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CHRONIC AND ACUTE TOXICITY OF THE CHLORINATED HYDROCARBON INSECTICIDES IN MAMMALS AND BIRDS

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Introduction

The chlorinated hydrocarbon (organochlorine) insecticides have been used extensively in the control of insect pests for over twenty years. Widespread acceptance of these compounds was due to the fact that they are chemically stable, potent, and extremely persistent when applied to plants, food crops, or other surfaces. Man initially overlooked the fact that the chlorinated hydrocarbon compounds are not specific poisons for insects and may kill other organisms.

The objective of this review is to describe the present state of knowledge concerning the toxicity of these compounds as they relate to mammals and birds which are of interest to the veterinarian.

Compounds mentioned in this review are listed and identified in Table I.

Toxicity and Symptoms

DDT: DDT is acutely toxic orally to both mammals and birds if large doses are administered (Table II). Chicks appear to be more resistant to acute oral poisoning than most laboratory animals. Cats and dogs are unpredictable in their response to oral administration of DDT, some animals surviving single doses as high as 500 mg/kg (71). Large domestic animals as a group are more resistant to massive, single doses of DDT than laboratory animals (56). Death may be delayed for several days following acute poisoning in animals. The clinical signs include hyperexcitability and generalized fine and coarse tremors. Spasticity, progressing to flaccid-type paresis of the extremities, does not appear for several hours (75). However, signs persist for a day or two in rabbits and rats and for several days in cats (83). Cats develop a persistent extensor rigidity with opisthotonos and muscular twitching (83).

The effects of DDT are cumulative, and when small single doses are given repeatedly, chronic poisoning develops. In such cases, however, the central nervous system (CNS) manifestations are milder than in acute intoxication. Chronic DDT toxicity in cockerels, in addition to causing neurological disturbances, suppresses secondary sex characteristics (12, 25). The chronic and acute signs of DDT poisoning in the domestic bird are described in detail elsewhere (25, 87). As little as 0.075 per cent DDT in the ration is toxic when fed to 4½ month old turkeys over a period of eight weeks (59). Rations containing 0.10 and 0.05 per cent DDT are lethal to chicks (59) and rats (82), respectively, death occurring much earlier in the former (22, 83). Daily oral administrations of 50 mg/kg DDT in oil are fatal to rabbits and cats, the former after a total accumulative dose of 0.75 to 1.25 mg/kg and the latter after a total dose of 300 to 500 mg/kg (83). Only inappetance and loss of weight occur in monkeys fed diets containing 5000 ppm of DDT (24).

The oral toxicity of DDT is approximately 1/10 the intravenous toxicity (71, 85). Dermal DDT application can be fatal, but skin hypersensitivity is not one of the signs of chronic dermal application (23). A study of the chronic effects of DDT and its analogues in dogs indicates decreasing toxicity in the following order: *o,p'*-DDT or 1,1,1-trichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethane; *p,p'*-DDT or 1,1,1-trichloro-2,2-bis (*p*-chlorophenyl) ethane; technical DDT mixture; DDD and DMDT (104). It should be noted that DDT toxicity varies according to the species, the route of administration, and formulation (15, 22).

BHC: BHC consists of a mixture of five

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TABLE I

IDENTITY OF COMPOUNDS MENTIONED IN THIS REVIEW

Common Name	Chemical Name
	DDT GROUP
DDT	1,1,1-trichloro-2,2-bis (*p*-chlorophenyl) ethane
DDA	bis (*p*-chlorophenyl) acetic acid
*DDD	1,1-dichloro-2,2-bis (*p*-chlorophenyl) ethane
DDE	1,1,-dichloro-2,2-bis (*p*-chlorophenyl) ethylene
DDMS	1-chloro-2,2,bis (*p*-chlorophenyl) ethane
DDMU	1-chloro-2,2-bis (*p*-chlorophenyl) ethylene
DDNU	Unsym-bis (*p*-chlorophenyl) ethylene
DDOH	2,2-bis (*p*-chlorophenyl) ethanol
*DMDT (methoxychlor)	1,1,1-trichloro-2,2-bis (*p*-methoxyphenyl) ethane
	CYCLODIENE GROUP
aldrin	1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene
*dieldrin	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo-exo-5,8-dimethanonaphthalene
chlordane	1,2,4,5,6,7,8,8-octachloro-3a-4,7,7a-tetrahydro-4,7-methanoindane
*endrin	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-exo-1,4-exo-5,8-dimethanonaphthalene
telodrin	1,3,4,5,6,7,8,8,octachloro-1,3,3a,4,7,7a-hexahydro-4,7-methanoisobenzofuran
heptachlor	1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene
*heptachlor epoxide	1,4,5,6,7,8,8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindene
toxaphene†	chlorinated camphene
	MISCELLANEOUS COMPOUNDS
BHC	1,2,3,4,5,6-hexachlorocyclohexane
lindane	Gamma isomer of BHC

Metabolites are shown idented under the parent compound.
*Note that certain metabolites are also insecticides that are produced commercially.
†Not truly a cyclodiene.

