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9. ABSTRACT

A total of 130 analogues of DDT were synthesized and investigated as "environmentally acceptable replacements for DDT". This paper summarizes research methodology and results, including numerous data tables. Extensive studies of structure vs. activity, of quantitative evaluation of toxicity to susceptible and resistant house fly, black blow fly, and Culex pepiens quinquefasciatus and Anopheles albimanus resulted in selection of a number of the most promising compounds. These were evaluated further for biodegradability and for feasibility and ease of synthesis. Killogram quantities of some compounds were made and are being further evaluated in several laboratories. The most promising compounds selected for intensive study were OMS-1715 (DECP) of 1, 1-bis-(p-ethoxyphenyl)-chloropropane and OMS-1856 (DEIB) or 1-(p-ethoxyphenyl)-1-(p-tolyl)-2,2,2-trichloroethane, with methoxychlor, and with DDT. Both DECP and DEIB showed long-lasting residual toxicity when applied to plywood surfaces or in plywood huts for knockdown and kill of Anopheles albimanus. DEIB was selected as the most generally suitable insecticide as it is only one-tenth to one-fiftieth as toxic as DDT to laboratory animals and contains no chlorine. It was concluded that it could be used in a variety of insect pest management programs without being deleterious to environmental quality.

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DEVELOPMENT OF ENVIRONMENTALLY ACCEPTABLE REPLACEMENT FOR DDT

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SUMMARY

A total of 130 analogues of DDT, most of them new, were synthesized and investigated as "environmentally acceptable replacements for DDT". Extensive studies of structure vs. activity, of quantitative evaluation of toxicity to susceptible and resistant house fly, black blow fly, and Culex pipiens quinquefasciatus and Anopheles albimanus resulted in selection of a number of the most promising compounds. These were evaluated further for biodegradability and for feasibility and ease of synthesis. Killogram quantities of some of the most promising were made and are being subjected to further evaluation in this and a number of other laboratories including the World Health Organization and National Cancer Institute.

The most promising compounds selected for intensive study were OMS-1715 (DECP) or 1,1-bis-(p-ethoxyphenyl)-chloropropane and OMS-1856 (DEIB) or 1,1-bis-(p-ethoxyphenyl-isobutane. These were compared with OMS-1476 or 1-(p-ethoxyphenyl)-1-(p-tolyl)-2,2,2-trichloroethane, with methoxychlor, and with DDT. Both DECP and DEIB showed long lasting residual toxicity (27-35 months) when applied to plywood surfaces or in plywood huts for knockdown and kill of Anopheles albimanus.

DEIB was selected as the most generally suitable insecticide as it is only one-tenth to one-fiftieth as toxic as DDT to laboratory animals, and contains no chlorine. A very simple synthetic process was developed which produced yields of >90% of high purity.

It is concluded that DEIB is a very safe, potentially cheap, and moderately effective residual insecticide with a reasonable degree of biodegradability. It could be used in a variety of insect pest management programs without being deleterious to environmental quality.

OBJECTIVES

The Contract was to provide funds for the synthesis and evaluation of biodegradable analogues of DDT applicable to vector borne diseases and agricultural pest control. This Contract was based on an eight-year program of laboratory studies at the University of Illinois which has produced a group of biodegradable DDT analogues which have interesting and potentially useful qualities.

The funding in this Contract was to permit the continuation of the search for new analogues and the preliminary screening of these; to fund the synthesis of killogram quantities of the most promising, to attempt to develop a simplified laboratory synthesis adaptable to commercial production, and to distribute samples to other laboratories for a wider range of testing against insect pests.

DEVELOPMENT OF ENVIRONMENTALLY ACCEPTABLE REPLACEMENT FOR DDT

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I. INTRODUCTION

Restrictions on the use of DDT and other persistent pesticides because of their carcinogenic potential and bioaccumulation in food and the living elements of the total environment, have posed severe problems in the worldwide control of insect pests of agriculture and public health. In addition many important insect pests have become resistant to the action of these insecticides. As a result insect control technology is undergoing a world-wide revolution with emphasis on ecological approaches to control, incorporating naturalistic methods to suppress insect populations wherever possible, with the use of insecticides carefully integrated into an overall pest control or management system. Thus the development of environmentally acceptable substitute insecticides which may be effective against DDT resistant species has a very high priority in many control programs both in public health and agriculture.

This laboratory has been working for the past 6 years, under the support of The Rockefeller Foundation in basic and applied research leading to "The Development of Novel, Non-Persistent Insecticidal Chemicals". From this work we have produced a considerable number of new insecticidal molecules related to DDT. A number of these compounds are of demonstrated biodegradability as evaluated in our laboratory model ecosystem technology (Metcalf et al 1971, Kapoor et al 1973) and are relatively persistent on inert surfaces but readily metabolized and degraded in living organisms. They have been screened against mosquitoes and houseflies in the WHO "Programme for the Evaluation of New Insecticides for Vector Control" and have been shown to be more effective than DDT against DDT resistant species. In addition, through an AID Contract (1973), "Preliminary Field Evaluation of Biodegradable Analogues of DDT" several of the more promising of these DDT-analogues have been evaluated for residual activity against *Anopheles albimanus* in plywood huts where they were found to be nearly as persistent as DDT, and for fish toxicity in pools, where they were found to be much less dangerous than DDT.

Several of the most promising of the DDT asymmetrical analogues are covered in U.S. Patent 3,787,505 and 3,939,277 "Insecticidal Biodegradable Analogues of DDT" (Metcalf et al 1971a,1974, 1976, 1976c) assigned to the University of Illinois Foundation. Other and newer groups of insecticidal analogues with altered bridging structures are covered in U.S. Patent 3,966,824 "*p,p'*-Disubstituted α-Trichloromethyl Benzylphenyl Ethers (Metcalf et al 1976a); and in U.S. Patent 3,941,842 "p,p'-Disubstituted α-Trichloromethylbenzylanilines" (Metcalf et al 1976b).

More recently a new group of DDT analogues with altered aliphatic moieties has been developed in this laboratory (Coats et al 1977) and submitted for patent protection, as U.S. Patent 4,003,950 "Diphenylmethane Biodegradable Insecticides"(Metcalf and Coats 1977). Some of these insecticides (see Table 2) are not only persistent, biodegradable, and effective but also contain no chlorine, being composed of only carbon, hydrogen, and oxygen.

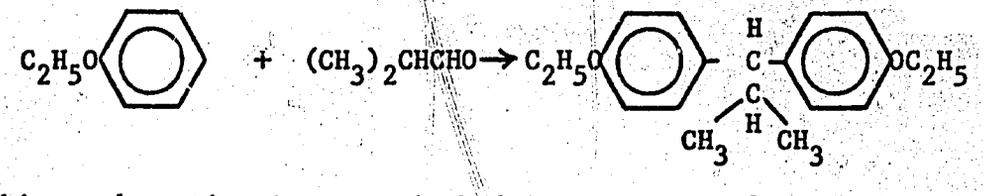
The purpose of Contract AID/ta-C-1228 was to develop information about the possible utility of these interesting new compounds in insect control and management schemes for pests of agricultural and public health importance. This has involved both intensive laboratory research to determine the most useful compounds and studies of the chemistry and production of larger samples of the most useful materials. Field evaluations of these have been carried out in cooperation with Abbott Laboratories, North Chicago, Illinois, and the World Health Organization, Geneva, Switzerland.

II. CHEMISTRY OF NEW DDT-TYPE ANALOGS

A. 1,1-bis-(p-ethoxyphenyl)-isobutane (DEIB) OMS-1856.

This compound was selected as highly promising for commercial development and methods were investigated for its efficient synthesis. A total of >2 kg. has been made in this laboratory.

DEIB is prepared by the following Bayer-type condensation, between ethoxybenzene (phenetole) and isobutyraldehyde:



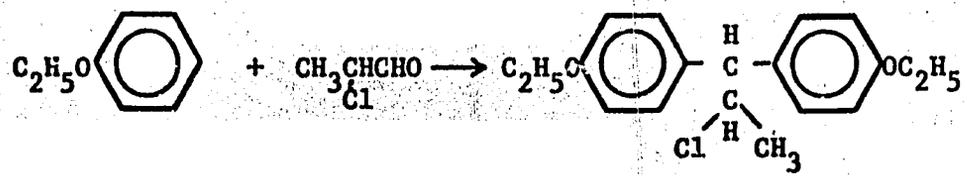
This condensation is accomplished in a mixture of sulfuric and acetic acids and a large number of runs were made to determine the most efficier mixture of acids and the optimum temperature, as shown in Table 1. After a number of experiments, the most satisfactory procedure was devised as follows:

1) prechill H_2SO_4 480 ml, and HOAc 720 ml in a 2 l. 3-necked flask.
2) stir mechanically at 5°C.
3) add at 4 ml per minute a mixture of 250 g. phenetol and 100 g. isobutylaldehyde, maintaining temperature at <15°C.
4) stir for an additional 30-60 minutes after addition.
5) pour reaction mixture over ice and filter off solid.
6) wash product with water to remove acid, then with sodium carbonate, and again with water.
7) recrystallize from 15% ethanol.

This procedure resulted in approximately 90% yield of a very pure product, almost 100% p,p'-isomer, m.p. 65°C. as shown by GLC. In subsequent work in cooperation with Abbott Laboratories it has been determined that DEIB can be produced in very high purity at >90% yield by the reaction under the conditions specified, without recrystallization.

B. 1,1-bis-(p-ethoxyphenyl)-2-chloropropane (DECP) OMS-1715.

This compound was also selected as highly promising for commercial development and methods were investigated for practical synthesis. DECP is prepared by the following reaction:



Using the same reaction conditions developed as optimal for DEIB (see above) a yield of 61.5% was obtained using a phenetole/2-chloropropionaldehyde ratio of 2 and a condensing mixture of H_2SO_4/HOAc-0.66. Changing the phenetole/2-chloropropionaldehyde ratio to 2.74 and the H_2SO_4/HOAc to 0.5, a yield of 61% was again obtained. Doubling the total amount of acid mixture reduced the yield to 44%. It appears that total yield of this compound will be lower than for DEIB.

Work on this compound has been hampered by commercial unavailability of 2-chloropropionaldehyde, formerly available from Aldrich Chemical Co. Laboratory preparation of this compound in substantial quantities has been difficult because of inherent difficulties in chlorination.

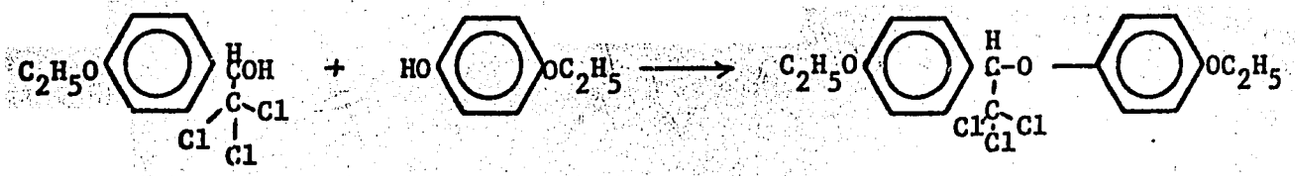
C. 1,1-bis-(p-ethylphenyl)-2-chloropropane (DEtCP) OMS-1980.

This compound is prepared by the procedure used for the preparation of DECP, using ethylbenzene instead of phenetol. The efficiency of condensation of ethylbenzene with 2-chloropropionaldehyde was reasonably satisfactory. However, the general problem of the difficulty in synthesizing 2-chloropropionaldehyde still remains a limiting factor in production.

D. OMS-1629 and OMS-1543

Compounds OMS-1629, α-trichloromethyl (p-ethoxyphenyl)-(p-ethoxybenzyl)-ether and OMS-1543 α-trichloromethyl (p-tolyl)-p-ethoxybenzyl)-ether represent a new type of DDT analog (Hirwe et al 1972). These two analogues were selected for further study of the α-trichloromethyl phenyl benzyl ethers in order to learn more about their insecticidal properties.

