Journal of Agricultural and Food Chemistry

Volume 21, Number 4 July/August 1973

A Century of DDT

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In the nearly 100 years that have elapsed since DDT was first synthesized, this substance has had an influence on human ecology perhaps unmatched by any other synthetic substance. Through its effectiveness in the conquest of malaria, typhus, and other insect-borne diseases it has played a decisive role in the population explosion. It has also become the classic example of an environmental micropollutant. Significant discoveries about the chemistry of DDT and its analogs are still being made. These have considerable theoretical interest in studies of the enigmatic mode of action of DDT and are of applied interest in control of resistant insects and in environmental quality control.

It is now almost exactly a hundred years since Othmar Zeidler synthesized the first molecules of DDT (2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane) in the laboratory of Professor Adolf von Baeyer at the University of Strassburg by the Baeyer Condensation between chlorobenzene and chloral in the presence of sulfuric acid (Zeidler, 1874). In the interim, this pleasant smelling, greasy white powder has had an influence on human ecology perhaps unmatched by any other chemical discovery including gunpowder, sulfanilamide, penicillin, and plutonium. Significant discoveries about the chemistry of DDT and its analogs and about their biological effects are still being made and it seems appropriate to review them here with the conviction that "the past is prologue." Surely if we are to have better insecticides in the future they will be constructed on the foundation, imperfect though it may be, that DDT has built.

Although the synthesis of DDT was an important part of the production of his Inaugural Dissertation for the Ph.D. degree in 1873, "Uber Verbindungen von Chloral mit Brom und Chlorbenzol," Zeidler received little else from it and ended his career as an apothecary in Vienna. His mentor, Adolf von Baeyer, became the foremost chemist of the age and received the Nobel Prize in 1905 "in recognition of his services in the development of organic chemistry and the chemical industry through his work on organic dyes and hydroaromatic combinations."

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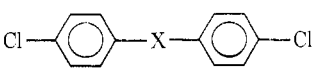
One wonders how the stream of history through the Franco-Prussian War, World War I, and the collapse of the Balkans and of Czarist Russia and that of Mainland China might have been altered had a stray insect crawled upon Zeidler's pile of shining crystals and the chemist had gained an inkling of the enormous powers of the insecticide in controlling typhus, malaria, plague, and the other vector-borne diseases of man. von Baeyer would have enjoyed the prestige of the discovery of DDT's outstanding insecticidal properties. However, it was not to be, and the compound slumbered on the shelf for another 65 years.

DDT was recreated on September 25, 1939, in the laboratories of J. R. Geigy A. G., a venerable Swiss dyestuff manufacturer. Dr. Paul Müller had begun a methodical investigation of compounds of the general formula



X = O, S, NH, SO, SO_2, C

recognizing that such compounds were effective stomach poisons against clothes moths and carpet beetles. Seeking a more general contact poison he repeated Zeidler's synthesis and found that the compound *d*ichloro*d*iphenyl*t*richloroethane or DDT was astonishingly effective against *Calliphora* flies and to a variety of other insects, including mosquitoes and the Colorado potato beetle *Leptinotarsa decemlineata* (Müller, 1955). The magnitude of his discovery (Swiss Patent, 1940) is measured by the award of the Nobel Prize in 1948 "for your discovery of the strong action of DDT against a wide variety of arthropods."

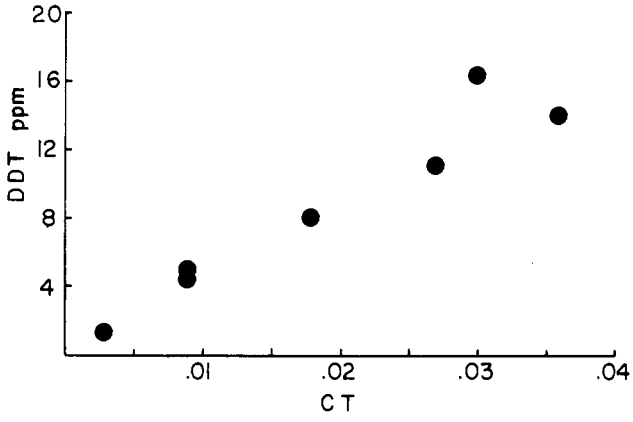


Figure 1. Storage of DDT by green sunfish (ppm) as function of concentration in water (ppm) × days of exposure (CT). Data from Reinbold *et al.* (1971).

DDT's insecticidal properties were discovered in a world just plunged into the catastrophe of World War II. Military sanitarians had grim memories of the ravages of louse-borne typhus which, in World War I, had been a critical factor in the fortunes of the Central powers in the Balkans and on the Eastern Front. The rapid enlargement of the conflict of World War II into Greece, North Africa, and later to the South Pacific focused attention on mosquito-borne diseases such as malaria, dengue fever, and filariasis. Thus there was immediate interest in a cheap synthetic chemical which was safe to apply directly to human bodies and was so persistent that it killed mosquitoes in treated houses for months after application. DDT's use resulted in the conquest of typhus in Naples in 1943 and in the eradication of malaria from the Latina Province of Italy and in Sardinia beginning in 1945 (Simmons, 1959). For the first time in history man had a safe, cheap, and durable weapon which could not only control but could often eradicate enclaves of vector-borne diseases. The World Health Assembly in 1955 proposed the global eradication of malaria by DDT residual house spraying and by 1972 malaria had been pronounced eradicated in 37 countries with a total population of 728 million and under complete or partial control in another 80 countries where 618 million persons are protected (WHO, 1972). In India, as an example, DDT residual spraying decreased the cases of malaria from 100 million annually in 1933–1935 to 150,000 by 1966, and decreased deaths from 750,000 annually to 1500 (WHO, 1968). The use of DDT in public health introduced "death control" on a global scale and it is estimated that DDT has saved approximately 50 million human lives and averted more than 1 billion human illnesses (see Knipling, 1953). In India during the malaria eradication program, human life expectancy increased from 32 years in 1948 to 52 years in 1970 (India News, December 1970). Death control from the use of DDT is perhaps the most important single factor in the world "population explosion."