TABLE II

ACUTE LETHAL TOXICITY OF CHLORINATED HYDROCARBON INSECTICIDES

Compound	Species	Oral LD_{50} (mg/kg)	Oral MLD (mg/kg)	References
DDT	Rats	♀ 118 (as sodium salt)	—	33
		♂ 113 (as sodium salt)	—	33
		200 (in oil)	—	22
		150 (in oil)	—	83
		400	—	66
	Mice	400 (in oil)	—	22
	Rabbits	300 (in oil)	—	56,83
		300	—	66
	Cats	300 > 400 (in oil)	—	71
		250 > 300	—	83
	Guinea pigs	400 (in oil)	—	22
	Chickens	>300	—	56,22
	Mature cattle	—	500–200	76
	Calves 1–2 wks old	—	250	76
	Goats	—	>1000	15
	Sheep	—	500	75
Lindane	Rats	125	—	66
		177	—	105
		♂ 88 (in oil)	—	33
		♀ 91 (in oil)	—	33
	Mice	86	—	66,105
	Guinea pigs	127	—	66,105
	Rabbits	200	—	66
		60	—	105
	Dogs	—	20–40	15

TABLE II—*continued*

Compound	Species	Oral LD_{50} (mg/kg)	Oral MLD (mg/kg)	References
	Mature cattle	—	25	75
	Calves 2 wks old	—	5	75
	Sheep	—	25	75
	Horses	—	50	75
Aldrin	Rats	40 (in oil)	—	15
		♂ 39 (in oil)	—	33
		♀ 60 (in oil)	—	33
		♂ 49	—	7
		♀ 38	—	7
	Mice	44	—	7
	Rabbits	50–80	—	7,34
	Cats	10–15	—	78
	Guinea pigs	33	—	7
	Chickens 3–6 wks old	10–15	—	1
	Dogs	65–95	—	7,34
		—	40–50	34
	Mature cattle	—	40–50	34
	Sheep	—	40–50	34
	Monkeys	—	40–50	34
Dieldrin	Rats	50.8–63.5	—	15
		♂ 46 (oil); 48 wettable powder	—	33
		♀ 46 (oil)	—	33
		♂ 47	—	8
		♀ 43	—	8
	Mice	75 (in oil)	—	15
		38	—	8
	Guinea pigs	25	—	15
		59	—	8
	Rabbits	45–50	—	8
	Cats	300–500	—	78
	Mature cattle	60	—	49
	Sheep	50–75	—	15
	Dogs	65–80	—	8
		—	35–50	34
	Monkeys	—	35–50	34
	Chickens 3–6 wks old	20–30	—	27
Endrin	Rats	♂ 17.8 (in oil)	—	33
		♀ 7.5 (in oil)	—	33
	Mice	♂ 2.98 (in oil)	—	101
		♀ 2.93 (in oil)	—	101
	Cats	3–6	—	78
	Chickens	2 > 4	—	61
Chlordane	Rats	200–250 (in oil)	—	86
		♂ 335 (in oil)	—	33
		♀ 430 (in oil)	—	33
	Rabbits	300 (in oil)	—	86
		100 (in Tween 20)	—	86
	Goats	180	—	10
	Dogs	200–700	—	10
		—	200–300	15
	Mature cattle	—	130	75
Heptachlor	Rats	♂ 162 (in oil)	—	33
		♀ 100 (in oil)	—	33
Toxaphene	Rats	60 (in oil)	—	10
		♂ 90 (in oil)	—	33
		♀ 80 (in oil)	—	33
	Rabbits	—	100–200	15
	Cats	60	—	10
	Sheep	200	—	10
	Goats	200	—	10
	Dogs	60	—	10
		—	20–40 (in oil)	15

LD_{50} = dose lethal to 50% of treated animals.
MLD = minimal lethal dose.

isomers. In mice and rabbits the order of decreasing acute toxicity both orally and intravenously is gamma, alpha, delta, and beta (105). The acute oral lethal values of the gamma isomer of BHC (lindane) for different animals are presented in Table II. Deaths may occur from lindane poisoning in dogs and horses following single oral doses of as little as 20–40 mg (15) and 50 mg/kg, respectively (75). The gamma isomer of BHC is generally more toxic for young animals than adults and is much more toxic for emaciated animals, particularly during lactation (15). The other isomers are generally 1/6 to 1/60 as toxic (105). The gamma isomer is a CNS stimulant, whereas the other isomers are CNS depressants (105). In both the rat and cockerel, gamma-BHC is more acutely neurotoxic than dieldrin and heptachlor (in an oil-lecithin-saline emulsion) by intracarotid injections (87).