Studies are underway to devise improved methods of synthesis of these compounds. The process used:



has given relatively poor yields using a variety of condensing agents and reaction conditions. The condensing agents employed have been sulfuric acid, phosphoric acid, and phosphorus trichloride. No generally satisfactory method has been devised to give a reasonably good yield.

E. Properties of 1,1-bis-(p-ethoxyphenyl)-isobutane (DEIB)

Using ^{14}C-labeled compound the following important environmental parameters were carefully determined and compared to p,p'-DDT:

	DEIB	DDT
water solubility (26°C)	1.659 ppm	0.0012 ppm
octanol/water partition	1332	10,000

III. PREPARATION AND EVALUATION OF NEW DDT ANALOGUES

A major objective of this investigation has been to complete the synthesis and basic biological evaluation of all the potentially useful, biodegradable DDT analogues with altered aliphatic substituents. As shown in Table 1, this has been an ambitious undertaking as 85 compounds have now been prepared and have been evaluated for toxicity to the susceptible S_{NAIDM} and DDT resistant R_{SP} house flies, to the black blow fly *Phormia regina*, and to larvae and adults of *Anopheles albimanus* and *Culex pipiens quinquefasciatus* (*Culex fatigans*). The test methods utilized were topical application of 1 microliter w/v acetone solutions to house flies and black blowfly, exposure to residual deposits on filter paper to the adult mosquitoes, and application of w/v acetone solutions to 100 ml. of water in paper cups containing the mosquito larvae. These test methods are the standard WHO stage I methods for investigation of new insecticides (Metcalf et al 1971).

The major series of DDT analogues investigated with altered aliphatic substituents (Table 2) were: A-$CH(CH_3)_2$, B-$CH(Cl)CH_3$, C-$CHCl_2$, D-CCl_2CH_3, E-$CCl(CH_3)_2$, and F-$C(CH_3)_3$. In each series aryl substituents with various alkyl and alkoxy degradophores, were compared with the non-degradable aryl chlorine derivatives characteristic of DDT, and DDD(C-I). Both symmetrical and asymmetrical arrangements of degradophores were investigated. All compounds were purified to 98-99% purity by recrystallization or column chromatography and their purity and chemical structure confirmed by NMR spectrometry.

The results (Table 2) showed that for the various aliphatic alterations studied in series A, B, C, D, E, and F, the most generally insecticidally effective analogues were those with p,p'-diethoxyphenyl-substituents, e.g. A-IV, B-VI, C-IV, D-IV, E-IV, and F-IV. The most effective compound overall was 1,1-bis-(p-ethoxyphenyl)-2-chloropropane (B-VI, OMS-1715) which was outstandingly active to susceptible and resistant flies, to the black blowfly and to mosquito larvae. The corresponding asymmetrical 1-(p-ethoxyphenyl), 1-(p-propoxyphenyl)-2-chloropropane (B-X) was also highly active.

Another compound in this series, 1,1-bis-(p-ethylphenyl)-2-chloropropane (B-III) was also highly effective against susceptible and resistant house flies and adults and larvae of both Culex and Anopheles mosquitoes.

The other outstanding compound investigated was 1,1-bis-(p-ethoxyphenyl)-isobutane (A-IV, OMS-1856) which was very effective to susceptible and resistant flies, the black blowfly, and adults and larvae of Culex and Anopheles. In this series of isobutanes the 1-(p-ethoxyphenyl)-1-(p-propoxyphenyl)-isobutane (A-X) was also highly effective.

Another highly active compound was 1,1-bis-(p-ethoxyphenyl)-2,2-dichloropropane (D-IV) which interestingly enough was many times superior to its isostere 1,1-bis-(p-ethoxyphenyl)-2-chloro-2-methylpropane (E-IV).

The asymmetrical combination of p-CH_3 and p-C_2H_5O degradophores which was very effective in the DDT series, i.e. 2-(p-ethoxyphenyl)-2-(p-tolyl)-1 1,1-trichloroethane (OMS-1476), showed effectiveness in the chloropropane series (B-XII) but was less effective in the isobutane series (A-XIV).

It is particularly interesting in the various series of analogues with altered aliphatic substituents that the p,p'-dichlorophenyl substitutents characteristic of DDT and DDD were generally much inferior to the p,p'-diethoxyphenyl substitutents (A-I, B-I, C-I). Compounds D-I and E-I were somewhat more active. Compounds with p,p'-dimethoxyphenyl substituents characteristic of methoxychlor were even less promising with the altered aliphatic substituents (A-III, B-V, C-III, D-III, and E-III). A discussion of the theoretical explanations for these interesting and somewhat unexpected results has been developed by Coats et al (1977).

Careful structure-activity analysis of these 85 DDT-type compounds (Coats et al 1977) has indicated that overall steric factors are the key parameters in determining the insect toxicity. It is clear from previous work e.g. Gunther et al (1954), Mullins (1955), Holan (1971), that DDT-type compounds interact at a critical receptor site in the insect nerve axon and that the magnitude of toxic effect is determined by the complementarity of the DDT-type molecule to the crucial dimensions of the receptor-site. Fahmy et al (1973) have related effectiveness to the steric parameter E_s for aromatic substituents and suspected steric interaction between both aromatic and aliphatic portions of the molecule but lacked the matrix of compounds to prove it by multiple-regression analysis.

In the present study, we have used the Van der Waals volumes of a total of 176 DDT-type molecules to demonstrate that there is consistently a region of optimal insect toxicity that can be correlated with a relatively narrow Van der Waals volume (Figure 1). This data shows conclusively that with p,p'-dichloro- substituents the compounds have a narrow range of optimum volumes and with p,p'-diethoxy-substituents the compounds have the broadest range of optimum volumes (Figure 1). A correlation of the total Van der Waals volume of 176 DDT-type analogues with the piperonyl butoxide synergized topical LD_{50} to the house fly (Table 2) gave the following equation.

$$LD_{50} = 2120 - 22.9\ (V_w^m) + 0.062\ (V_w^m)^2$$

$$r = 0.40 \text{ and } r^2 = 0.16$$

The correlation coefficient for 174 degrees of freedom indicates significance at $P < 0.01$.

It is interesting that the optimum Van der Waals volume range varies with different insect species suggesting that each species has its own individually sized and shaped DDT receptor site (Coats et al 1977).

This work has been extended and amplified by Lee et al (1977) who examined the related prolan series of DDT-type molecules with the $-CH(CH_3)NO_2$ (R) aliphatic moiety. This series permits ultimate steric flexibility because of the free rotatability of the NO_2-group and demonstrates insecticidal activity over a very wide range of alkoxy-phenyl substitutes, e.g. up to $CH_3OC_6H_4CH(R)C_6H_4OC_8H_{17}$. Multiple regression analyses of a variety of molecular parameters such as Van der Waals radii, parachor, E_s, σ, F, and R revealed that the highest correlation coefficient was obtained between LD_{50} for the house fly and the steric substituent constant E_s for p,p'-substituents which explained 82% of the variation between molecules.

Thus, in summary, it is evident that the size and shape of the aliphatic portion of the DDT-type molecule is critical and that there is an overall interaction between aromatic and aliphatic substituents such that the overall size and shape of the molecule are critical. This information has considerable practical value for the design of new DDT-type insecticides, and it was, in fact, from these considerations that the interesting insecticidal properties of 1,1-bis-(p-ethoxyphenyl)- isobutane (OMS-1856, DEIB) and 1,1-bis-(p-ethoxyphenyl)-2-chloropropane (OMS-1715, DECP) were discovered.

IV. RESIDUAL ACTIVITY OF BIODEGRADABLE DDT ANALOGUES

Most of the strategy of WHO, AID and the nations with which they collaborate in malaria control has been based on the use of residual insecticides as interior surface sprays in human habitations. Such treated dwellings serve in effect as traps baited with humans. The female Anopheles mosquito after taking a blood meal, rests on a treated wall or ceiling and normally is killed, thus interrupting the cycle of malaria transmission between gamatocyte and sporozoite formation.

DDT has been outstandingly effective as a residual spray for malaria control because of its low vapor pressure and stability on a variety of building materials. However, increasing problems of Anopheles resistant to DDT and concern about its effects on environmental quality have resulted in steadily decreasing effectiveness in malaria control.

The DDT analogues developed at the University of Illinois are substantially more biodegradable than DDT. They have been shown to be effective against some DDT resistant insects. A major goal of this project has been to demonstrate their residual effectiveness. This has been done in two ways: (1) by confining 20 Anopheles albimanus and Culex pipiens mosquitoes on treated plywood panels sprayed with DDT-emulsions at 1 g. per m^2, and (2) by liberating Anopheles albimanus mosquitoes in plywood "huts" 4' x 4' x 8', whose interiors were sprayed at 2 g. per m^2 with DDT-emulsion. These huts are equipped with two window traps so that excitorepellency can be determined along with duration of residual effectiveness.

A. Residual Effectiveness of DDT Analogues on Plywood Boards.
The 0.25 m^2 panels of 1/4" plywood were sprayed with the test compounds at 1 g. per m^2 from an emulsion in water prepared by diluting a concentrate of compound 20%, Triton X-100 2%, and xylene 78%, 1 part to 4 parts of water. The results of these "Board Tests" which have now been evaluated for as much as 60 months, with boards held under laboratory conditions are shown below.

Against Culex pipiens quinquefasciatus adults, the effective residual activities (>50% mortality in 24 hours, after 60 minutes exposure) were:

compound	months
DDT	9
methoxychlor	36
DEIB (OMS-1856) 1/	30
DECP (OMS-1715) 2/	32
DTDT (OMS-1476) 3/	22
OMS-2112 4/	7
OMS-2070 5/	2

1/ 1,1-bis-(p-ethoxyphenyl)-isobutane
2/ 1,1-bis-(p-ethoxyphenyl)-2-chloropropane
3/ 1-(p-ethoxyphenyl)-1-(p-tolyl)-2-,2,2-trichloroethane
4/ 1-(p-ethoxyphenyl)-1-(p-tolyl)-2-chloropropane
5/ 1-(p-ethoxyphenyl)-1-(p-tolyl)-isobutane

Against Anopheles albimanus adults, the effective residual activities were:

compound	months
methoxychlor	62
DEIB (OMS-1856)	45 (95% mortality)
DECP (OMS-1715)	52 (100% mortality)
OMS-2112	15
OMS-2070	5

Thus all three of the biodegradable DDT's DTDT, DEIB, and DECP showed very acceptable persistence on the plywood substrate as did methoxychlor. DDT was of rather short persistence to Culex pipiens quinquefasciatus as was to be expected from its relatively poor activity against this species, which contains a large titre of inactivating DDT'ase enzyme.

B. Residual Effectiveness of DDT Analogues in Plywood Hut Tests. The 4' x 4' x 8' huts were sprayed at 2 g. per m^2 with the test compounds using the standard emulsive concentrates described above, diluted 1:4 with water. The spray was applied with a hand atomizer of the "Flit-gun" type, wetting the plywood with the test emulsion, to the run-off point.

At approximate intervals for evaluation, approximately 100 adult Anopheles albimanus, 2-4 days old, were liberated into each hut, the door tightly closed, and the exit covers fitted with 1 gallon cardboard ice-cream cartons to serve as exit traps. These contained cloth sleeves and screen-wire bottoms. The mosquitoes were left in the treated huts for three hours during mid-day, after which the window exit traps, were removed and the mosquitoes "knocked down" inside the huts were picked up and caged. The interior of the hut was then lightly sprayed with a pyrethrins aerosol to determine the total number of mosquitoes liberated. The escapees in the window traps and the mosquitoes collected from the floor were provided with sugar water and were observed for 24 hour mortality after storage under laboratory insectary conditions at 26°C. The compounds under study were evaluated at biweekly intervals over a 2-3 year period. Mortalities in both hut and window traps were corrected for natural mortality by comparison with an unsprayed control hut.