DDT has also had signal success in the control of insect pests of agriculture. More than 4 billion pounds have been used for insect control since 1940, about 80% in agriculture, and production in the United States reached a peak of about 160 million pounds in 1961. In this period DDT was registered for use in the United States on 334 agricultural commodities. It gave phenomenal results in controlling insects such as those attacking the potato, and yields in New York and Wisconsin increased from 56 to 68% over those previously obtained with the best protection from lead arsenate and bordeaux mixture (Metcalf, 1965). DDT became the standard remedy for the control of such major pests as the codling moth, *Carpocapsa pomonella*, attacking deciduous fruits and the pink bollworm, *Pectinophora gossypiella*, attacking cotton. For the first time it was possible to control the two great defoliators of American forests, the gypsy moth, *Porthetria dispar*, and the spruce budworm, *Choristoneura fumiferana*. DDT became a household word for the control of insect pests of vegetable and flower gardens and as a home mothproofing agent against clothes moths and carpet beetles.

DDT AS AN ENVIRONMENTAL POLLUTANT

The very factors that make DDT such an effective insecticide, its low vapor pressure (1.5×10^{-7} mm at 20°), its stability to photooxidation, its high fat solubility (*ca.* 100,000 ppm), and its low water solubility (0.0012 ppm at 25°) (Bowman *et al.*, 1960) have resulted in DDT becoming the prototype environmental micropollutant. As a result of the enormous worldwide production and of the stability of its primary degradation product DDE (2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethylene), which has almost identical chemical properties (water solubility 0.0013 ppm; Metcalf *et al.*, 1973), DDT and its degradation products are found everywhere in the global environment. The average U. S. inhabitants have 2.3–4.0 ppm of DDT and 4.3–8.0 ppm of DDE stored in their body fat and those of India, where usage is higher, have 16 ppm of DDT and 10 ppm of DDE. Even Eskimos have 0.8 ppm of DDT and 2.2 ppm of DDE (Durham, 1969), although they use none in their native habitat. DDT and DDE are concentrated in organisms of the trophic webs, increasing roughly tenfold in concentration stored in lipids and in percentage of DDE at each trophic level (Woodwell *et al.*, 1967). As an example, Harrison *et al.* (1970) have recorded the average level of DDT in Lake Michigan water as 0.000002 ppm, in amphipods as 0.410 ppm, in fish such as coho salmon and lake trout as 3–6 ppm, and in herring gulls, at the top of the food chain, as 99 ppm. Thus the overall concentration from water to gull is about 1×10^7.

Over wide limits, the storage of DDT in fat of laboratory animals and humans is directly proportional to intake (Mrak, 1969), although it appears that a plateau level is eventually attained. Warm-blooded animals slowly metabolize and excrete stored DDT, and its biological half-life in humans is about 0.5 years. The processes of accumulation are especially dramatic in fish and other aquatic poikilotherms where rates of detoxication and elimination are very low. Accumulation in the green sunfish *Lepomis cyanellus*, for example, is proportional to the concentration in water × time of exposure or CT (Figure 1). A highly significant correlation ($r = 0.94$) has been found between the age of lake trout, *Salvelinus namaycush*, and total body residues of DDT, DDE, and DDD, which ranged from about 1 ppm at 1 year to as much as 28 ppm at 11 to 12 years of age (Youngs *et al.*, 1972). This long-term accumulation in fish, together with the very long water retention times in the Great Lakes such as Michigan (30.8 years) and Superior (189 years), makes their contamination with micropollutants such as DDT a major disaster for which no apparent solution exists (Rainey, 1967).

Despite the very high rates of usage of DDT over the past 44 years, knowledge of its degradative pathways in the living and nonliving environment has been obtained very slowly and major discoveries are still being made. The microsomal oxidation of DDT at the α-carbon to dicofol or 4,4′-dichloro-α-trichloromethylbenzhydrol was first described in *Drosophila melanogaster* by Tsukamoto (1959). The pathway by reductive dechlorination to form DDD (2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethane) was first elucidated in yeast (Kallman and Andrews, 1963) and later in the rat (Datta *et al.*, 1964; Peterson and Robinson, 1964). A major new anaerobic degradation product DDCN (bis-(*p*-chlorophenyl)acetonitrile) has been identified only within the past year (Albone *et al.*, 1972; Jensen

et al., 1972). The degradative pathways of DDT are shown in Figure 2.

DDT ANALOGS AND INSECT RESISTANCE

Insect resistance to DDT and its analogs is one of the most interesting of the biochemical phenomena involved in pesticide action and has played a critical role not only in the use of DDT for insect control but also in the development of the other insecticides of the past 25 years. *Time* magazine (1947) described a DDT offensive as "No Flies in Iowa," and the *Readers Digest* (Arundel, 1948) had an article "Entire Towns Abolish Flies." Had DDT's activity in the control of insect pests continued undiminished, these and similar prophecies about insect extermination might have materialized. However, the very widespread usage of DDT exercised a marked degree of selection on naturally occurring mutant forms of insects and resistant races were developed through accelerated microevolution. Brown and Pal (1971) present a thorough description of DDT resistance and its physiological and genetic background and point out that over the 25 years since DDT resistance was first demonstrated in the housefly and *Culex molestus* in Italy, a total of 98 species of economically important insects have become resistant to this insecticide. These include 14 species of *Anopheles* vectors of malaria, the human body louse, *Pediculus humanus,* vector of typhus, the oriental rat flea, *Xenopsylla cheopis,* vector of plague and four other fleas, 18 species of culicine mosquitoes including *Culex fatigans* vector of filariasis, *Culex tarsalis* vector of western equine encephalitis, *Aedes aegypti* vector of yellow fever, *Simulium* blackflies, and the human bedbug, *Cimex lectularius,* and its tropical cousin *C. hemipterus.*

Among agricultural pests (Brown, 1971), 27 species have developed DDT resistance, including such destructive forms as the pink bollworm, *Pectinophora gossypiella,* the Colorado potato beetle, *Leptinotarsa decemlineata,* the corn earworm, *Heliothis zea,* the cabbage looper, *Trichoplusia ni,* the imported cabbageworm, *Pieris rapae,* the beet armyworm, *Spodoptera exigua,* and the green peach aphid, *Myzus persicae.* DDT resistance has virtually eliminated successful area chemical control of the housefly, adversely affected the global malaria eradication program of WHO, jeopardized the control of other vector-borne diseases and of pest mosquitoes, and caused many serious problems in the control of agricultural pests.

The genetics of DDT resistance are too complex to describe here (see Brown and Pal, 1971). In the housefly a dominant gene on chromosome II controls the production of an enzyme DDT'ase which functions to dehydrochlorinate DDT to the noninsecticidal DDE. A recessive gene on chromosome III also contributes to dehydrochlorination and a gene on chromosome V determines the conversion by microsomal oxidation of DDT to polar metabolites such as α-hydroxy-DDT or dicofol (Figure 2).