In chronic poisoning in the rat, all isomers not only disturb nutrition and retard growth, but when fed at 800 ppm or more, also increase the mortality rate (29). The beta isomer, the most lethal isomer due to its prolonged storage in fat, is two to three times as toxic as the alpha isomer and technical BHC, and just as toxic as DDT (29). Repeated applications of BHC sprays or dips containing 0.15–0.25 per cent of gamma-isomer have no effect on adult cattle, sheep, goats, horses and pigs (15).

Cyclodienes: Aldrin is one of the most toxic of the cyclodiene group of insecticides and the acute oral lethal doses for various species are shown in Table II. The cat (78) and chicken (1) are among the most sensitive species. Although the acute lethal dose for lambs is not known, an outbreak of fatal poisoning in suckling lambs, treated for contagious pustular dermatitis by a farmer is reported elsewhere (68). The muzzles of 107 lambs were immersed for a few seconds in aldrin concentrate and 45 per cent mortality occurred within 36 hours. On the seventh day following poisoning, only five lambs were still alive. The signs of acute poisoning are primarily related to the CNS and the autonomic nervous system; hyperactivity ultimately leads to convulsions, depression, and death (38, 68). The cutaneous (78) and chronic oral toxicities are also high (15).

Dieldrin, the epoxide metabolite of aldrin, is slightly less toxic than aldrin when given orally (49). The acute lethal oral doses for dieldrin in various species are given in Table II. The cat is extremely resistant. When rats are exposed to dieldrin fogs four times daily for 0.5–1.5 hours at air concentrations of 75, 150, 300 μg/1, fifty per cent may die after total exposure times of 40, 20, and 12 hours, respectively (32). The cutaneous toxicity of dieldrin (750 mg/kg) in cats is lower than that of aldrin which is 75 mg/kg (78).

Telodrin produces effects in poisoned animals which are similar to dieldrin (75). Water-based spray containing 0.025% telodrin produces death in calves under 2 weeks of age, while sprays containing 0.025 or 0.05% are not harmful to mature cattle (75).

Endrin, the epoxide of isodrin is more acutely toxic than its isomer dieldrin (Table II). The cutaneous toxicity of endrin (150 mg/kg) in cats is lower than that of aldrin and higher than that of dieldrin (78).

The acute toxicity of chlordane (Table II) is about three-fourths that of DDT when the compounds are fed to rats; while in rabbits the oral LD_{50} values of both compounds are the same (86). The chronic toxicity of chlordane is greater than that of DDT in rats, rabbits (86), and chickens (80) due to its greater cumulative and absorptive actions. The signs seen in chicks poisoned by chlordane differ from those of DDT toxicity. In the former, inappetance, nervous chirping, and terminal agonal excitability are manifestations of toxicity; whereas only neurological signs are seen in the latter (80).

Tolerance to chlordane in the chicken increases from 3 to 6 weeks of age (81), and laying pullets are highly refractory to the pesticide (82). However, levels of 0.15 to 0.50 per cent in the ration result in molting, reduced egg production, inappetance, and weight loss (82). Chlordane is more chronically toxic to female than male rats when given intragastrically (51). In dogs, 700 mg of chlordane (as a wettable powder) per kg of body weight produces neurological signs without fatal terminations (97). Neurological signs with fatal terminations may occur in sheep, goats, and cattle sprayed with 1.5 and 2.0 per cent wettable powder (75).

Heptachlorepoxide is ten times as toxic to young calves as is technical heptachlor. The maximum nontoxic oral dose of the former appears to be between 1 and 2.5 mg/kg compared with 15 to 25 mg/kg for the latter (11). Repeated daily doses of as little as 1 mg/kg of heptachlor epoxide (504 mg total intake) may be fatal to calves within 15 days (11). In contrast, 2.5 mg/kg of heptachlor (1447 mg total intake) is needed to produce death in the same time period (11). The female rat is more susceptible to acute heptachlor poisoning than the male (Table II). The effects of these pesticides in hyperactive mammals, such as the mink, are unknown.

Toxaphene is of moderate toxicity (Table II) and animals poisoned by it may show very severe signs of poisoning, then recover, all within a few minutes (75).