Residual Effectiveness. The results of the residual effectiveness (>70% total mortality) in the hut tests are summarized in Table 3 . These data represent the total results from 273 individual hut tests involving approximately 30,000 Anopheles albimanus. The CH_3S analogue of methoxychlor (OMS-1395) was very short-lived showing about 23 days of appreciable residual activity. This rapid loss of activity

was also observed in the laboratory board tests and is due to rapid oxidation to the CH_3SO derivative which makes the compound very susceptible to dehydrochlorination to the ethylene (Metcalf and Fukuto 1971). All of the other compounds in Table 3 showed good residual activity to Anopheles albimanus comparable to that of DDT. The most effective of the biodegradable DDT analogues was DEIB (OMS-1856) which showed a longer effective residual activity (35 months) than any other compound evaluated. DECP (OMS-1715) was also highly persistent showing effective activity for 27 months. DTDT (OMS-1476) showed substantially lower effective residual activity of 13 months, but its CH_3O analogue (OMS-1406) was substantially more persistent with an effective residual activity of 30 months. This may be related to the physical properties of the two compounds as OMS-1476 is a liquid and OMS-1406 is a crystalline solid.

Excitorepellency. The percentages of Anopheles albimanus caught in the window traps, (demonstrating excitorepellency) was quite valuable with weather conditions as shown in Table 3. Higher temperatures activated the mosquitoes into flight and this flight tended to be upwind into the window traps. As shown in Table 3 , DEIB (OMS-1856) had the lowest degree of excitorepellency of all the compounds evaluated over the three year period and consistently gave >95% total mortality for over 500 days. This low excitorepellency of DEIB should be advantageous in residual house spraying, as it has be shown with DDT that some Anopheline vectors may be repelled from treated houses before absorbing a lethal dosage of insecticide. The excitorepellency of DECP (OMS-1715) was the highest of all the compounds evaluated including DDT and methoxychlor and although this compound showed good residual action, this could be a disadvantage in use for malaria control. DTDT (OMS-1476) also showed a moderate excitorepellency.

The 24 hour mortality of Anopheles albimanus in window traps was determined and remained at essentially 100% for DDT, methoxychlor, DTDT, DEIB, and DECP for approximately 12 months after residual spraying. DEIB was still producing 100% mortality of the mosquitoes in window traps after 35 months, as compared with about 21 months for DDT.

C. Comparison between Susceptibility of Anopheles albimanus and Anopheles stephensi to DDT and Analogues.
Laboratory reared adult populations of the two malaria vectors were evaluated for comparative susceptibility to the test compounds using the standard WHO Stage I evaluation procedure of 60 minutes exposure to residues on filter paper. THE LC_{50} values were determined by log-dosage vs. probit mortality plots:

	LC_{50} g per cm^2				
	DDT	methoxychlor	DTDT	DECP	DEIB
A. albimanus	0.23	13.0	0.75	7.9	4.5
A. stephensi	5.4	89.9	12.5	7.8	3.9

D. Residual Effectiveness of DEIB WDP on Bricks.
A 70% WDP of DEIB prepared by Abbott Laboratories was sprayed on commercial bricks at 1 g. per m^2 and the treatment evaluated by confining 20 adult A. albimanus or C. pipiens adults on the treated surface for 60 minutes under a petri dish cover. The mortality was determined at 24 hours.

	per cent kill - 24 h.		
	30 days	60 days	90 days
Brick I			
Culex	15%	57%	28%
Anopheles	100%	100%	95%
Brick II			
Culex	33%	53%	4%
Anopheles	100%	100%	67%

V. DEGRADATION OF ^{14}C 1,1-bis-(p-ethoxyphenyl)-isobutane IN INSECTS

Extensive investigations of the degradation and fate of 1,1-bis-(p-ethoxyphenyl)-isobutane (DEIB) were carried out using ^{14}C radiolabeled insecticide (1-^{14}C labeled), radiopurity >99%, specific activity 5.7 mCi per mM, kindly furnished by Abbott Laboratories, Chicago, Illinois. These studies are particularly valuable in contrasting the high biodegradability in mouse (q.v.) and in model ecosystem (q.v.) with the substantial stability in the various species of insects. The techniques used were topical application, or oral feeding followed by homogenization, extraction, thin-layer chromatography, radioautography and qualitative and quantitative determination of degradation by liquid scintillation spectrometry.

House Fly. Two strains of house fly Musca domestica L. were studied, the susceptible S_{NAIDM} and the DDT and cyclodiene resistant. R_{SP} LD_{50} values by topical application (Table 2) are: DDT, S 14 and R 170 mg per kg; DEIB, S 21.5 and R 38.0 mg per kg,

The ^{14}C DEIB was applied topically at 0.02 µg per female fly to lots of 50, 3 day old flies, confined in erlenmeyer flasks stoppered with cotton wicks saturated with 20% sucrose. At intervals of 1, 2, 4, 8, and 24 hours the groups of flies were frozen and worked up as follows:

1) washed 3X in acetone to remove unabsorbed insecticide
2) ground in mortar and pestle and extracted 3X with acetonitrile.
3) residue extracted overnight with 50% methanol containing HCl to determine hydrolyzed conjugates
4) residue subjected to combustion to determine unextractable ^{14}C
5) excreta extracted with methanol
6) residue extracted overnight with 50% methanol containing HCl

All of the extracts were concentrated and subjected to TLC to separate various degradation products. These cochromatographed with known standards were used to confirm the identity of many of the degradation products (Table 4). The percent recovery of the applied dosage was adequate in both strains although it was somewhat higher in the R strain. There were no obviously significant differences in penetration, excretion, or partition of the total radioactivity recovered.

The qualitative and quantitative degradation of the total ^{14}C recovered from body homogenates and excreta is shown in Table 5 . Again there was little evidence of significant differences in the qualitative or quantitative fate in the S and R flies. This is to be expected as the topical LD_{50} values are not very different in the two strains (Table 2) and diethoxyphenyl-isobutane (DEIB) is quite effective against the DDT and cyclodiene resistant R strain.

Substantial amounts of parent compound (9-11%) were isolated from body homogenates of both S and R flies with appreciable amounts (3-5%) in the excreta. The dominant degradative pathway was by O-deethylation and the monophenol 1-(p-ethoxyphenyl)-1-(p-hydroxyphenyl)-isobutane (R_f 0.49) and diphenol 1,1-bis-(p-hydroxyphenyl)-isobutane (R_f 0.21) were the two most abundant species in both homogenates and excreta. However, side chain oxidation of the isobutyl moiety is also an important pathway and 1,1-bis-(p-ethoxyphenyl)-2-methyl-3-hydroxy-propane (R_f 0.32) was also a major detoxication product together with bis-(p-hydroxyphenyl)-acetic acid (R_f 0.03) which represented the principal product of both types

of microsomal attack. Hydroxylation at both alpha- and beta- carbons was less effective as a detoxication pathway. The various phenols and acids are subject to conjugation as polar radioactivity present in both homogenates and excreta.

Effects of Piperonyl Butoxide

Pretreatment of the susceptible house fly with 25 μg of piperonyl butoxide synergist applied to the abdomen, 1 hour before topical application of ^{14}C DEIB to the prothorax greatly altered the detoxication pathways, and no degradation products could be detected on the radioautograms of TLC plates except for polar conjugates (R_f 0.0) which represented only 0.16% of the ^{14}C in the body homogenate and 22% in the excreta (Table 6). Piperonyl butoxide is a specific inhibitor of microsomal oxidase systems and clearly prevented these detoxication pathways of DEIB in the house fly. Piperonyl butoxide also greatly inhibited the penetration of the insecticide as 31% was recovered in the surface wash following the synergist treatment as compared to 4% in the non-synergized flies (Table 6). Similarly the excretion of ^{14}C radiolabeled products was greatly inhibited by the piperonyl butoxide treatment and represented only 0.013 μg (13%) vs. 0.4069 μg (41%) in the non-synergized flies (Table 6). Thus this comparison provides an exceptional demonstration of the effect of the piperonyl butoxide synergist in preventing microsomal detoxication in the insect.

Salt marsh caterpillar. This large 4th instar larva of Estigmene acrea was treated orally with ^{14}C DEIB by treating 200 mg. of artificial diet (Vail Moth Medium) with 2 μg of insecticide applied topically from acetone solution. Two larvae were starved for 4 hours and then allowed to feed until the diet was totally consumed. The insects were kept for 24 hours after feeding and homogenate and feces were worked up as described for the house fly. The results shown in Table 7 indicate that this insect does not degrade the insecticide as readily as does the house fly. The parent insecticide was recovered as 60.32% of the recovered ^{14}C in homogenate and excreta and only traces of other products (<1% of total ^{14}C were found, except for a substantial amount (14.04%) of polar conjugates (R_f 0.0). Although there was indication of the trace formation of mono- (R_f 0.49) and diphenols (R_f 0.21), and of alpha- (R_f 0.60) and beta-hydroxylation (R_f 0.55), no 1,1-bis-(p-ethoxyphenyl)-2-methyl-3-hydroxy propane (R_f 0.32) was detected and only a trace of the bis-(p-hydroxyphenyl)-acetic acid (R_f 0.03) was found in the excreta. It is evident that microsomal oxidase action in the salt marsh caterpillar is not as effective as in the house fly.

Mexican Bean Beetle. This insect is very susceptible to DEIB, with a topical LD_{50} of topical treatment of female beetles with 0.04 μg of ^{14}C labeled DEIB (0.05 μg per g) followed by workup of homogenate and excreta after 24 hours as described for the house fly, gave the results shown in Table 7. The Mexican bean beetle is clearly deficient in microsomal capacity to detoxify the insecticide as 84.54% of the ^{14}C recovered from homogenate and feces was present as parent compound and only 3.46% was present as polar conjugates. Only trace amounts of the customary degradation products were recovered with the monophenol (R_f 0.49) as the major product. Clearly, the inability of the Mexican bean beetle to degrade DEIB is the reason for the very high toxicity of this insecticide.

Anopheles stephensi larva. In studies with this mosquito, ^{14}C DEIB was added to 10 ml of water containing 50 4th instar larvae, at 0.02 ppm. After 24 hours exposure the water was extracted with diethyl ether and the insects were homogenized and extracted with acetonitrile.

The results of this experiment are shown in Table 8 . Clearly the Anopheles larva degrades DEIB by the same microsomal pathways of O-deethylation and side chain oxidation found in other insects and in the mouse.

VI. MOUSE METABOLISM OF ^{14}C 1,1-bis-(p-ethoxyphenyl)-isobutane

Two female Swiss white mice were dosed orally with ^{14}C diethoxyphenyl isobutane (DEIB), at 50 mg per kg, using 0.66% in olive oil, administered orally with a micrometer driven Hamilton microsyringe. The treated mice were confined individually in Plexiglass^{R} metabolism cages and urine and feces were collected separately over a 10 day period. The total radioactivity in urine and feces was determined by liquid scintillation counting. The urine and feces were extracted and aqueous remainder was determined to give hexane and polar fractions.

Elimination of total ^{14}C.

The total elimination of ^{14}C metabolites in urine and feces is shown in Table 9. An average of 71.7% of the administered ^{14}C was eliminated after 3 days and 79.4% after 10 days. After 10 days an average of 46.72% of the administered ^{14}C was eliminated in the urine and 32.65% in the feces.