Although the original workers with metabolism of DDT in resistant houseflies were able to demonstrate only the metabolism of DDT to DDE (Perry *et al.*, 1955; Sternburg and Kearns, 1950), Tsukamoto (1961) showed the presence of the α-hydroxy derivative dicofol, and with modern tlc and radioisotope techniques it is now apparent that relatively large amounts of this compound may be produced. In the R_{SP} housefly, for example, after treatment with ^{14}C-DDT, the excreta contained 40% DDT, 35.3% DDE, 30.9% dicofol, and 30.5% conjugates (Kapoor *et al.*, 1970). Therefore it is not surprising that pretreatment of R_{SP} houseflies with 50 μg of the microsomal oxidase inhibitor piperonyl butoxide decreased the LD_{50} from 170 to 40 μg/g (Kapoor *et al.*, 1970).

DDT'ase. Recognition of dehydrochlorination of DDT to DDE as a major biochemical step in the insect resistance mechanism led to studies on enzymatic dehydrochlorination in the housefly (Sternburg *et al.*, 1954). The enzyme DDT-dehydrochlorinase (DDT'ase) was concentrated by $(NH_4)_2SO_4$ precipitation and dialysis and was found to have optimum pH 7.4, temperature 35–37°, and to require glutathione as a cofactor (Sternburg *et al.*, 1954). Lipke and Kearns (1959) achieved a 46,000-fold purification of DDT'ase and found it to be a simple protein with a molecular weight of 36,000 and an isoelectric point of 6.5.

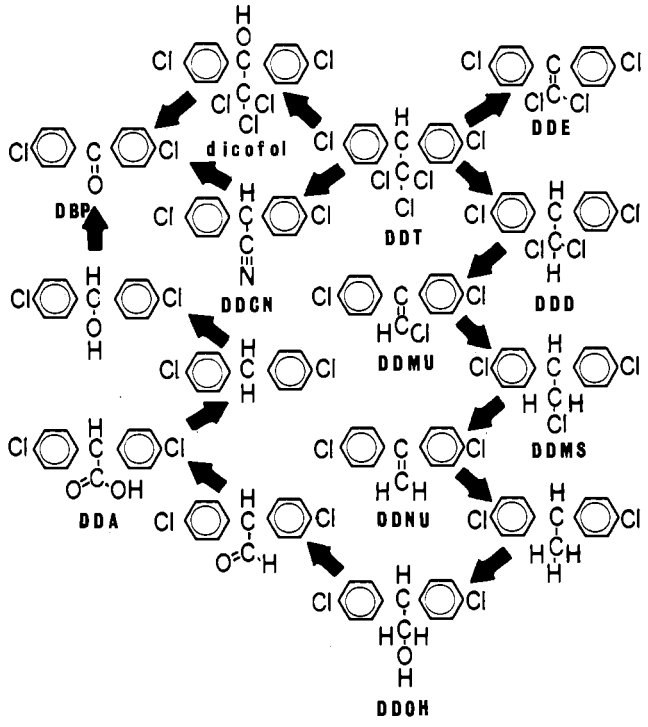
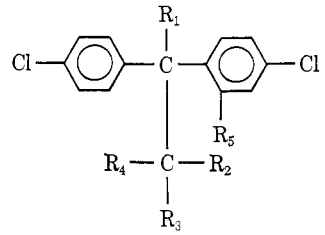


Figure 2. Degradative pathways of DDT in the environment.

"Resistance Proof Analogs." The identification of DDT'ase as a critical factor in DDT resistance in the housefly suggested chemical means for "resistance-proofing" of DDT analogs. The dehydrochlorination mechanism is an E_2-type elimination controlled by the availability of electrons at the α-carbon of the DDT-type molecule. The rate of OH^--catalyzed dehydrochlorination of various *p,p'*-disubstituted DDT analogs is therefore controlled by the polar nature of the aromatic substituents, as they affect the availability of electrons at the α-carbon (Cristol, 1945). The *in vivo* resistance mechanism in the DDT-resistant fly must be similar, as shown by the deuterium isotope effect resulting from replacement of α-H with α-D to form α-deutero-DDT (II). In OH^--catalyzed dehydrochlorination, α-D-DDT ($k \times 10^5 = 8.9 \times 10^2$ l./min/mol) reacted only 0.14 as rapidly as DDT ($k \times 10^5 = 6.1 \times 10^3$) for a deuterium isotope effect of 6.8 (Metcalf and Fukuto, 1968), indicating the primary role of the α-H in dehydrochlorination. Studies of the comparative toxicity of DDT and α-deutero-DDT to houseflies have shown deuterium isotope effects of 1.25–1.5 (Barker, 1960; Moorefield *et al.*, 1962) and ranging up to 1.7 for 2,2-bis-(*p*-bromophenyl)-1,1,1-trichloroethane and 3.0 for 2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethane (III) (Metcalf and Fukuto, 1968). Although deutero-DDT (LD_{50} > 500 ppm) was not appreciably effective against strains of houseflies highly resistant to DDT, it was substantially more toxic than DDT to *Culex* mosquito larvae (Table I). α-Deutero-methoxychlor (LD_{50} = 34 ppm) was more effective than methoxychlor (LD_{50} > 500 ppm), showing that the decreased reactivity of the C–D bond acting in conjunction with the higher electron density produced by the *p,p'*-CH_3O groups reduced detoxication to a level permitting a substantial por-

Table I. Effectiveness of DDT Analogs to Susceptible and DDT-Resistant Houseflies and Mosquito Larvae[a]



Compd	R_1	R_2	R_3	R_4	R_5	*Musca domestica*, topical LD_{50}, μg/g: Susceptible	*Musca domestica*, topical LD_{50}, μg/g: Resistant	*Culex pipiens*, LC_{50}, ppm
I	H	Cl	Cl	Cl	H	2.0	>500	0.07
II	D	Cl	Cl	Cl	H	2.3	>500	0.016
III	H	Cl	Cl	H	H	19.5	>500	0.038
IV	F	Cl	Cl	H	H	4.1	15.5	0.024
V	H	Cl	Cl	Cl	F	4.6	>500	0.041
VI	D	Cl	Cl	Cl	F	4.3	33	0.020
VII	H	Cl	Cl	Cl	Cl	11.0	36	0.054
VIII	D	Cl	Cl	Cl	Cl	9.5	22	0.023
IX	H	Cl	Cl	Cl	Br	25.5	>500	0.118
X	H	CH_3	CH_3	CH_3	H	30	95	0.39
XI	H	CH_3	NO_2	H	H	8.5	45	0.064
XII	Cl	H	Cl	Cl	H	18.5	>500	0.24
XIII			Cyclopropyl-Cl_2			12.0	105	0.042

[a] Metcalf and Fukuto (1968).