Absorption

The organochlorine insecticides are similar in their insolubility in water and their solubility in fat and fat solvents. They are thus best absorbed from oily solutions. Since these compounds can all penetrate intact skin when applied in organic solvents (33) or in the form of oily solutions or emulsions (15), the veterinarian should only recommend wettable powders for the treatment of ectoparasites in domestic animals.

Tissue Distribution and Storage

Very little data is available on the levels of insecticides present in the brains of animals fatally poisoned by the organochlorine insecticides (18). Available data indicate that the brain levels of insecticides associated with fatal intoxication are highly unpredictable (5, 18, 25, 83).

Following absorption, the chlorinated hydrocarbons are widely distributed in the tissues, particularly in the fat depots. After administration of a single oral dose of DDT to dogs the highest concentration of DDT is found in the bile (83). The CNS and blood have moderate levels while the concentrations in the kidney and liver are small and variable. After feeding DDT and DDD to dogs at 25 mg/kg daily for two weeks, the main sites of storage in descending order of concentration are: (a) fat and skin; (b) muscle; and (c) kidney (28). Until the fourth week of treatment other organs may have none or very little. Only DDD and DDT are present in the liver and mammary glands, respectively (28). The storage and distribution of DDD and DDT appear to increase with the time and level of administration (28, 92). The severity of signs in rats after a single dose of DDT is directly proportional to the concentration of the compound in the brain (18), and a similar relationship is found in birds (5, 43). Thus in suspected cases of fatal insecticide poisoning it is important that the brains of the dead animals be analyzed for the toxicant. However, continual ingestion of amounts which do not cause signs of toxicity can result in body storage of greater amounts than would be fatal if given as a single intravenous lethal dose. As much as 940 mg of DDT per kg can be stored in the fat of dogs over a period of 747 days without evidence of toxicity (106). In contrast, the lethal intravenous dose of DDT in dogs is 0.40 mg/kg (105). DDT accumulates in the gonads (2, 90) and also crosses the placental barrier (2, 28) into fetal liver and fat depots (2).

Of the BHC isomers, the beta compound is stored more readily in rats (19, 29) and dogs (19). In decreasing order, the tendency for storage of the isomers (beta, alpha, and gamma) by tissues is fat, kidney, brain, muscle, and liver (19, 29). Species differences exist. Unlike the rat, the dog stores more alpha, beta, and gamma isomers in its adrenal glands and the delta isomer is not found in the liver, kidney, and adrenal glands (19).

Tissue distribution studies indicate that when rats and dogs are fed heptachlor in daily doses as low as 30–35 ppm and 1 mg, respectively, the compound accumulates as heptachlor epoxide primarily in the fat and to a much lesser extent in the liver, kidney, and muscle; none is found in the brain (77). In dogs, unlike rats, the administration of high levels of heptachlor results in incomplete epoxidation by the liver with traces of heptachlor appearing in the body fat (77).

Chlorinated hydrocarbons may be mobilized from fat depots during catabolism. During starvation in rats (18) and chickens (26), previously fed chronic sublethal levels of DDT, the mobilization of body fat results in an increase of DDT-derived material in fat, brain, and other tissues. These animals show signs of poisoning. However, one report indicates that when rats are fed a DDT ration for 15 days and then starved (until a 60 per cent reduction in body weight occurs) the DDT in the adipose tissue is mobilized but is not shifted to the lipoid brain matter and no signs of poisoning are observed (50). More investigation is required to determine the effect of starvation and other forms of stress on mobilization of insecticides from fat storage to lipoid brain matter.

The distribution of dieldrin is shown by autoradiographic methods to be like that of DDT (2). It is not known whether aldrin crosses the placental barrier after first undergoing epoxidation. Although dieldrin accumulates in yolks of eggs, without affecting egg hatchability (55), poisoning may occur in the hatched chick following the absorption of the residual yolks and the concomitant mobilization of the insecticide (55).