Degradative Fate in Mouse Excreta

Pooled samples of urine and feces of Mouse II over a two day period after administration of ^{14}C DEIB were examined in detail by TLC, radioautography, and quantitative determination by liquid scintillation counting. The degradative products isolated in the hexane extracts of urine and feces are shown as percentages of total ^{14}C in Table 9 . The aqueous extracts of urine and feces were hydrolyzed in 0.1 N HCl for 24 hours and then extracted with diethyl ether to give the polar fractions in Table 9 . The compounds isolated were identified as shown in Table 10by R_f values , cochromatography with known model metabolites and by mass spectrometry as discussed below.

The data in Table 10indicates the high degree of biodegradability of DEIB as at least 17 distinct ^{14}C labeled compounds were isolated after TLC (n-pentane, diethyl ether, acetone, acetic acid - 122, 20, 14, 4). This data can be contrasted with an identical experiment using ^{14}C DDT (Kapoor et al 1972). With DDT 73.0% of the recovered ^{14}C was excreted in feces and 27.0% in urine as compared to the present experiment with DEIB where 38.8% of the recovered ^{14}C was excreted in the feces and 62.2% in the urine. After feeding ^{14}C DDT, 43.3% of the radioactivity in the urine was in the hexane fraction compared to 0.47% after feeding ^{14}C DEIB. Following the DDT treatment, 8.55% of the recovered ^{14}C was eliminated as intact DDT in the urine, and 22.78% in feces. This compared with the DEIB treatment

where 0.70% of the ^{14}C of the intact parent compound in urine and 2.91% in feces. After feeding DDT, 3.24% of the ^{14}C was eliminated as polar conjugates in the urine and 15.77% in feces. With DEIB the comparable elimination of ^{14}C as polar conjugates was 48.92% in urine and 2.09% in feces.

Degradative Pathways.

The information in Table 10 shows clearly that the predominant degradative pathways for DEIB were (1) by O-deethylation to produce 1-(p-ethoxyphenyl)-1-(p-hydroxyphenyl)-isobutane or monophenol (R_f 0.49) that was by far the most important fecal metabolite (16.37% total ^{14}C recovered). O-deethylation of this molecule subsequently produced 1,1-bis-(p-hydroxyphenyl)-isobutane or diphenol (R_f 0.17), the second most abundant fecal metabolite (7.42% total ^{14}C recovered). The diphenol was also an important urinary metabolite. Pathway (2) was side chain oxidation to produce 1,1-bis-(p-ethoxyphenyl)-2-methyl-2-hydroxypropane (R_f 0.32) that was the third most abundant fecal metabolite (3.28% total ^{14}C recovered). Further microsomal degradations of these compounds to more polar compounds obviously occurred and the most important urinary metabolite was the highly polar bis-(p-hydroxyphenyl)-acetic acid (R_f 0.03) (4.02% of total ^{14}C recovered).

Hydroxylations of DEIB at alpha (R_f 0.60) and beta-carbons (R_f 0.55) were relatively minor metabolic pathways. These degradative pathways are shown in Figure 2 .

VII. LABORATORY MODEL ECOSYSTEM STUDY.

The terrestrial-aquatic model ecosystem was developed as a laboratory tool to provide quantitative information about the biodegradability of DDT and its analogues (Metcalf et al 1971, Kapoor et al 1970, Kapoor et al 1972, Kapoor et al 1973, Coats et al 1974). This system was used to evaluate the environmental fate and biodegradability of DEIB following topical application of 5.0 mg of ^{14}C-(p-ethoxyphenyl)-isobutane to 50 Sorghum vulgare plants grown on the terrestrial portion of the sloping sand shelf in the 10 gallon aquarium. The sorghum was eaten by 10 salt marsh caterpillars (Estigmene acrea) and the ^{14}C labeled products were dispersed throughout the aquatic portion of the system where their nature and uptake were evaluated in a series of food chain organisms including the alga, Oedogonium cardiacum, the snail Physa spp., the water flea, Daphnia magna, the mosquito larva Culex pipiens quinquefasciatus, and the fish Gambusia affinis. The results are shown in Table 11.

The principal degradative pathways were by O-deethylation to form 1-(p-ethoxyphenyl)-1-(p-hydroxyphenyl)-isobutane (R_f 0.49) and by side-chain oxidation to form 1,1-bis-(p-ethoxyphenyl)-2-methyl-3-hydroxypropane (R_f 0.32). These two products were found in appreciable amounts in water, snail, alga, and fish (Table 11). Further degradation clearly

proceeded through O-deethylation of the remaining ethoxy group and additional oxidation of the aliphatic portion to the 4,4'-dihydroxy benzophenone (R_f 0.05). The environmental degradative pathways identified were very similar to those found in mouse (q.v.) and in several species of insects (q.v.).

The important model ecosystem parameters of ecological magnification or E.M. (ppm of parent compound in organism/ppm in water) and biodegradability index or B.I. (ppm polar[1/] degradation products in organism/ppm non-polar products) were evaluated for DEIB as shown in Table 11 where DEIB is compared with DDT and 2,2-bis-(p-ethoxyphenyl)-1,1,1-trichloroethane (ethoxychlor). These data provide interesting information on the environmental properties of this new DDT analogue. The snail which is almost devoid of microsomal oxidase degradative enzymes accumulated large amounts of the parent compound, as has been found previously with methoxychlor (Kapoor et al 1970), and ethoxychlor and methylchlor (Kapoor et al 1972). However, the fish Gambusia is clearly able to degrade the parent compound to highly polar products. Thus the fish has a relatively low E.M. value 760 and a relatively high B.I. 1.59 as compared to the snail E.M. 72,012 and B.I. 0.13. Thus DEIB can be classed as substantially biodegradable as compared to DDT which showed E.M. 84,500 and B.I. 0.015 to the fish Gambusia in identical model ecosystem evaluation. Compared to ethoxychlor (Table 12), the DEIB appears to be somewhat less bioaccumulative in both fish and snail but shows lower B.I. values. The higher B.I. values for ethoxychlor probably are the result of the environmentally recalcitrant CCl_3 and CCl_2 groups of the parent compund as principal degradative product that force detoxication toward O-deethylation thus providing relatively large amounts of dihydroxydiphenylethanes readily conjugated to highly polar products.

Unlike DDT and ethoxychlor (Kapoor et al 1972) where the ethylene degradation products i.e. DDE and 2,2-bis-(p-ethoxyphenyl)-1,1-dichloroethylene (ethoxychlor ethylene) are themselves significant environmental pollutants not readily subject to further degradation with E.M. values of approximately the same order as the parent compounds, e.g. DDE E.M. 112,308, and ethoxychlor ethylene E.M. 955 in the fish Gambusia (Kapoor et al 1970, 1972); no single degradation product of DEIB plays any major role as an environmental pollutant (Table 11).

1/ From Table 11, all the products with R_f values below the parent compound were defined as polar products because of the semi-polar solvent mixture used for TLC (see Kapoor et al 1973).

Comparisons of DEIB with the other important biodegradable DDT analogue methyl ethoxychlor (Kapoor et al 1973) shows that the two compounds have very comparable E.M. and B.I. values in snail and fish (Table 12). There is, however, a major difference in the mosquito larvae, suggesting that this animal is able to oxidize aromatic methyl groups more readily than aliphatic methyl groups.

In summary, DEIB is a substantially biodegradable DDT-type insecticide and forms a wide spectrum of degradative products of increasing polarity and water solubility when exposed to a variety of terrestrial and aquatic organisms. There is no evidence of a high degree of bioaccumulation in the fish Gambusia at the top of the food chain. The relatively large number and variety of microsomal oxidation products formed by O-deethylation of the aromatic C_2H_5O groups and by side chain oxidation of the $CH(CH_3)_2$ moiety indicate the importance of these degradophores in promoting environmental biodegradability. The microsomal oxidation products containing phenolic (C_6H_4OH) and acidic [$CH(CH_3)COOH$] groups are readily conjugated to water partitioning substances which are excreted by living organisms rather than stored in tissue lipids.

Thus DEIB strongly resembles methoxychlor in its biological behavior in laboratory animals, insects, and in the laboratory model ecosystem (Kapoor et al 1970, Metcalf et al 1971). Some 30 years of real world experience with methoxychlor as a practical insecticide indicate that the use of methoxychlor results in minimal effects on environmental quality. From the available evidence, DEIB should have an equally favorable environmental impact.

VIII. DETERMINATION OF STRUCTURES OF KEY DEGRADATION PRODUCTS

Although some of the degradation products of 1,1-bis-(p-ethoxyphenyl) -2-isobutane (DEIB) were known with certainty by their cochromatographic behavior upon TLC with known standard model compounds, there were obvious gaps in knowledge of the identity of ^{14}C labeled products obtained in the excreta of insects and the mouse (Tables 8 and 9) and in the model ecosystem study from water, alga, snail, mosquito and fish (Table 11).

In order to identify as many of these "unknown" degradation products as possible, 50 mg per kg of ^{14}C DEIB was given orally in olive oil to two Swiss laboratory mice and the urine and feces collected over a 3-day period. The radiolabeled products were fractionated as described above and after extraction, TLC, and radioautography, major ^{14}C-labeled degradation products whose identity was uncertain (R_f 0.32, 0.25, 0.10, Table 11) were removed from the TLC plates, eluted in spectrograde acetone, concentrated, and injected into tiny gold crucibles for mass spectrometric analysis by CH-5 Varian Mass Spectrometer.

Parent Compound. The mass spectrum 1,1-bis-(p-ethoxyphenyl)-isobutane, R_f 0.91 (Table 11) showed the following: m/e 298 (M^+) 255 ($M-C_3H_7$), 227 ($M-C_3H_7-C_2H_5$), and 199 ($M-C_3H_7-2C_2H_5$). This is consistent with fragmentation to give bis-(p-ethoxyphenyl)-methyl (255), (p-ethoxyphenyl-p-hydroxyphenyl)-methyl (227) and bis-(p-hydroxyphenyl)-methyl (199).

Compound R_f 0.32. (Table 11). This was identified as 1,1-bis-(p-ethoxyphenyl)-2-methyl-3-hydroxypropane. The mass spectrum showed m/e 314 (M+), 284 ($M-C_2H_5$), 256 ($M-2C_2H_5$), 255, 227, and 199 as identified above, and 58 (OCH_2CHCH_3).

Compound R_f 0.25. (Table 11). This was identified as 1-(p-ethoxyphenyl)-1-(p-hydroxyphenyl)-2-carbomethoxypropane. The mass spectrum showed m/e 314 (M+), 299 ($M-CH_3$), 255 ($M-COOCH_3$), 227, and 199 as identified above.

Compound R_f 0.10. (Table 11). This was identified as 1,1-bis-(p-ethoxyphenyl)-2-carboxy-propane. The mass spectrum showed m/e 312 (M-0), 311 (M-OH), 286 ($M-HOCH_3$), 227, 199 as identified above, 105 ($C_6H_5C=0$), and 45 ($CH_2CH=OH$).

IX. SUMMARY OF LABORATORY SCREENING TESTS

An important objective of the study was to evaluate 1,1-bis-(p-ethoxyphenyl)-isobutane (DEIB) and 1,1-bis-(p-ethoxyphenyl)-2-chloropropane (DECP) in precise laboratory against a variety of insects. The method chosen was the topical application by micrometer-driven Hamilton syringe of 1.0 microliter w/v acetone solutions containing various amounts of the test compounds. The applications were made to replicates of 10 or 20 insects, under CO_2 anesthesia and the treated insects were provided with food and water and kept under constant temperature (26° C) for 24 hours, when mortalities were determined. Generally, a range of 5 different dosages was used to prepare standard dosage vs. mortality curves from which the 24 h. LD_{50} values were calculated by computer program as shown in Table 13. Comparisions of DEIB and DECP were generally made with DDT, methoxychlor, and with 1-(p-ethoxyphenyl)-1-(p-tolyl)-2,2,2-trichloroethane (ETDT or OMS-1476) another promising biodegradable DDT analogue (Kapoor et al 1973, Metcalf et al. U.S. Pat. 3,787,505).