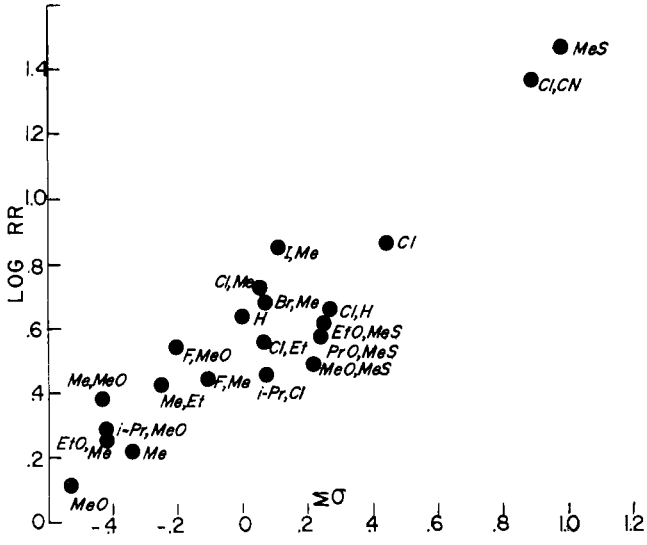


Figure 3. Relationship of summed σ values for para substituents of DDT analogs to resistance ratio (RR or LD_{50} R/S houseflies). MeS substituents are plotted as MeSO primary oxidation product.

tion of the compound to reach the site of action (Metcalf and Fukuto, 1968).

α-F Analogs. C–F bonds with energy of 107 kcal/mol are substantially stronger than C–H bonds, with an energy of 87 kcal/mol. Hennessey and Villarica (1969) synthesized a variety of α-F analogs of DDT highly toxic to R_{DDT} flies (Table I) and not readily attacked by DDT'ase. The α-F DDT (LD_{50} = 125) is of low toxicity to the housefly, presumably because of adverse steric factors at the site of action, but α-F DDD (2,2-bis-(*p*-chlorophenyl)-2-fluoro-1,1-dichloroethane, IV) is about five times more effective to S flies than DDD (III) and had a resistance ratio (RR) of 4 between R_{SP} and S_{NAIDM} flies as compared with RR value of >25 for DDD (Table I).

The $-CHBr_2$ analog of TDE is such an excellent DDT'ase substrate that it has an LD_{50} of >500 to S_{NAIDM} flies. However the α-F analog, 2,2-bis-(*p*-chlorophenyl)-2-fluoro-1,1-dibromoethane, had an LD_{50} of 7 and a RR to R_{SP}/S_{NAIDM} of 4.4 (Metcalf and Fukuto, 1968).

o-Chloro-DDT. *o*-Chloro-DDT (2-(4-chlorophenyl)-2-(2′,4′-dichlorophenyl)-1,1,1-trichloroethane , VII) is highly toxic to both S and R flies (Hennessey *et al.*, 1961). The bulky *o* substituent evidently interferes sterically with dehydrochlorination as the compound ($k \times 10^5$ = 1.07 × 10^3 l./mol/min) undergoes OH^--catalyzed dehydrochlorination only about 0.17 as rapidly as *p,p′*-DDT ($k \times 10^5$ = 6.1 × 10^3) (Metcalf and Fukuto, 1968). The LD_{50} values to S flies for DDT analogs with various ortho substituents were in the order H (DDT) > F > Cl < Br (Table I), while CH_3 and CH_3O were inactive presumably because of *in vivo* oxidation. Simultaneous incorporation of α-D and *o*-F (VI) or *o*-Cl (VIII) substantially improved the toxicity to both S and R flies (Table I). It is suggested that the impressive action of *o*-Cl-DDT to R flies is due to a combination of increased stability of the α-HC bond to DDT'ase attack, together with a decreased affinity of *o*-Cl-DDT for the detoxication enzyme (Metcalf and Fukuto, 1968).

Effects of para Substituents. A striking example of the role of the electron density of the α-carbon of DDT analogs is shown in Figure 3, where the resistance ratio (RR or LD_{50} R_{SP} fly/LD_{50} S_{NAIDM} fly) is plotted against the $\Sigma\sigma$ for the various analogs. The relationship is clearly significant (correlation coefficient of 0.83) to the line RR = $14.753\sigma + 5.049$, where y = RR and x = σ constant. As predicted, DDT analogs with para substituents that are strong electron donors such as CH_3O, C_2H_5O, CH_3, and C_2H_5 are most effective against DDT resistance resulting from enhanced DDT'ase production. As a practical example, methoxychlor still gives adequate control of R_{DDT} houseflies in many areas in the early part of the year before selection increases DDT'ase to maximum levels.

Chlorfenthol (DMC) and Other Synergists for DDT. Chlorfenthol (1,1-bis-(*p*-chlorophenyl)ethanol) was found to be a very effective synergist for DDT against R flies (Summerford *et al.*, 1951), giving a synergistic ratio (SR) or LD_{50} DDT/LD_{50} DDT plus synergist of 60. Chlorfenthol was shown by Perry *et al.* (1953) to inhibit *in vivo* de-

toxication of DDT to DDE in R flies. When a range of 0.06 to 6.5 μg of chlorfenthol was applied topically to the flies with a constant dosage of 0.65 μg of DDT, the mortality was increased from 2 to 100%, the amount of DDT recovered internally from 9.4 to 77%, and the amount of DDE decreased from 63 to 12%. Chlorfenthol proved to be an effective *in vitro* inhibitor of DDT'ase at a molar ratio of 0.001 that of DDT (Lipke and Kearns, 1960). Many other structural analogs of DDT are synergists for R flies, including 1,1-bis-(*p*-chlorophenyl)ethane SR 100, bis-(*p*-chlorophenyl)chloromethane SR 140, and the CF_3 analog of chlorofenthol (F-DMC) or 1,1-bis-(*p*-chlorophenyl)-2,2,2-trifluoroethanol SR 78-127 (Metcalf, 1967). The high activity of synergists such as *p*-chlorobenzenesulfon-*p*-chloroanilide (SR 108) was described by Speroni (1952) and emphasized the structural similarity of such compounds to DDT. This led to the development of *p*-chlorobenzene *N,N*-dibutylsulfonamide as an oil-soluble synergist for DDT (Neeman *et al.*, 1957).