Metabolites and Excretion

The absorption of chlorinated hydrocarbon insecticides from the digestive tract is poor

and the major part of an oral dose is excreted unchanged in the feces. Contrary to Smith and Stohlman (84), DDA is the urinary excretion product of DDT (24, 28, 102). DDA is relatively hydrophilic and because the toxicity of DDT is related to its lipophilic properties, it is assumed that DDA is the end product of DDT metabolism. DDA may be excreted in rats as urinary conjugates of aspartic acid and serine in equimolar proportions (73). The nature of DDT metabolism, however, is not certain. Tissue degradation of DDT in the rabbit probably involves (a) dehydrohalogenation of DDT and DDE, (b) hydroxylation of DDE with replacement of ethylenic chlorine atoms to give the enol form of DDA, and (c) ketonization of the enol to yield DDA (102). The overall sequence of reaction is: DDT→ DDE→DDA. The biological conversion of DDT to DDA probably occurs via the intermediate compound DDE (46). The oral administration of DDT in man results in an absolute increase in DDE storage and the excretion of DDA is proportional to DDT dosage (46). Both DDE and DDA are major metabolites in birds (25), but in monkeys fed DDT, very little or no DDE is stored (24) implying species variation in intermediary metabolism. DDD is a major metabolite of DDT in rats, in which species the conversion of DDT to DDE takes place very slowly (70). That portion of the metabolism of DDT in the rat which leads to DDA is elucidated to have the following sequence: DDT→DDD→ DDMU→ DDMS→ DDNU→ DDOH → hypothetical aldehyde→ DDA (70). When rats are fed *o,p'*-DDT, the compound undergoes isomeric transformation to *p,p'*-DDT in the fat depots, and also appears in the transformed state in the liver (54). No DDD is found in the fat (54). However, when DDD is fed to rats and dogs, it is deposited in fat and tissues in a manner similar to DDT (28). In chronic poisoning, the concentration of DDT excreted in the urine increases to a maximum then forms a plateau (84). In acute toxicity urinary DDT concentration reaches a peak in rabbits within two to three days (84), and in man within 24 hours (85), following which it declines slowly over a variable period. DDT is excreted unchanged (28, 91, 106) in milk which is toxic if ingested (91) so that milk from animals recently treated with any of the chlorinated hydrocarbon insecticides should not be consumed by man. The bile is another major route of DDT excretion (83). Since the liver is the site of detoxification, bile secreted into the intestine will contain products of DDT metabolism. The major fecal products in rats, are DDA and DDA conjugates of aspartic acid and serine (73).

The excretion of BHC occurs in milk, urine, and feces (15). The liver probably destroys the gamma isomer (94). The alpha, gamma, and delta isomers are excreted more rapidly than the beta isomer (19). Chlordane probably undergoes detoxification in the liver since organically bound chlorine is excreted in the urine of rabbits fed the compound (86). The more toxic heptachlor epoxide is a metabolite of heptachlor in the dog and rat (77). In these animals, fat is the main storage site of the epoxide, the brain having none. The rate of elimination of heptachlor epoxide from the fat of rats appears to be the same as that of the beta isomer of BHC, faster than DDT, and slower than the other isomers of BHC (19). Heptachlor epoxide is excreted in milk unchanged (35). Aldrin, like heptachlor, undergoes epoxidation to dieldrin before excretion (75). Dieldrin is stored in the body unchanged and eliminated in the urine in the form of dieldrin and at least three unidentified metabolites (47). Endrin is accumulated in the body fat of cows and is excreted in small amounts in their milk (15).

Pathology

In spite of the pronounced neurological signs seen in chlorinated hydrocarbon poisoning, histologic alterations in the CNS are relatively slight or nonexistent (49, 87, 103). After DDT poisoning, vacuolation around large nerve cells (in both the cord and cerebral motor nuclei) and fragmentation of Nissl bodies (tigrolysis) may occur (57). Degenerative changes restricted to the cerebellum (chiefly in the dentate and roof nuclei) may also occur in dogs chronically poisoned by DDT (48). The most striking lesions are seen in the liver, and include hyaline degeneration, fatty degeneration, and central areas of coagulation necrosis (57, 62). Necrosis of skeletal muscle may occur in the guinea pig (62). Moderate colloidal depletion of thyroid glands is observed in rabbits, dogs, rats, and guinea pigs (62). Focal necrosis of the gall bladder may be observed in the rabbit (62). Minor to moderate kidney lesions are seen in large domestic animals, rabbits, and rats (57, 62). Marked adrenal cortical atrophy occurs in dogs fed DDD (63, 104). The *o,p'* isomer is the adrenocorticolytic agent (63). Mild anemia may occur in DDT intoxicated rabbits (83). Testicular atrophy is a common sign of DDT poisoning in cockerels (12, 25). DDD may cause disturbances in chondrogenesis and osteogenesis in dogs and rats (41).