The results of these precise toxicity tests on 13 species of insects of 5 orders, indicate the rather specific nature of the action of these DDT-type molecules. DECP was very toxic to Japanese beetle, Mexican bean beetle, and milkweed bug and was quite effective to the three species of corn rootworms, the striped cucumber beetle and the milkweed bug. DEIB was quite effective against Mexican bean beetle, corn rootworms, and striped cucumber beetle. All of the 4 new DDT analogues were effective against the house fly and black blow fly and were especially toxic to the DDT resistant strain.

Evaluated against an important lady bird beetle predator, DECP and DEtCP were toxic while DEIB and ETDT were much safer. Evaluated aginst a hymenopterous parasite of the house fly both DEIB and DECP were highly toxic while DEtCP was safer and ETDT was non-toxic.

X. SUMMARY OF FIELD TRIALS*
with
DIETHOXYPHENYL ISOBUTANE (DEIB) and DIETHOXYPHENYL CHLOROPROPANE (DECP)

Agricultural, Ornamental, Forest Pests

A. Corn rootworm (Diabrotica spp) on corn:

1. DEIB better than DDT, but not as active as terbufos (Counter[R]) or carbofuran (Furadan R).
2. At 2 lb. per A. DEIB was equal to carbofuran at 1 lb. per A.
3. At 0.5, 1.0, 2.0 lb/A, DEIB was less effective than terbufos at 1.0 lb.

B. Alfalfa weevil (Hypera punctata) on alfalfa:

DECP and DEIB at 1 lb. per A. gave control equivalent to carbofuran at 0.5 lb. and phosmet (Imidan) at 1 lb.

C. Colorado potato beetle (Leptinotarsa decemlineata) on potatoes:

1. DEIB gave excellent control of larvae at 2 lb/A, but poor control of adults.
2. DEIB gave good control.

D. Mexican bean beetle (Epilachne varivestis) on beans:
DEIB gave moderate to good control.

E. Cotton bollworm (Heliothis zea) on cotton:

1. DEIB gave poor control of Heliothis spp.
2. DEIB gave very poor control of Heliothis spp.
3. DEIB at 1.5 and 3.0 lb/A provided similar control to EPN plus methyl parathion standard at 0.5 + 0.5 lb/A.

F. Corn earworm (Heliothis zea) on corn.

DEIB provided poor control at 1-2 lb/A.

G. Corn earworm (Heliothis zea) on tomatoes:

5 treatments on 10 day schedule gave good control, also controlled leafminer without upset of parasites.

H. Black cutworm (Agrotis ipsilon) on onions:

DECP provided moderate control at 1-2 lb/A.
DEIB provided excellent control at 2 lb/A., moderate control at 1 lb/A.

I. Cabbage looper (Trichoplusia ni) on cruciferae:

1. DEIB provided poor to moderate control at 0.5-2.0 lb/A.
2. DEIB provided poor control at 2.0 lb/A.

* The information summarized in this section was obtained by Abbott Laboratories in cooperation with entomologists in various Experiment Stations and Field Laboratories. Formulations used 20% emulsive concentrate and 10% granular

J. Imported cabbageworm (Pieris rapae) on cabbage:

DEIB gave poor control at 2 lb/A.

K. Diamond back (Plutella xylostella) on cabbage:

DEIB gave poor control at 2 lb/A.

L. Grape leafhopper (Erythroneura spp) on grapes:
DEIB gave 100% control when sprayed at 1 and 2 lb/100 gal.

M. Squash bug (Anasa tristis) on squash; 20% emulsion concentrate 100% control when sprayed at 1 and 2 lb/100 gal.

N. Japanese beetle (Popillia japonica)

1. DEIB was ineffective in turf for grub control at 2 lb/A.
2. DECP and DEIB were ineffective for grub control

O. European chafer (Amphimallon majalas)
Ineffective at 2 lb/A.

P. Apple pests
DEIB at 2 lb/100 gal. gave control of codling moth (Laspeyresia pomonella) lesser appleworm (Grapholitha prunivora), oblique banded leaf roller (Archips rosaceana), red banded leaf roller (Argyrotaenia velutinana), rosy apple aphid (Anuraphis roseus), and white apple leafhopper (Typhlocyba pomaria) equal to or better than azinphos methyl (Guthion) standard at 0.5 lb/A. Control of apple maggot (Rhagoletis pomonella), and plum curculio (Conotrachelus nenuphar) was less effective than with azinphos methyl.

Q. Cotton pests
DEIB gave fair control of pink bollworm (Pectinophora gossypiella), cotton leaf perforator (Buccalatrix thurberiella) and tobacco budworm (Heliothis virescens. Control of Lygus bugs was poor.

R. Sugar beet pests
DEIB at 1-2 lb/A was ineffective against beet armyworm (Spodoptera exigua). At 2 lb/A DEIB gave good control of beet leafhopper (Circulifer tenellus).

S. Gypsy moth (Porthetria dispar)
DEIB gave little or no control at 2 lb/A, DECP gave moderate control at 2 lb/A.

T. Omnivorous leafroller (Onephasia logana?)
DEIB gave moderate control at 2 lb/A.

U. Citrus mealy bug (Pseudococcus citri)
DEIB gave moderate control at 2 lb/A.

V. Two-spotted spider mite (Tetranychus bimaculatus)
DEIB was inactive at 2 lb/A.

W. European corn borer (Pyrausta nubilalis)
DEIB was ineffective at 1-2 lb/A.

X. Carrot weevil (Listronotus oregonensis)
DEIB was ineffective at 2 lb/A.

Y. Ground mealy bug (Rhizoecus spp)
DEIB gave good control at 2 lb/A.

Z. Seed corn maggot (Hylemya platura)
DEIB and DECP gave poor to moderate control as seed treatments at 1-2 oz/cwt. lima bean seeds.

AA. Southwestern corn borer.
DEIB inactive at 0.5, 1.0, and 2.0 lb/A. on corn.

AB. Greenbug (Toxoptera graminum)
DEIB was ineffective against OP-resistant greenbugs.

AC. Citrus thrips (Scirtothrips citri)
DEIB gave fair knockdown and residual activity.

AD. Dichondra flea beetle
DEIB gave good control at 1 and 2 lb/A.

AE. Soybean pests
DEIB gave poor control of soybean looper (Plathypene spp), velvet bean caterpillar (Antacarsia gemmatalis) and green stinkbug (Acrosternum bilare).

Medical, Veterinary, and Household Pests

A. House fly (Musca domestica)
1. DEIB and DEBP showed good activity, in same range as organochlorines.
2. DEIB and DCBP showed moderate control of susceptible strains and poor control of diazinon and DDT resistant strains.
3. DEIB and DCBP were of low activity as manure treatments and feed through agents.

B. Mosquito larvae
1. DEIB and DCBP showed good activity, in same range as organochlorines
2. DEIB and DCBP were effective against Culex tarsalis at 0.1-0.25 lb/A.
3. Culex quinquefasciatus

		LC_{50} ppm		LC_{90} ppm	
		DEIB	DECP	DEIB	DECP
	OP-S	0.105	0.105	0.145	0.160
Culex tarsalis					
	OP-S	0.081	0.097	0.150	0.163
	OP-R	0.103	0.123	0.173	0.235

C. Triatoma protracta
1. DEIB and DCBP were not promising.

D. German cockroach (Blattela germanica) and brown-banded cockroach.
1. DEIB and DCBP were ineffective
2. 2% DEIB and DBCP showed moderate activity against malathion and diazinon resistant strains of B. germanica.

E. Face fly (Musca antumnalis)
DEIB and DECP were of low activity as manure treatments and feed through agents.

XI. MAMMALIAN TOXICITY OF DDT ANALOGUES

The oral LD_{50} values were determined by the Swiss white mouse for some of the more interesting compounds listed in Table 2. The materials were administered orally in weight/volume olive oil solutions using a micrometer driven Hamilton syringe.

	mouse oral LD_{50} mg/kg.
$C_2H_5OC_6H_4HCCH(CH_3)_2.C_6H_4OC_2H_5$ (OMS-1856)	>2100
$C_2H_5OC_6H_4HCCHCl(CH_3).C_6H_4OC_2H_5$ (OMS-1715)	1000
$C_2H_5OC_6H_4HCCCl_3.C_6H_4OCH_3$ (OMS-1476)	>1000
$C_2H_5OC_6H_4HCCCl_3.C_6H_4OCH_3$	325
methoxychlor	>1000
DDT	200

OMS-1856 (DEIB) was of outstanding safety and mice treated at 2100 mg/kg the highest dosage that could be given showed no signs of toxicity. Independent evaluation by Abbott Laboratory using the laboratory rat reported an oral LD_{50} of >7000 mg/kg. OMS-1856 is thus from 10 to 50 times less toxic to mice and rats than DDT. This safety is confirmed by the mouse degradation studies with ^{14}C labeled OMS-1856 (Tables 9 and 10) which indicated the metabolism to more than 16 degradation products which were readily eliminated.

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XIV. DISSEMINATION AND UTILIZATION

Two research publications on the basic evaluation of structure vs. activity of a total of 130 DDT analogues, most of them new, have already been published under the aegis of this Contract (Coats et al 1977, Lee et al 1977). Other manuscripts dealing with the principles of residual toxicity of DDT analogues to adult mosquitoes and with residual activity vs. chemical structure are in process of preparation.

The compounds prepared have been submitted to WHO for incorporation in the "Insecticide Testing and Development Scheme" and further evaluation is in progress.

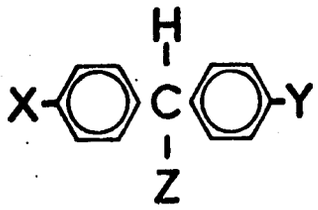
XV. OUTLOOK

Termination of funding for this Contract by AID has left continuing progress up to WHO and to Abbott Laboratories or other licensees of the University of Illinois Foundation for useful development of these insecticides.

Table 1. Conditions for Efficient Bayer Condensation of Phenetole and Isobutyraldehyde.

experiment	ratio phenetole/isobutyral	ratio H_2OSO_4/HAc	time reaction	yield % theory
1	1.5	1	3	69.5
2	0.63	1	1	29
3	0.63	1.5	1	34
4	0.63	0.25	1	0
5	0.63	1.31	1	gum
6	2.5	0.67	1	22
7	stepwise	0.67	1	37
8	1.67	0.67	1	63
9	2.5	0.67	1	70
10	2.5	0.67	1	85
11	2.5	0.67	1	84
12	2.5	0.67	1	85
13	2.5	0.67	1	89

Table 2 EFFECTS OF VARIOUS ALTERATIONS OF ALIPHATIC AND AROMATIC SUBSTITUENTS ON INSECT TOXICITY OF THE DDT-TYPE MOLECULE