MODE OF ACTION OF DDT

It is intriguing that there is little certain or specific knowledge about the critical biochemical lesion produced in DDT poisoning despite 30 years of intensive study, the utilization of more than 4 billion pounds of DDT, the death of countless billions of insect victims, and the elucidation of numerous promising theories. Some of the more interesting of the latter, especially as they relate to physicochemical interaction between DDT and a biochemical substrate, are illustrated in Figure 4.

It is certain that DDT is a nerve poison to both insects and mammals, producing symptoms of intoxication marked by hyperexcitability, tremors of increasing severity leading to convulsions, prostration, and death. Physiologically, the tremors are the result of initiation of repetition after discharge in the nerve, a multiplication of nerve impulses so that a single impulse from a sensory nerve in the insect produces a prolonged volley of afferent impulses. These have the effect of literally stimulating the insect to death that may result from metabolic exhaustion or endogenously produced neurotoxins (Sternburg, 1963). The nerve axon is the site of DDT action and this action is associated with an effect on the nerve action potential, increasing the negative after potential. DDT also produces prolongation of the action potential of the nerve (Narahashi and Haas, 1968). This effect may result from specific inhibition of the potassium efflux of the nerve axon.

The many other interesting physiological and biochemical theories of the mode of action of DDT have been well reviewed by O'Brien (1967). They fall outside the scope of this discussion, which is focused primarily on chemical aspects. At the molecular level this effect has been related to a variety of theories of action. Nearly all of these can be faulted in a chemical sense because they fail to account for the biological activity of one or more analogs of DDT. Lauger *et al.* (1944) and Martin and Wain (1944) related the action of DDT to the classical pharmacological concept of conductophore and toxaphore (Figure 4); however, they had opposing views as to the molecular moieties responsible for the two functions. Lauger *et al.* (1944) related DDT to the inhalation narcotics and suggested the $>CHCCl_3$ moiety as the conductophore (after chloroform) and the bis-(*p*-chlorophenyl)methylene moiety as the toxaphore. Their theory fails to account for the insecticidal activity of the dimethylpropane analogs such as 1,1-bis-(*p*-chlorophenyl)-2,2-dimethylpropane (X, Table I) (Stringer *et al.*, 1955) or the nitropropane analogs such as 1,1-bis-(*p*-chlorophenyl)-2-nitropropane (XI) (Haas *et al.*, 1951), since neither dimethylpropane nor nitropropane are inhalation narcotics. Martin and Wain (1944) visualized the bis-(*p*-chlorophenyl)methylene moiety as the conductophore and the intracellular release of HCl as the toxaphoric mechanism. Their theory, based on the inactivity

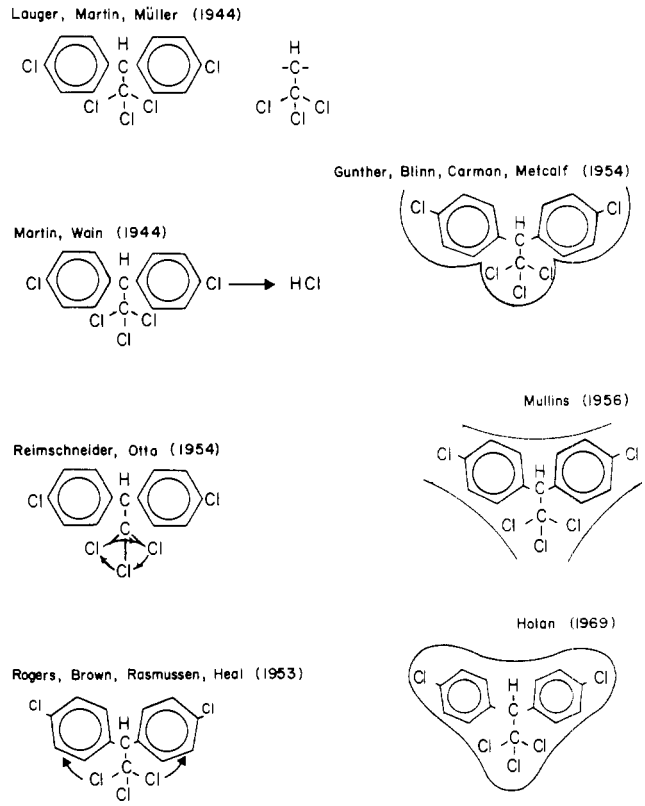


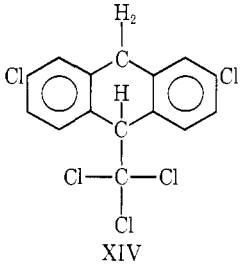
Figure 4. Some theories of the mode of action of DDT.

of DDE and 2,2-bis-(*p*-chlorophenyl)-2,1,1,1-tetrachloroethane, clearly fails to explain not only the activity of the nitropropanes and dimethylpropanes but also the high toxicity of such compounds as 2,2-bis-(*p*-chlorophenyl)-2-fluoro-1,1-dichloroethane (IV) and 1,1-bis-(*p*-chlorophenyl)-2,2-dichlorocyclopropane (XII) (Table I).

Second generation theories of Rogers *et al.* (1953) and Riemschneider and Otto (1954) involved the optimal stereochemical configuration of DDT. The former, in their trihedralization theory, suggested that the bulk of the $-CCl_3$ group interacts with the *p*-chlorophenyl groups to produce an essentially nonrotatable configuration where the aryl rings tend to assume positions of maximum clearance. Such trihedralization is not found with DDE or the inactive 2,2-bis-(*p*-chlorophenyl)-1,1,1-trifluoroethane.