Lesions of BHC poisoning in rats include testicular atrophy and liver enlargement with focal necrosis of the hepatic cells (29). Hepatic focal coagulation necrosis is observed in chlordane poisoned rabbits (86). Other lesions seen in rabbits include hyaline degeneration of the proximal kidney tubules, cellular infiltration of the intestinal submucosa (86) and centrilobular necrosis of the liver (29). In large domestic animals, there is much pathological similarity between DDT and chlordane poisoning (75). The pathological changes in goats are more severe in toxaphene than chlordane poisoning (14). Chronic aldrin or dieldrin poisoning in rats and dogs produces degenerative changes in liver and kidney and reduced cellularity in bone marrow (30). However, the macroscopic and microscopic changes seen in organs of animals poisoned by aldrin, dieldrin and endrin are not pathognomonic (77). Chronic feeding of heptachlor (6 mg/kg daily) to adult rats produces cataracts, both in the suckling offspring and in the parent rats (60).

Disturbances of Biological Functions

It appears that DDT does not affect the vasomotor or respiratory centers, because blood pressure and respiration responses in DDT-intoxicated, pentobarbital-anesthetized cats are normal (84). The only significant unusual effect is insensitivity to peripheral vagal nerve stimulation, with retention of the depressor effect. It is possible to restore irritability by intravenous injection of choline. The site of action of DDT is not clear and appears to involve widespread facilitation within the cerebrospinal axis (36). According to Lauger *et al* (1946) as cited by Bleiberg *et al* (6) cholinesterase levels are not depressed in DDT-poisoned animals. When acetylcholine (ACh) is synthesized *in vitro* by a choline acetylase system, added DDA depresses the acetylcholine synthesis by inhibiting the acetate-activating enzyme system (Acetate + Coenzyme A + Adenosine-5'triphosphate → Adenosine-5'phosphate + Pyrophosphate + Acetyl Coenzyme A) (6). However, pyruvate is the immediate precursor and principal source of acetyl coenzyme A in the intact animal (74). Recent data indicate that total brain acetylcholine is increased following acute DDT, dieldrin, and heptachlor poisoning in rats and cockerels (87). In contrast, acute lindane toxicity has little effect on normal levels of brain ACh (87).

One report indicates (65) that DDT, and perhaps other chlorinated hydrocarbon pesticides, owe their activity in the cockroach to the formation of a charge transfer complex with a component of the nerve axon. It is believed that the induced localized semiconductivity disturbs the normal function of the nervous system (65). It would be interesting to evaluate this hypothesis in mammals and birds.

Recent data indicate that increases in brain levels of ammonia occur during acute chlorinated hydrocarbon insecticide poisoning (44, 45, 88). Increased brain ammonia is regarded by many workers as a probable cause of CNS excitation (79, 95, 98, 99, 100). Fatal ventricular fibrillation, as a concomitant of DDT intoxication, occurs in rabbits, dogs, and monkeys (72). The rabbit, however, is the least sensitive in this respect. This phenomenon has not been investigated in large domestic animals or birds. The mechanism whereby DDT causes sudden death by ventricular fibrillation is not known but it is suggested that DDT both sensitizes the myocardium and causes sympathetic discharges (72). This phenomenon may not be characteristic of all the chlorinated hydrocarbon insecticides, since both aldrin (38) and dieldrin (37) cause bradycardia and other signs of parasympathomimetic action.

Apart from neurological disturbances, the chlorinated hydrocarbons also disturb hormonal activity. Cholesterol is a precursor of progesterone, and a reduction in ovarian cholesterol content occurs in DDT-intoxicated rats (90). However, unlike its methoxy analogue (DMDT), DDT does not have any estrogenic activity on ovariectomized rats.

During prolonged DDT-intoxication the number of living rats in the second generation may be smaller than the first (90). Heptachlor (6 mg/kg body weight daily) chronically administered for 18 months to adult rats, produces no clinical toxicological signs, but results in a marked reduction of litter size in the first generation as well as in successive generations (60). As little as 10 ppm aldrin in the diet interrupts estrus in rats (4). Further studies are needed with regard to litter characteristics, fetal mortality, and teratogenicity.

Existing data indicate that administration of *o,p'*-DDD to dogs (a) produces atrophy of adrenal cortex (zona fasciculata and zona reticularis), (b) suppresses secretion of 17 hydroxycorticoids, (c) inhibits glucose-6-phosphodehydrogenase activity, and (d) does not affect 6-phosphogluconate dehydrogenase (13, 16, 39, 64, 96). Since reduced nicotinamide adenine dinucleotide phosphate (NADPH) is required by the adrenal cortex for the conversion of cholesterol to corticosterone (40), decreased steroid secretion may be caused by glucose-6-phosphodehydrogenase inhibition.