No.	Z	X	Y	Musca domestica HAIDM (♀) LD_{50} (µg/g) alone	with P.B.	Musca domestica R_{SP} (♀) LD_{50} (µg/g) alone	with P.B.	Phormia regina adults LD_{50} (µg/g) alone	with P.B.	Culex fatigans LC_{50} (ppm) larvae	LC_{50} (µg/cm²) adults	Anopheles albimanus LC_{50} (ppm) larvae	LC_{50} (µg/cm²) adults	Synthetic Method	m.p. (°C.)
A-I*	$CH(CH_3)_2$	Cl	Cl	>500	500	>500	>500	>250	>250	2.8	160	12	50		
A-II*		CH_3	CH_3	>500	310	>500	>500	>250	>250	0.85	16	> 1	15		
A-III*		OCH_3	OCH_3	480	36	>500	120	122.5	95	0.48	>160	> 1	27		
A-IV		OC_2H_5	OC_2H_5	21.5	3.5	38	12.5	14.5	6.7	0.08	14.3	0.028	9.5	A	65
A-V		OC_3H_7	OC_3H_7	100	21.5	185	185	155	140	0.30	>160	0.25	>160	A	17
A-VI		OC_4H_9	OC_4H_9	>500	>500	>500	>500	>250	>250	100	>160	>100	>160	A	-
A-VII		OCH_3	OC_2H_5	65	12	110	17.5	28.75	13	0.13	16.5	0.17	6.3	B	38
A-VIII		OCH_3	OC_3H_7	120	28	235	140	157.5	135	0.25	>160	0.34	>160	B	33
A-IX		OCH_3	OC_4H_9	240	160	>500	260	>250	>250	1.5	>160	0.3	>160	B	-
A-X		OC_2H_5	OC_3H_7	21	6.5	42	22.5	60	26	0.39	>160	0.056	35	B	-
A-XI		OC_2H_5	OC_4H_9	90	65	180	130	>250	>250	0.24	>160	0.09	>160	B	-
A-XII		OC_3H_7	OC_4H_9	>500	400	>500	>500	>250	>250	12	>160	3.5	>160	B	-
A-XIII		CH_3	OCH_3	>500	175	>500	>500	>250	>250	1.4	>160	3.5	160	C	-
A-XIV		CH_3	OC_2H_5	70	18	150	31	35	24	0.051	5	0.275	5	C	-
A-XV		CH_3	OC_3H_7	175	100	370	220	>250	>250	0.54	>160	0.42	29	C	-
A-XVI		CH_3	OC_4H_9	>500	240	>500	>500	>250	>250	1.1	>160	0.19	>160	C	-
A-XVII		C_2H_5	OC_2H_5	35	22.3	85	33	55	47.5	0.064	10	0.19	4.4	C	-
B-I	$CHClCH_3$	Cl	Cl	180	37	250	225	>250	107.5	0.10	17	0.064	11.7	A	71-3
B-II		CH_3	CH_3	500	24.5	>500	140	>250	125	0.22	9.7	3.5	6.9	A	-
B-III		C_2H_5	C_2H_5	20	3.25	30	11.5	75	70	0.042	12.7	0.055	8	A	-
B-IV		C_3H_7	C_3H_7	55	45	120	90	255	250	0.145	>160	0.068	17	A	-
B-V		OCH_3	OCH_3	935	3.5	>500	41	>250	40	0.18	>160	0.21	63	A	78
B-VI		OC_2H_5	OC_2H_5	9.5	2.0	18	4.9	4.62	4.62	0.054	56	0.047	7.9	A	47-8
B-VII		OC_3H_7	OC_3H_7	28	10	85	42	42.5	22.5	0.12	>160	0.16	>160	A	19
B-VIII		OC_4H_9	OC_4H_9	445	90	500	220	250	250	4.2	>160	3.8	>160	A	-
B-IX		OCH_3	OC_2H_5	47	4.7	100	4.8	12	12.5	0.15	>160	0.15	27	B	38
B-X		OC_2H_5	OC_3H_7	15.5	3.2	25	5.5	62.5	29.5	0.05	>160	0.075	14.5	B	-
B-XI		CH_3	OCH_3	320	38.5	>500	85	97.5	10	0.163	52	0.43	13	C	-
B-XII		CH_3	OC_2H_5	39	10	95	14	6.75	5.75	0.08	10	0.09	1.1	C	36-8
B-XIII		CH_3	C_3H_7	65	29	155	85	97.5	62.5	0.18	12	0.18	7.2	B	-
B-XIV		$C(CH_3)_3$	OC_2H_5	>500	>500	>500	>500	>250	>250	0.08	>160	2.5	>160	B	-
C-I*	$CHCl_2$	Cl	Cl	72.5	35	>500	>500	15.25	9	0.038	> 16	0.01	1.4		
C-II*		CH_3	CH_3	120	11.5	225	26	10.7	8.5	0.025	5.5	0.156	2.2		
C-III*		OCH_3	OCH_3	850	10	>500	21.5	250	7.5	0.037	>160	0.088	16		
C-IV *		OC_2H_5	OC_2H_5	9	2.15	22	3.6	3.75	2.75	0.033	>160	0.02	1.6		
C-V		OC_3H_7	OC_3H_7	55	13.5	170	41	47.5	32.5	0.21	>160	0.074	>160	A	-
C-VI		OC_4H_9	OC_4H_9	305	100	500	185	>250	>250	1.25	>160	0.45	>160	A	-
C-VII		OC_5H_{11}	OC_5H_{11}	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	45-7
C-VIII		OCH_3	OC_2H_5	50	11	72.5	10.5	8.5	6.75	0.035	32.5	0.07	6	B	56-8
C-IX		OC_2H_5	OC_3H_7	16.5	8.0	36	18	20.5	12.5	0.029	125	0.031	37	B	-
C-X		CH_3	OC_2H_5	39	10	65	21.5	85	7.25	0.62	9.4	1.0	1.1	B	-
D-I	CCl_2CH_3	Cl	Cl	47	17.5	65	42	7.25	3.75	0.023	52	0.0084	1.1	A	75-7
D-II		CH_3	CH_3	145	18	270	7	8	7.25	0.20	8.0	0.13	5	A	74-7
D-III		OCH_3	OCH_3	65	8	155	9.5	13.5	7.25	0.061	160	0.18	1.63	A	70
D-IV		OC_2H_5	OC_2H_5	17.5	7	90	23.5	24	18	0.094	>160	0.041	49	A	84-5
D-V		OC_3H_7	OC_3H_7	>500	90	>500	115	>250	>250	0.80	>160	3.4	>160	A	-
D-VI		OCH_3	OC_2H_5	110	14	140	25	12.2	11.7	0.068	8	0.076	5	B	69-70
D-VII		OC_2H_5	OC_3H_7	155	82	180	90	77.5	62.5	0.086	>160	0.16	>160	B	-
E-I*	$CCl(CH_3)_2$	Cl	Cl	55	29	60	45	35	27.5	0.3	30	1.8	56		
E-II*		CH_3	CH_3	>500	>500	-	-	>250	>250	-	-	-	-		
E-III		OCH_3	OCH_3	>500	12	>500	26	75	2	> 1	>160	> 1	16	A	95
E-IV		OC_2H_5	OC_2H_5	115	12	180	25.5	>250	13.2	> 1	>160	> 1	>160	A	94
E-V		OC_3H_7	OC_3H_7	>500	240	>500	>500	>250	>250	4.2	-	50	-	A	-
E-VI		OCH_3	OC_2H_5	400	30	>500	55	>250	155	5.1	75	11	34	B	83-4
F-I*	$C(CH_3)_3$	Cl	Cl	85	15.5	240	105	70	55	0.39	-	-	-		
F-II*		CH_3	CH_3	1250	37.5	-	-	>250	>250	> 1	-	> 1	-		
F-III*		OCH_3	OCH_3	95	19	62.5	12	17.5	5.75	0.36	> 22	0.85	4.5		
F-IV*		OC_2H_5	OC_2H_5	37.5	9	40	18	100	92.5	0.267	> 16	0.01	1.2		
F-V		OC_3H_7	OC_3H_7	>500	>500	>500	>500	>250	>250	0.6	>160	> 10	>160	A	-
F-VI		OCH_3	OC_2H_5	38.5	14.5	70	37	45	37.5	0.18	65	0.15	21	B	36
F-VII		OC_2H_5	OC_3H_7	240	130	310	190	>250	>250	0.35	>160	0.29	>160	B	-
G-I*	CH_2Cl	CH_3	CH_3	>500	>500	>500	>500	>250	>250	4.1	>160	2.1	>160		
G-II*		OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	3.5	>160	> 10	>160		
G-III		OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	>250	>10	>160	> 10	>160	A	48-50
G-IV		OC_3H_7	OC_3H_7	>500	>500	>500	>500	>250	>250	>10	>160	> 10	>160	A	-
H-I	CH_2CH_3	OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	0.35	>160	19	>160	A	-
H-II		OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	>250	5	>160	4	>160	A	28
H-III		OC_3H_7	OC_3H_7	>500	390	>500	>500	>250	>250	>10	>160	> 10	>160	A	28
I-I	CH_2Br	CH_3	CH_3	>500	>500	>500	>500	>250	>250	5.5	>160	30	>160	A	-
I-II		OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	6.6	>160	> 10	>160	A	-
I-III		OC_2H_5	OC_2H_5	>500	460	>500	>500	>250	>250	3	>160	> 10	>160	A	43-4
J-I	$CHBrCH_3$	Cl	Cl	>500	500	>500	500	250	>250	.075	>160	.5	>160	A	65-7
J-II		OCH_3	OCH_3	>500	500	>500	>500	75	75	.93	>160	> 1	22	A	72
J-III		OC_2H_5	OC_2H_5	37	10	185	60	45	4	.058	4.3	.063	3.7	A	50
K-I*	$CHBr_2$	OCH_3	OCH_3	>500	>500	>500	>500	90	47.5	.175	>160	5	>160		
K-II*		OC_2H_5	OC_2H_5	150	110	>500	500	7.25	3.5	.038	>160	.048	3.9		
K-III		OC_3H_7	OC_3H_7	65	15.5	>500	27.5	70	26.25	.083	>160	.175	11	A	62
K-IV		OC_4H_9	OC_4H_9	>500	>500	>500	>500	>250	>250	>10	>160	> 10	>160	A	-
L-I *	CBr_3	OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	200	1.5	>160	3	>160		
M-I	$CH(CH_3)C_2H_5$	OC_2H_5	OC_2H_5	67.5	42	170	120	>250	91.25	0.125	>160	0.09	70	C	-
N-I	$CH(CH_3)C_3H_7$	OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	>10	>160	> 10	>160	A	-
N-II		OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	>250	2	>160	> 10	>160	A	-
O-I	$CH(C_2H_5)_2$	OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	>10	>160	> 10	>160	A	-
O-II		OC_2H_5	OC_2H_5	150	85	>500	200	>250	>250	.55	>160	> 1	>160	A	44
P-I	$CHClC_2H_5$	OC_2H_5	OC_2H_5	23	16.3	45	20.5	45	15	0.038	>160	0.074	36	A	35-6
DDT *	CCl_3	Cl	Cl	14	5.5	170	40	11.5	8.25	0.07	6.9	0.015	0.23		

* not a novel analog ; see methods and materials.

Table 3. Summary of Hut Tests with DDT and Analogues Against *Anopheles albimanus*

Compound	Duration 70% kill months */	Per Cent in Window Traps highest	lowest	average
$ClC_6H_4HCCl_3.C_6H_4Cl$ (DDT)	22	54	0	24
$CH_3OC_6H_4HCCl_3.C_6H_4OCH_3$ (methoxychlor)	20	59	0	23
$C_2H_5OC_6H_4HCCl_3.C_6H_4OC_2H_5$ (ethoxychlor)	28	50	1	21
$C_2H_5OC_6H_4HCCl_3.C_6H_4CH_3$ (DTDT, OMS-1476)	13	44	0	19
$CH_3OC_6H_4HCCl_3.C_6H_4CH_3$ (OMS-1406)	30	73	0	20
$CH_3OC_6H_4HCCl_3.C_6H_4SCH_3$ (OMS-1395)	0.1	34	4	20
$CH_3C_6H_4HCCl_3.C_6H_4Cl$ (OMS-1425)	21	41	0	18
$C_2H_5OC_6H_4HCCH(CH_3)_2.C_6H_4OC_2H_5$ (DEIB, OMS-1856)	35	25	0	9
$C_2H_5OC_6H_4HCCHCl(CH_3).C_6H_4OC_2H_5$ (DECP, OMS-1715)	27	66	6	26

* Total 24 hour mortality in hut plus in window traps.