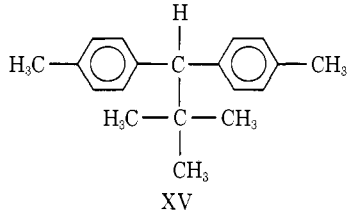
Rogers *et al.* (1953) cited the strong DDT-like activity of 1,1-bis-(*p*-methoxyphenyl)-2,2-dimethylpropane (fly LD_{50} 26 ppm), the decreased activity of 1,1-bis-(*p*-methoxyphenyl)-2-methylpropane, and the inactivity of 1,1-bis-(*p*-methoxyphenyl)propane as support for their theory. The high activity of Prolan (1,1-bis-(*p*-chlorophenyl)-2-nitropropane, XI) also fits this concept. Riemschneider and Otto (1954) argued plausibly that it was necessary for the aryl rings to rotate about the trichloromethyl group for a high degree of DDT-like activity. They regarded the 2,2-bis-phenyl-1,1,1-trichloroethane moiety as a conductophore which formed an effective insecticide by incorporation of positive auxocontacts such as F, Cl, Br, CH_3, C_2H_5, CH_3O, and C_2H_5O. Support for this concept was adduced from the inactivity of *o,o*-DDT (2,2-bis-(*o*-chlorophenyl)-1,1,1-trichloroethane) and from the greatly decreased activity of *o,p'*-DDT (2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-1,1,1-trichloroethane) (fly LD_{50} 183 ppm) which is nonrotatable. Unfortunately for this theory, Hennessey *et al.* (1961) showed that *o*-Cl-DDT (VII), in which the rings are also nonrotatable, approached DDT in activity (Table I). The theories of both Rogers *et al.* and Riemschneider and Otto are in conflict with the unmistakable DDT-like activity of the nonrotatable fused ring an-

alog 2,7-dichloro-9-trichloromethyl-9,10-dihydroanthracene (XIV) (Vingiello and Newallis, 1960). This compound (LC_{50} = 0.35 ppm) approaches DDT (LC_{50} = 0.066 ppm) in toxicity to *Culex pipiens* larvae but has very low activity to the housefly (Hirwe and Metcalf, 1973).

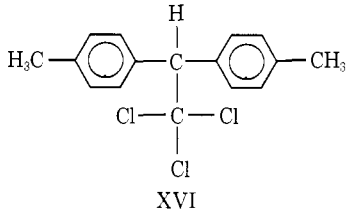


XIV

Third generation theories related the action of DDT to adsorption at a critical lipoprotein interface. This concept was stimulated by the challenging resemblance in insect toxicity and similarity of toxic symptoms between DDT and its totally methylated isostere 2,2-bis-(*p*-methylphenyl)-2,2-dimethylpropane (XV, fly LD_{50} = 1250 ppm) (Stringer *et al.*, 1955) and the comparison of other mixed Cl and CH_3 isosteres such as "methylchlor" (2,2-bis-(*p*-methylphenyl)-1,1,1-trichloroethane) (XVI, fly LD_{50} = 100 ppm) especially when *in vivo* degradation was repressed by synergism with the multifunction oxidase inhibitor, piperonyl butoxide (Metcalf *et al.*, 1972). Gunther *et al.* (1954), contemplating the similar van der Waals' radii of Cl 1.85 Å and CH_3 2.0 Å, suggested that these isosteres should provide comparable fit into a protein cavity such as an apoenzyme and that closely fitting molecules would provide optimal insecticidal activity, while steric hindrance would prevent the fit of larger molecules. They correlated the log LC_{50} values for *Culex quinquefasciatus* mosquitoes with Σ log K_0 for Cl, CH_3, and H van der Waals' radii for DDT analogs substituted in aromatic and ethane positions and obtained, for active compounds, lines of similar slope, suggesting that both ends of the molecule were important and essentially equivalent in the interaction with the protein.



XV



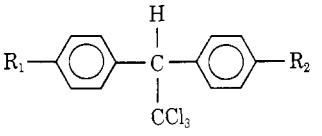
XVI

Very recently (Fahmy *et al.*, 1973) this sort of approach has been evaluated by multiple regression analysis using LC_{50} to *Culex quinquefasciatus* larvae and topical LD_{50} to *Musca domestica* for a large number of DDT analogs (Metcalf and Fukuto, 1968; Metcalf *et al.*, 1971a) and incorporating the linear free energy parameters of σ^*, E_S, F, R, and π. The multiple regression analysis showed the steric substituent parameter E_S (Taft, 1956) was the critical parameter and for *Culex quinquefasciatus* the data fitted the equation

$$LC_{50} = 1.63\ (\pm 0.21)\ \Sigma E_S + 0.93\ (\pm 0.12)\ \Sigma E_S^2 \quad (r = 0.933)$$

This study confirmed the previous views that size and shape of the DDT-type molecule are critical to insect toxicity and suggested that the DDT receptor site is quite flexible and can adjust to accommodate DDT analogs with marked asymmetry in aryl substituents such as XIX and XX (Table II). Clearly, the size and shape of substituents on both ethane carbon atoms are interrelated (compare III and XII, Table I) and the effects of ring substituents are not independent of those on α- and β-carbons. This model offers a logical explanation to the inactivity of DDT analogs substituting Si for C in both aliphatic positions (Fahmy *et al.*, 1973).

Table II. Effectiveness of Some Asymmetrical DDT Analogs as Compared with Methoxychlor and Ethoxychlor[a]



Compd	R_1	R_2	*Musca domestica*, topical LD_{50}, μg/g: Susceptible	*Musca domestica*, topical LD_{50}, μg/g: Resistant	*Culex pipiens*, LC_{50}, ppm
XVII	CH_3O	CH_3O	45	48	0.067
XVIII	C_2H_5O	C_2H_5O	7.0	11.0	0.04
XIX	CH_3O	C_4H_9O	21	29	0.18
XX	CH_3	C_4H_9O	33	55	0.063
XXIII	CH_3	CH_3O	23.5	62.5	0.085
XXIV	CH_3	C_2H_5O	9	27	0.13
XXV	CH_3O	CH_3S	32	80	0.11

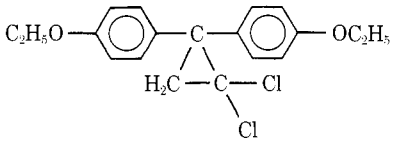
[a] Metcalf *et al.* (1971a).

Mullins (1956) proposed a promising theory relating the action of DDT to its appropriate size and shape to fit into the interstices of cylindrical lipoprotein strands forming the membrane lattices of the nerve axon. Mullins estimated the diameter of these lipoprotein strands at about 40 Å and, when packed together in hexagonal array with a 2 Å separation, they provide hypothetical pores into which the DDT molecule should fit snugly in end-on position (Figure 4), distorting the membrane and presumably producing ion leaks causing excitation. This theory explains nicely the activity of simple DDT isosteres such as methoxychlor, methylchlor, and dianisyl neopentane. From study of Fisher, Hirschfelder, and Taylor molecular models, it appears that the inactive α-chloro-DDT (2,2-bis-(*p*-chlorophenyl)-2,1,1,1-tetrachloroethane) may have too large an end-on cross-section to enter the pore space. However, 2,2-bis-(*p*-chlorophenyl)-2,1,1-trichloroethane (XII), which is moderately active, can assume a reduced end-on cross-section as can the highly active α-F analog 2,2-bis-(*p*-chlorophenyl)-2-fluoro-1,1-dichloroethane (IV). The Mullins' theory is less comfortable with the highly active 2,2-bis-(*p*-ethoxyphenyl)-1,1,1-trichloroethane (Table II, XVIII) and with asymmetrical analogs such as the active 2-*p*-methoxy-2-*p*-butoxyphenyl-1,1,1-trichloroethane (XIX) and particularly with the fused ring analog 2,7-dichloro-9-trichloromethyl-9,10-dihydroanthracene (XIV) with planar ring configuration (Vingiello and Newallis, 1960). DDE, also inactive, can assume a configuration nearly identical to DDT and has a smaller end-on cross-section. It can be rationalized that its tightness of fit is not sufficient to produce the required leaks of sodium ion.