The transformation of a 3β-hydroxy-Δ^5-steroid (3β,-17-dihydroxy-Δ^5-pregnene-20-one-7α-H^3) to its 3α-hydroxypregnane analogue is inhibited *in vivo* in *o,p'*-DDD treated dogs (9). The inhibitory action of DDD on steroid production does not occur in hamsters or rats (39). A marked decrease in α cells and an increase in β cells in the anterior pituitary gland occurs when DDD is administered to dogs and rats; disturbances in chondrogenesis and osteogenesis are observed also (41). More work is required in the area of hormonal disturbances. It is possible that DDT and related compounds have adverse effects on thyroid activity (62).

Intraperitoneal administration of chlordane to rats increases hepatic enzyme activity for certain drugs and it is postulated that chlordane or its metabolites enhance enzyme activity by increasing protein synthesis (42). Repeated administration of phenobarbital (50 mg/kg daily) to rats receiving dieldrin (0.5 mg/kg daily) also stimulates microsomal drug metabolism to the extent that the rate of elimination of the pesticide is increased (17). In rats, dietary DDT at levels as low as 5 ppm significantly reduces the activity of hepatic glucose-6-phosphodehydrogenase although it has no effect on 6-phosphogluconate dehydrogenase (93). To explain the inhibition of glucose-6-phosphodehydrogenase, the hypothesis postulated by Tinsley (93) that (a) an alternate but less effective enzyme is involved, and (b) the synthesis of glucose-6-phosphate dehydrogenase is reduced is in keeping with the consensus of opinion (42, 93).

Tumorigenic Potential

Existing data indicate that (a) DDT does not promote leukemia in the Sherman strain rat (53) and (b) aldrin and dieldrin are not carcinogenic or tumorigenic in rats (31). However, a significant increase in the incidence of hepatomas is observed in C_3HeB/F mice following prolonged feeding of 10 ppm of aldrin and dieldrin (20). Falk (1963), as cited by Kay (52), reports that high dietary levels of methoxychlor fed over 18 months is hepatocarcinogenic.

Induced Resistance

Insecticide resistant insect strains present a problem to the entomologist and parasitologist. Conversion of DDT to DDE is implied as the mechanism of resistance by the house fly (69) and Assassin bug or *Triatoma infestans* (21). Reduced glutathione is required by DDT-dehydrochlorinase for this detoxification to occur (58). The only case to date of resistance in mammals followed selective breeding of a colony of survivors of DDT-intoxicated mice, (*Mus musculus domesticus L*), in which a tolerant strain was developed by the ninth generation (67). The level of tolerance was assessed by comparing intraperitoneal LD_{50} values with those of a control colony started from the same parent colony and reared under similar conditions. In contrast, another report (33) indicates that when generations of the Sherman strain rat are tested for signs of DDT tolerance over four years, no change in susceptibility to the pesticide (oral LD_{50} values) is detected. Until further work is done, the question of true resistance in mammals remains unsettled.

Potentiation, Synergism and Antagonism

Greater than additive toxicity is observed when DDT and pyrethrin are administered in combination (69). Mixtures of equal parts of alpha and gamma isomers of BHC are more toxic than would be expected from the individual LD_{50} values (105). The toxicity of parathion in rats pretreated with aldrin is markedly reduced (3). A marked decrease occurs in storage of dieldrin in adipose tissue of female rats when DDT and dieldrin are fed simultaneously (89), but the significance of this antagonism to dieldrin storage is not clear. Whether this indicates a greater mobilization of dieldrin and thus increased toxicity, or increased conversion into an excretory hydrophilic compound remains to be answered.

Summary

The chlorinated hydrocarbon insecticides (DDT, the cyclodienes, BHC and its isomers) are toxic to both mammals and birds. In spite of the pronounced neurological signs seen in poisoning, histologic alterations in the CNS are relatively slight or nonexistent. The macroscopic and microscopic changes seen in organs of poisoned animals are not pathognomonic. Thus in suspected cases of fatal poisoning, the brains of the dead animals should be analyzed for the toxicant.

All the chlorinated hydrocarbon insecticides tend to be stored more extensively in adipose tissue than in other tissues. The insecticides may be released from fat depots during starvation. The elimination of unabsorbed insecticide is a protection from poisoning and this elimination must be measured in any balance study. True excretion (elimination of previously absorbed material) of the insecticides may occur

by way of urine, feces, milk, eggs, and even the fetus. Knowledge of the metabolism of DDT is incomplete and knowledge of the metabolism of cyclodienes, BHC and its isomers is fragmentary in comparison.

Apart from causing neurological disturbances, the insecticides may disturb hormonal function and reproduction, but further studies are needed with regard to litter characteristics, fetal mortality and teratogenicity. The data on the ability of the chlorinated hydrocarbon insecticides to induce tumors or resistance to toxicity in mammals and birds are confusing and limited. Until further work is done, the question of tumorigenic potential and true resistance in animals remains unsettled.