Table 4. Degradation of 1,1-bis-(p-ethoxyphenyl)-isobutane in Susceptible and DDT Resistant House Fly at 24 hours.

		Percent total ^{14}C			
		S_{NAIDM}		R_{sp}	
		homogenate	excreta	homogenate	excreta
6.45% wash, 49.74% excreta, 31.39% homogenate, 12.42% unextractable = 81.80% recovery				4.49% wash, 60.28% excreta, 36.76% homogenate, 16.88% unextractable = 97.88% recovery	
$EtOC_6H_4HCCHMe_2 \cdot C_6H_4OEt$	(R_f 0.91) 1/	11.56	2.95	9.20	4.65
$EtOC_6H_4C(OH)CHMe_2 \cdot C_5H_4OEt$	(R_f 0.60)	0.84	0.90	0.66	0.53
$EtOC_6H_4C(O) \cdot C_6H_4OEt$	(R_f 0.58	0.66	0.88	2.15	--
$EtOC_6H_4HCC(OH)Me_2 \cdot C_6H_4OEt$	(R_f 0.55)	0.73	0.83	1.62	0.65
$EtOC_6H_4HCCHMe_2 \cdot C_6H_4OH$	(R_f 0.49)	1.54	1.91	1.60	2.61
Unknown	(R_f 0.43)	0.87	1.01	0.09	0.62
Unknown	(R_f 0.38)	0.09	1.02	0.08	--
$EtOC_6H_4HCCH(Me)CH_2OH \cdot C_6H_4OEt$	(R_f 0.32	1.07	0.85	1.42	0.55
Unknown	(R_f 0.28)	1.09	1.37	0.95	1.46
$HOC_6H_4HCCHMe_2 \cdot C_6H_4OH$	(R_f 0.21)	2.50	3.54	2.27	4.69
Unknown	(R_f 0.09)	--	0.95	0.80	--
Unknown	(R_f 0.06)	0.14	0.51	0.64	0.36
$HOC_6H_4C(O) \cdot C_6H_4OH$	(R_f 0.05)	0.93	0.7	0.82	0.55
$HOC_6H_4HCC(O)OH \cdot C_6H_4OH$	(R_f 0.03)	1.15	2.25	1.45	4.27
Polar	(R_f 0.0)	5.15	29.73	4.08	28.86

Table 5. Distribution of Radioactivity in Susceptible and Resistant House Fly Treated Topically with 1,1-bis-(p-ethoxyphenyl)-isobutane ^{14}C recovered after 24 hours as parent compound.

	S_{NAIDM}		R_{sp}	
	µg	percent	µg	percent
body				
wash	0.0526 µg	7.37%	0.0364 µg	4.49%
acetonitrile	0.2172 µg	30.30%	0.2379 µg	29.23%
acid hydrolysis	0.0156 µg	2.2%	0.0366 µg	4.49%
aqueous	0.024 µg	3.37%	0.0124 µg	1.52%
unextractable	0.1017 µg		0.1653 µg	
sub total	0.4110 µg		0.4886 µg	
excreta				
methanol	0.3859 µg	53.86%	0.4745 µg	58.34%
acid hydrolysis	0.0183 µg	2.55%	0.0126 µg	
aqueous	0.0027 µg	0.34%	0.0031 µg	
sub total	0.4069 µg		0.4902 µg	
total revovery	0.8179 µg		0.9788 µg	

Table 6. Metabolism of 1,1-bis-(p-ethoxyphenyl)-isobutane in Susceptible House Fly Pretreated with 25 μg Piperonyl Butoxide

		Percent Total ^{14}C S_{NAIDM}	
		homogenate	excreta
31.23% wash, 1.20% excreta, 56.16% homogenate, 13.01% unextractable = 101.60% recovery			
$EtOC_6H_4HCCHMe_2C_6H_4OEt$	(R_f 0.95) 1/	63.23	1.09
Polar conjugates	(R_f 0.0)	0.10	0.24

1/ TLC with n-pentane, diethyl ether, acetone, acetic acid - 122, 20, 14. 4

Table 7. Metabolism of 1,1-bis-(p-ethoxyphenyl)-isobutane in Salt Marsh Caterpillar and Mexican Bean Beetle

		Percent Total ^{14}C			
		salt marsh caterpillar		Mexican bean beetle	
		homogenate	excreta	homogenate	excreta
		11.95% wash		4.59% wash	
$EtOC_6H_4HCCHMe_2 \cdot C_6H_4OEt$	(R_f 0.91) 1/	22.48	37.84	53.51	30.94
$EtOC_6H_4C(OH)CHMe_2 \cdot C_6H_4OEt$	(R_f 0.60)	0.38	2.06	--	--
$EtOC_6H_4C(O)C_6H_4OEt$	(R_f 0.58)	0.41	1.92	0.27	0.30
$EtOC_6H_4HCC(OH)Me_2 \cdot C_6H_4OEt$	(R_f 0.55)	0.34	1.85	0.07	--
$EtOC_6H_4HCCHMe_2 \cdot C_6H_4OH$	(R_f 0.44)	0.36	2.69	0.75	--
$EtOC_6H_4HCCH(Me)CH_2OH \cdot C_6H_4OEt$	(R_f 0.32)	--	--	0.40	0.04
Unknown	(R_f 0.28)	--	--	0.22	--
$HOC_6H_4HCCHMe_2 \cdot C_6H_4OH$	(R_f 0.21)	0.32	1.74	0.07	0.49
$HOC_6H_4C(O)C_6H_4OH$	(R_f 0.05	0.12	0.76	--	--
$HOC_6H_4HCC(O)OH \cdot C_6H_4OH$	(R_f 0.03)	--	0.08	--	--
Polar	(R_f 0.0)	0.34	13.70	2.23	1.23
Unextractable		0.66	--	4.80	--

1/ TLC with n-pentane, diethyl ether, actone, acetic acid - 122, 20, 14, 4

Table 8. Metabolism of 1,1-bis-(p-ethoxyphenyl)-isobutane in *Anopheles stephensi* larvae

		Percent Total ^{14}C recovered in	
			water
		2.08% - wash	
$EtOC_6H_4HCCHMe_2 \cdot C_6H_4OEt$	(R_f 0.91) 1/	2.49	66.97
$EtOC_6H_4HCC(OH)Me_2 \cdot C_6H_4OEt$	(R_f 0.55)	0.16	--
$EtOC_6H_4HCCHMe_2 \cdot C_6H_4OH$	(R_f 0.49)	0.87	1.46
$EtOC_6H_4HCCH(Me)CH_2OH \cdot C_6H_4OEt$	(R_f 0.32)	0.14	--
$EtOC_6H_4HCC(O)OMe \cdot C_6H_4OEt$	(R_f 0.25)	0.23	--
$HOC_6H_4HCCHMe_2 \cdot C_6H_4OH$	(R_f 0.21)	1.23	2.28
$HOC_6H_4C(O) \cdot C_6H_4OH$	(R_f 0.08)	0.48	3.34
$HOC_6H_4C(O)OH \cdot C_6H_4OH$	(R_f 0.03)	0.67	2.04
Polar conjugates	(R_f 0.0)	1.95	6.58
Unextractable		8.05	--

1/ TLC with n-pentane, diethyl ether, acetone, acetic acid - 122, 20, 14, 4

Table 9. Elimination of ^{14}C Degradation Products from Female Swiss Mice Treated Orally with 50 mg per kg Diethoxyphenyl Isobutane

percent elimination ^{14}C

	mouse I			mouse II		
	urine	feces	total	urine	feces	total
day 1	23.63	5.34	28.97	30.92	4.40	35.35
2	34.75	12.35	41.1	43.9	26.67	70.57
3	39.05	21.66	60.71	46.56	36.06	82.62
4	40.64	23.48	64.12	48.06	37.66	85.72
5	41.87	24.87	66.74	48.63	38.15	86.78
6	42.62	25.43	68.05	49.00	38.59	87.59
7	43.01	25.79	68.8	49.21	38.86	88.07
8	43.39	26.08	69.47	49.47	38.99	88.46
9	43.72	26.25	69.95	49.68	39.04	88.72
10	43.72	26.26	69.96	49.71	39.05	88.76

10 day average - two mice: urine 46.72%, feces 32.65% = total 79.37%

Table 10. Metabolism of ^{14}C 1,1-bis-(p-ethoxyphenyl)-isobutane in Mouse

		Percent total radioactivity recovered in			
		Urine (62.20% ^{14}C)		Feces (37.80% ^{14}C)	
		hexane	polar	hexane	polar
		0.47%	99.53%	58.70%	41.30%
$EtOC_6H_4HCCHMe_2.C_6H_4OEt$ 2/	(R_f 0.91) 1/	0.46	0.67	5.78	1.73
Unknown	(R_f 0.70)	-	-	0.26	-
$EtOC_6H_4C(OH)CHMe_2.C_6H_4OEt$ 3/	(R_f 0.60	-	-	0.30	0.19
$EtOC_6H_4C(O).C_6H_4OEt$ 3/	(R_f 0.58)	-	-	0.26	0.21
$EtOC_6H_4HCC(OH)Me_2.C_6H_4OEt$ 3/	(R_f 0.55)	-	-	0.84	0.33
$EtOC_6H_4HCCHMe_2.C_6H_4OH$ 3/	(R_f 0.49)	-	0.42	39.68	2.52
Unknown	(R_f 0.43)	-	1.03	-	1.29
Unknown	(R_f 0.38)	-	0.79	-	0.62
$EtOC_6H_4HCCH(Me)CH_2OH.C_6H_4OEt$ 2/	(R_f 0.32)	-	0.61	7.81	0.64
$EtOC_6H_4HCCH(Me)C(O)OMe.C_6H_4OH$ 2/	(R_f 0.25)	-	0.89	0.82	0.66
Unknown	(R_f 0.21)	-	1.23	0.17	0.69
$HOC_6H_4HCCHMe_2.C_6H_4OH$ 3/	(R_f 0.17)	-	2.66	1.04	18.40
Unknown	(R_f 0.15)	-	1.29	0.26	0.78
$EtOC_6H_4HCCH(Me)C(O)OH.C_6H_4OEt$ 2/	(R_f 0.10)	-	3.87	0.36	4.12
$HOC_6H_4C(O)C_6H_4OH$ 3/	(R_f 0.05)	-	1.49	0.26	2.00
$HOC_6H_4HCC(O)OH.C_6H_4OH$ 3/	(R_f 0.03)	-	5.94	0.43	2.17
Polar conjugates	(R_f 0.0)	0.01	78.64	0.43	4.96

1/ TLC with n-pentane, diethyl ether, acetone, acetic acid - 122, 20, 14,4
2/ identity by mass spectrometry
3/ identity by co-chromatography

Table 11. Environmental Fate of ^{14}C-1,1-bis-(p-ethoxyphenyl)-isobutane in a Terrestrial-Aquatic Model Ecosystem.