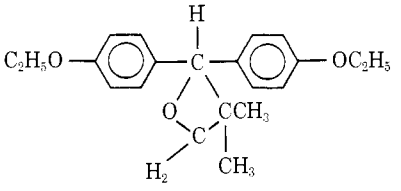
Holan (1969) has developed an extension of the general ideas of Mullins to further refine the locus of fit of the DDT-type molecule to act as a "molecular wedge" to block the sodium gates of the nerve axon in the open posi-

tion (Figure 4), consequently delaying the falling phase of the Na^+ ion potential. Holan envisions the phenyl rings as forming a molecular complex with the overlying protein layer, while the apex containing the trichloromethyl or equivalent group fits into the pore channel so as to keep it open to Na^+ ions. Matsumura and Patil (1969) have added a further refinement through the finding that DDT (I_{50} 3 × 10^{-7} *M*) inhibits the Na^+, K^+, and Mg^{2+} ATP'ases from rat brain homogenate. They suggest that the involvement of ATP'ase in Na^+ and K^+ transport through the nerve membrane makes this enzyme a likely biochemical lesion for DDT action.

From careful measurements of the planar projections of the active DDT analogs, Holan (1969, 1971a,b) has developed a pictorial concept of the "sodium gate" and has devised several new active DDT-like molecules which conform to his postulated spatial requirements. These include 1,1-bis-(*p*-ethoxyphenyl)-2,2-dichlorocyclopropane (XXI) and 2,2-bis-(*p*-ethoxyphenyl)-3,3-dimethyloxetane (XXII).

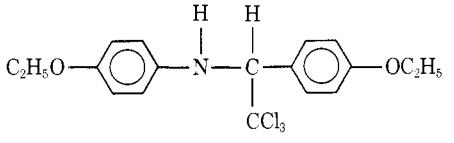


XXI

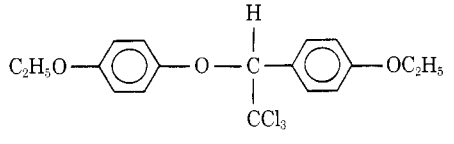


XXII

DDT-Like Benzylanilines and Benzyl Phenyl Ethers. The diphenylmethane moiety is not uniquely essential for DDT-like insecticidal activity and it has now been shown that a hetero-atom N, O, or S can be interposed between the two aryl moieties to produce compounds that approach DDT in toxicity to insects (Table III, Hirwe *et al.*, 1972). These compounds produce characteristic DDT-like symptoms of intoxication (Miller and Kennedy, 1972). Observations upon molecular models show that these substituted benzyl anilines and phenyl benzyl ethers assume configurations almost identical to those of typical DDT analogs, supporting previous conclusions about the critical nature of the size and shape of the DDT-type molecule.



XXIX

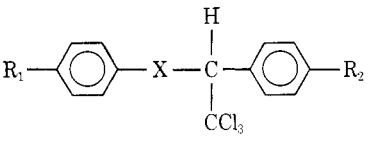


XXXV

DDT ANALOGS AND ENVIRONMENTAL QUALITY

The persistence of DDT in the environment and its biomagnification in living organisms, together with its degradation products DDE and DDD, have become fundamental issues of environmental quality. Although the chemical stability of DDT on surfaces is its most important insecticidal attribute, conversely its biochemical stability in living tissues is its greatest weakness. There is urgent need to replace DDT with persistent yet biodegradable pesticide molecules which would have long residual life on walls, foliage, and animal hair but which, when absorbed into living systems, would be converted rapidly to water-partitioning polar products and excreted rather than stored in tissue lipids. Replacement of the chlorinated aryl rings of DDT with rings containing *degradophores*, *i.e.*, chemical groupings which act as substrates for the multifunction oxidases (MFO) or "drug metabolizing" enzymes, provides an avenue for the development of such insecticides. Methoxychlor with its two *p*-CH_3O groups which are degraded *in vivo* by O-dealkylation and excreted as mono- and bis-phenols (Kapoor *et al.*, 1970) (Figure 5) is a good example of such a persistent biodegradable

Table III. Effectiveness of Some DDT-Like Benzylanilines and Benzyl Phenyl Ethers[a]



Compd	R_1	R_2	X	*Musca domestica*, topical LD_{50}, μg/g: Susceptible	*Musca domestica*, topical LD_{50}, μg/g: Resistant	*Culex pipiens*, LC_{50}, ppm
XXVI	Cl	Cl	-NH-	115	220	0.026
XXVII	CH_3	CH_3	-NH-	43	43	0.68
XXVIII	CH_3O	CH_3O	-NH-	>500	500	>1.0
XXIX	C_2H_5O	C_2H_5O	-NH-	15.5	20.5	0.19
XXX	C_2H_5O	Cl	-NH-	19.5	45	0.22
XXXI	Cl	C_2H_5O	-NH-	19.0	31	0.032
XXXII	Cl	Cl	0	90.0	>500	0.035
XXXIII	CH_3	CH_3	0	265	>500	0.12
XXXIV	CH_3O	CH_3O	0	300	>500	0.51
XXXV	C_2H_5O	C_2H_5O	0	27.0	42	0.11
XXXVI	Cl	C_2H_5O	0	18.5	31	0.067

[a] Hirwe *et al.* (1972).

