidal activity with chemical structure.

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