		H_2O	Oedogonium (alga)	Physa (snail)	Culex (mosquito)	Gambusia (fish)
Total ^{14}C		0.01633	0.7719	29.4129	9.6809	0.7096
$EtOC_6H_4HCCHMe_2.C_6H_4OEt$	(R_f 0.91) 1/	0.00036	0.6692	25.9245	8.3885	0.2737
$EtOC_6H_4HCCHMe_2.C_6H_4OH$	(R_f 0.49)	0.00095	0.0556	0.8706	0.0949	0.0986
$EtOC_6H_4HCCH(Me)CH_2OH.C_6H_4OEt$	(R_f 0.32)	0.00027	0.0054	0.0412	0.2062	0.0133
Unknown	(R_f 0.25)	0.00002	--	--	--	--
Unknown	(R_f 0.22)	0.00005	--	--	--	--
Unknown	(R_f 0.20)	0.00022	0.0051	0.1500	0.2081	0.0085
$HOC_6H_4HCCHMe_2.C_6H_4OH$	(R_f 0.17)	0.00181	0.0021	1.8393	0.1143	0.0161
$EtOC_6H_4HCCH(Me)C(O)OH.C_6H_4OEt$	(R_f 0.10)	0.00016	0.0087	--	--	--
$HOC_6H_4HCC(O).C_6H_4OH$	(R_f 0.05)	0.00043	0.0021	0.1177	0.1016	0.0067
$HOC_6H_4HCC(O)OH.C_6H_4OH$	(R_f 0.03)	0.00028	0.0012	0.1088	0.1539	0.0038
Polar	(R_f 0.0)	0.00746	0.0225	0.3608	0.4134	0.2889
Unextractable		0.00432	1.2922	3.8340	0.6087	0.3927

1/ TLC with n-pentane, diethyl ether, acetone, acetic acid - 122, 20, 14, 4

Table 12. Comparison of the Model Ecosystem Parameters of Ecological Magnification (E.M.) and Biodegradability Index (B.I.) for DDT, Ethoxychlor and Two Biodegradable Analogues.

		snail	mosquito	fish
DDT	E.M.	34,500	8182	84,500
	B.I.	0.045	0.203	0.015
Ethoxychlor	E.M.	97,645	1513	1536
	B.I.	0.39	0.133	2.69
Methyl Ethoxychlor 1/	E.M.	42,000	916	400
	B.I.	0.25	0.92	1.20
Diethoxyphenyl Isobutane 2/	E.M.	72,012	23,301	760
	B.I.	0.134	0.154	1.59

1/ $CH_3C_6H_4HCCCl_3 \cdot C_6H_4OEt$

2/ $EtOC_6H_4HCCHMe_2 \cdot C_6H_4OEt$

Table 13. LD_{50} Values from Topical Application of DDT and Analogues

insect	topical LD_{50} micrograms per gram DDT	methoxychlor	ETDT 1/	DECP 2/	DEIB 3/	DEtCP 4/
German cockroach (*Blattella germanica*)-female	9508	11,311	21,311	1586	5295	820
-male	115	1064	897	109	162	128
Mexican bean beetle (*Epilachne varivestis*	10,471	5236	1469	47.7	74.6	
Japanese beetle (*Popillia japonica*)	19.5	151.5		5.0	521.6	
Northern corn rootworm (*Diabrotica longicornis*)	4.4	11.3	24.7	20.6	23.6	32.3
Southern corn rootworm (*Diabrotica undecimpunctata*	39.6	25.0	58.3	42.5	68.8	
Western corn rootworm (*Diabrotica virgifera*)	5.2	19.5	29.0	13.6	40.8	85.7
Striped cucumber beetle (*Acalymma vittata*)	10.1	14.0	21.1	14.0	15.4	
Milkweed bug (*Oncopeltus fasciatus*)	2363	5636	31,272	21.8	13,818	2618
House Fly (*Musca domestica* (S_{NAID})	14.0	45.0	9.0	9.5	21.5	20.0
(R_{SP})	170	48.0	27.0	18.0	38.0	30.0
Black blow fly (*Phormia regina*)	11.5	10.0	5.2	4.6	14.5	75.0
Drug store beetle (*Stegobium paniceum*)	1728	2357	1886	2200	786	1886
Lady bird beetle (*Coleomegilla fascilabris*)	4.7	13.7	57.5	1.1	39.7	1.4
Mucidifurax raptor (House fly parasite)	5.7	47.1	1728	2.2	2.1	12.6

1/ ETDT is 1-(*p*-ethoxyphenyl)-1-tolyl-2,2,2-trichloroethane (OMS-1476)
2/ DECP is 1,1-bis-(*p*-ethoxyphenyl)-2-chloropropane (OMS-1715)
3/ DEIB is 1,1-bis-(*p*-ethoxyphenyl)-isobutane (OMS-1856)
4/ DEtCP is 1,1-bis-(*p*-ethylphenyl)-2-chloropropane (OMS-1980)

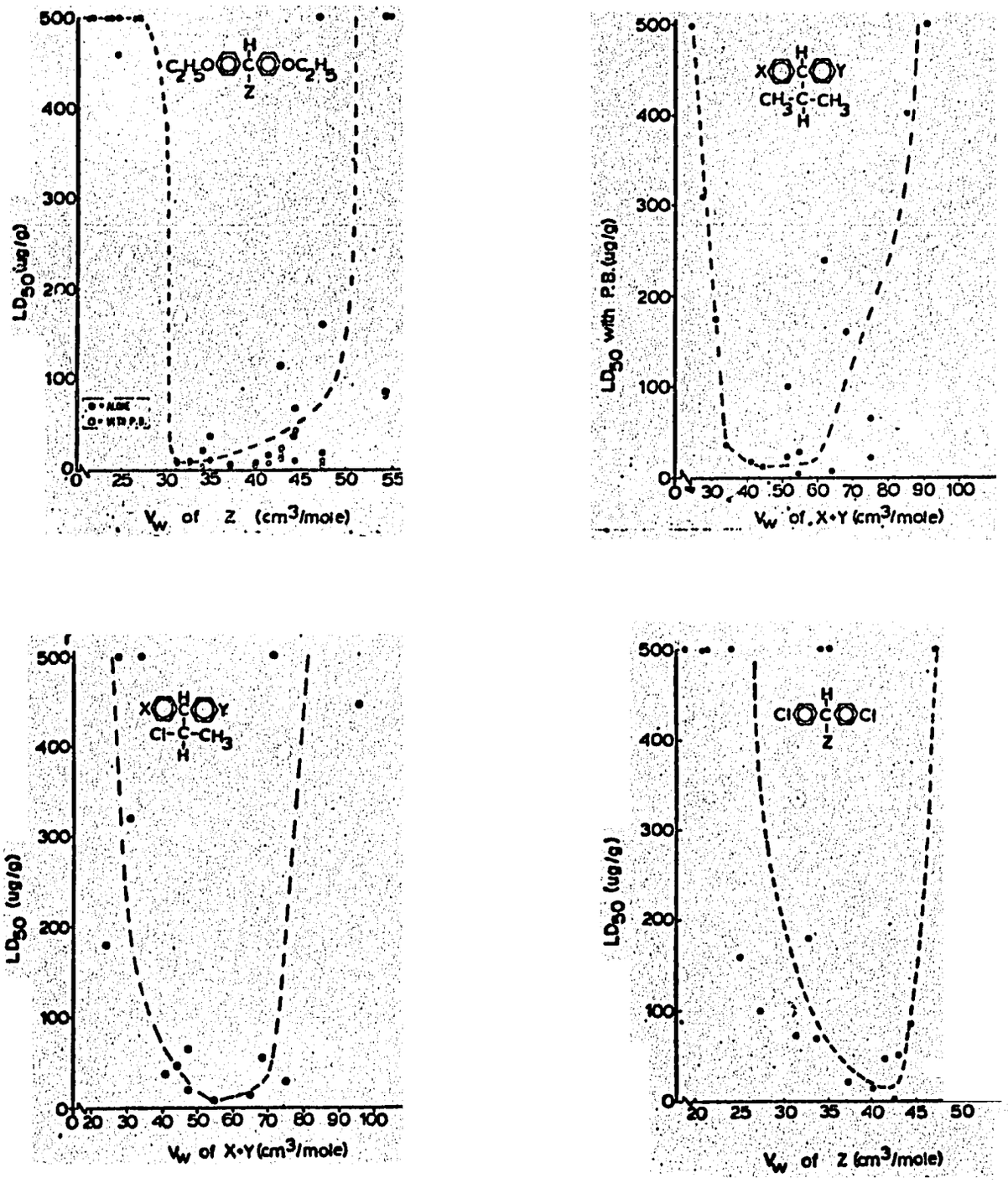


Figure 1. Relation of van der Waals volumes for indicated substituents to LD_{50} to the house fly (Coats et al 1977)

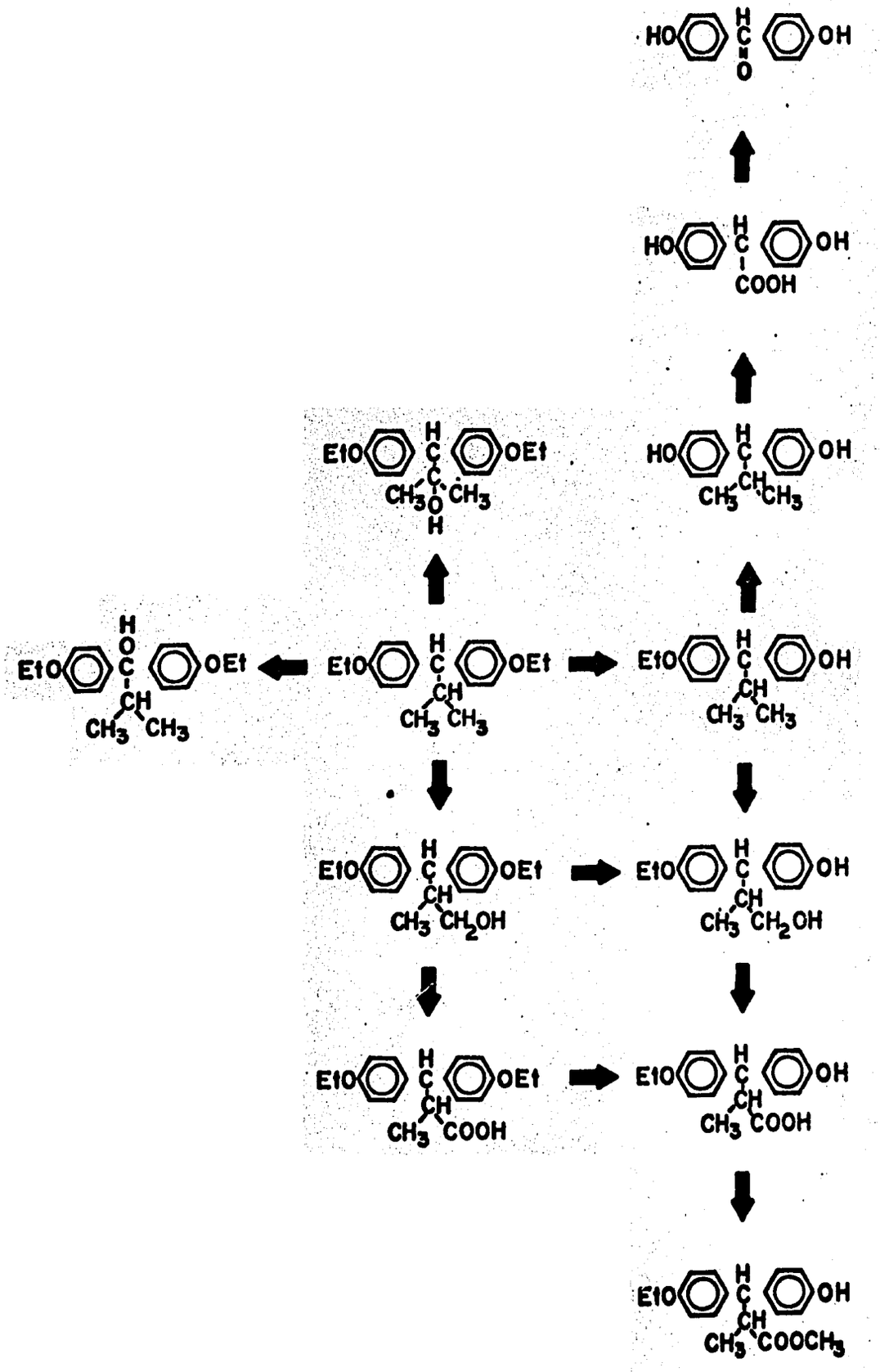


Figure 2. Degradation pathways for 1,1-bis-(p-ethoxyphenyl)-isobutane.