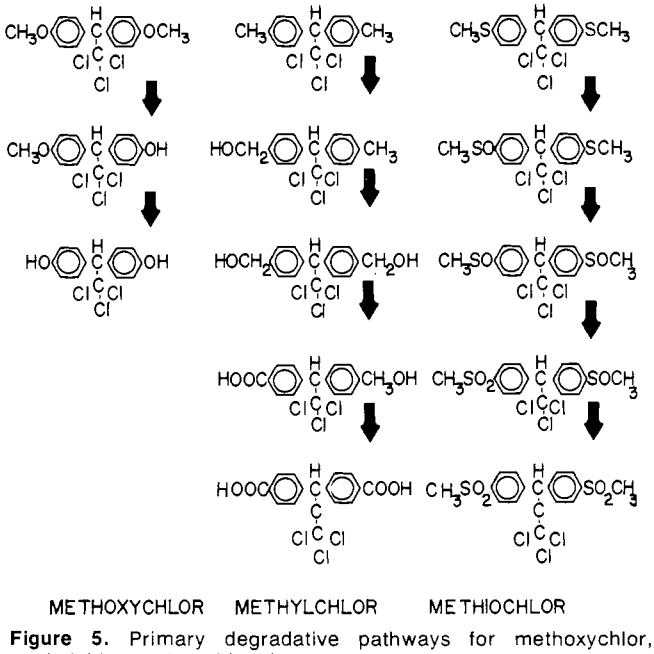


Figure 5. Primary degradative pathways for methoxychlor, methylchlor, and methiochlor.

Table IV. Some Environmental Properties of DDT Analogs[a]

	LD_{50}, mg/kg mouse oral	Ecological magnification, fish	Biodegradability index, fish
$ClC_6H_4CHCCl_3C_6H_4Cl$ (DDT)	200	84,500	0.015
$CH_3OC_6H_4CHCCl_3C_6H_4OCH_3$ (methoxychlor)	1850	1,545	0.94
$C_2H_5OC_6H_4CHCCl_3C_6H_4OC_2H_5$	250	1,536	2.69
$CH_3SC_6H_4CHCCl_3C_6H_4SCH_3$	1000	5.5	47
$CH_3C_6H_4CHCCl_3C_6H_4CH_3$	3350	140	7.14
$CH_3C_6H_4CHCCl_3C_6H_4OC_2H_5$	1000	400	1.20
$CH_3OC_6H_4CHCCl_3C_6H_4SCH_3$	1000	310	2.75
$CH_3C_6H_4CHCCl_3C_6H_4Cl$		1,400	3.43
$ClC_6H_4CHCHCl_2C_6H_4Cl$ (DDD)		83,500	0.054

[a] Metcalf *et al.* (1971a); Kapoor *et al.* (1973).

compound. Methoxychlor, rat oral LD_{50} > 6000 mg/kg, is much less acutely toxic than DDT, rat oral LD_{50} 118 mg/kg (Hayes, 1963). When fed to rats at 100 ppm, methoxychlor was present in adipose tissue at only 1 ppm (Kunze *et al.*, 1950) as compared to DDT fed at 50 ppm and stored at 284 ppm in male and 588 ppm in female (Laug *et al.*, 1950). When present in water at 1 ppb, methoxychlor was accumulated by *Tilapia* and the green sunfish to 0.2 ppm over 31 days, compared to DDT which was accumulated to 6.8 ppm by *Tilapia* and 3.9 ppm by the green sunfish (Reinbold *et al.*, 1971). Methylchlor (2,2-bis-(*p*-methylphenyl)-1,1,1-trichloroethane) is another analog whose *p*-CH_3 groups can also serve as degradophores for side-chain oxidation to benzoic acid derivatives (Kapoor *et al.*, 1972) (Figure 5). Methiochlor (2,2-bis-(*p*-methylthiophenyl)-1,1,1-trichloroethane) is a DDT analog whose *p*-CH_3S groups can be oxidized successively to CH_3SO- and CH_3SO_2-, providing increasingly polar moieties that affect partition and elimination from animals (Kapoor *et al.*, 1970).

Methoxychlor is, however, nearly as toxic to fish as DDT and under cold water conditions fish such as Atlantic salmon accumulate it to objectionable levels (Kruzynski and Leduc, 1972). Methylchlor is substantially less toxic to fish and it appears that side-chain oxidation is a more efficient microsomal oxidative process than O-dealkylation (Kapoor *et al.*, 1970, 1972). However, methylchlor is not a very effective insecticide.

Asymmetrical DDT Analogs. These compounds incorporating two dissimilar *p,p'* substituents offer a variety of insecticidal compounds which have been studied extensively (Metcalf *et al.*, 1971a, 1972) and provide useful features as biodegradable compounds. Methyl-methoxychlor (XXIII, Table II), methyl-ethoxychlor (XXIV), and methoxy-methiochlor (XXV) incorporate degradophores responding to two different types of microsomal oxidation. These compounds are of notably low toxicity to mice (Table IV). Their degradative pathways have been explored in detail (Kapoor *et al.*, 1973).

In order to quantitize the biodegradation of these various DDT analogs, the "model ecosystem" technology has proved useful (Metcalf *et al.*, 1971b). Radiolabeled compounds are followed quantitatively from *Sorghum* plants through the leaf-eating salt-marsh caterpillar (*Estigmene acrea*) into an aquatic system of alga (*Oedogonium cardiacum*) to the snail *Physa* and into plankton to the mosquito larva (*Culex quinquefasciatus*) and finally into the mosquito-eating fish (*Gambusia affinis*). From data of this kind (Kapoor *et al.*, 1970, 1972, 1973; Metcalf *et al.*, 1971b, 1972) the parameters "ecological magnification" or ratio of parent compound in fish to parent compound in water, and "biodegradability index" or ratio of polar degradation products in fish/nonpolar products, have been calculated as shown in Table IV. All of the DDT analogs investigated are much superior in biodegradability to DDT, DDE, and DDD.

The dimethyloxetane analogs of DDD (*e.g.*, XXII) show a high degree of degradability, forming formaldehyde and inactive 1,1-diaryl-2,2-dimethylethylenes (Holan, 1971b). The α-trichloromethylbenzylanilines (*e.g.*, XXIX) were found to degrade environmentally by dehydrochlorination, rearrangement, and cleavage to aniline and benzoic acid moieties (Hirwe *et al.*, 1972). These mechanisms, together with O-dealkylation or side-chain oxidation, produce degradation products readily excretable *in vivo* which prevent these degradable compounds from accumulating to high levels in living organisms.

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Received for review April 4, 1973. Accepted May 10, 1973. International Award Address for Research in Pesticide Chemistry, Presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 12, 1972. Preparation of the manuscript and the unpublished studies considered were supported in part by grants from The Rockefeller Foundation and the Herman Frasch Foundation.