Résumé

Les insecticides à base d'hydrocarbone chloriné (le DDT, les cyclodiènes, le BHC et ses isomères) sont toxiques à la fois pour les mammifères et les oiseaux. En dépit des symptômes neurologiques prononcés que l'intoxication par ces insecticides entraine, on n'observe, à l'examen histologique du système nerveux central, que peu ou pas de lésions. Les changements macroscopiques ou microscopiques notés dans les organes des animaux intoxiqués ne sont pas pathognomoniques. Il faut donc effectuer la recherche de l'agent toxique dans le cerveau des animaux morts, soupçonnés d'avoir été empoisonnés par ces agents. Tous les insecticides à base d'hydrocarbone chloriné ont tendance à s'accumuler davantage dans le tissu adipeux. Ils peuvent être remis en circulation à partir des dépôts de graisse lors des périodes de jeûne. L'élimination de l'insecticide non-absorbé prévient l'empoisonnement et cette élimination doit être mesurée dans toute étude de leur métabolisme. L'excrétion véritable (définie comme étant l'élimination de substances préablement ingérées) des insecticides peut se faire par voie urinaire, par voi intestinale, par le lait, par les œufs et même par le fœtus. Notre connaissance du métabolisme du DDT est incomplète, et celle du métabolisme des cyclodiènes ainsi que du BHC et de ses isomères est plutôt fragmentaire.

En plus de causer des désordres nerveux, ces insecticides peuvent perturber les systèmes hormonal et reproducteur. De plus amples études sont cependant nécessaires sur les portées qui y ont été exposées, sur la mortalité fœtale et sur les effets tératogènes qu'ils pour raient avoir. Les données disponibles sur les effets carcinogènes de ces insecticides, ou sur la résistance que leur opposent les mammifères et les oiseaux, ne sont ni claires ni nombreuses. Tant que d'autres travaux ne seront pas complétés, ces derniers points doivent demeurer en suspens.

References

1. Arant, F. S. Toxicity of aldrin to chickens. J. econ. Ent. 45: 121. 1952.
2. Bäckström, J., E. Hansson and S. Ullberg. Distribution of C^{14}-DDT and C^{14}-Dieldrin in pregnant mice determined by whole-body autoradiography. Toxic. appl. Pharmac. 7: 90. 1965.
3. Ball, W. L., J. Sinclair, M. Crevier and K. Kay. Modification of parathion's toxicity for rats by pretreatment with chlorinated hydrocarbon insecticides. Can. J. Biochem. Physiol. 32: 440. 1954.
4. Ball, W. L., K. Kay and J. W. Sinclair. Observations on toxicity of aldrin. I. Growth and estrus in rats. AMA Archs ind. Hyg. 7: 292. 1953.
5. Bernard, R. F. Studies on the effects of DDT on birds. "Biological Series." Publications of the Museum, Michigan State University. 2: 159. 1963.
6. Bleiberg, M. J., M. Cefaratti, N. Klinman and P. Kornblith. Studies of choline acetylase inhibition by DDA (dichlorodiphenylacetic acid) and its possible relationship to DDT toxicity. Toxic. appl. Pharmac. 4: 292. 1962.
7. Borgmann, A. R., C. H. Kitselman, P. A. Dahm, J. E. Pankaskie and F. R. Durta. Toxicological studies of aldrin on small laboratory animals. Unpublished report of Kansas State College. March, 1952.
8. Borgmann, A. R., C. H. Kitselman, P. A. Dahm, J. E. Pankaskie and F. R. Durta. Toxicological studies of dieldrin on small laboratory animals. Unpublished report of Kansas State College. July, 1952.
9. Bradlow, H. L., D. K. Fukushima, B. Zumoff, L. Hellman and T. F. Gallagher. A peripheral action of *o,p'* DDD on steroid biotransformation. J. clin. Endocr. Metab. 23: 918. 1963.
10. Brown, A. W. A. Insect Control by Chemicals. p. 467. New York: John Wiley & Sons. 1951.
11. Buck, W. B., R. D. Radeleff, J. B. Jackson, H. V. Claborn and M. C. Ivery. Oral toxicity studies with heptachlor and heptachlor epoxide in young calves. J. econ. Ent. 52: 1127. 1959.
12. Burlington, H. and V. F. Lindeman. Effect of DDT on testes and secondary sex characteristics of white leghorn cockerels. Proc. Soc. exp. Biol. Med. 74: 48. 1950.
13. Cazorla, A. and F. Moncloa. Action of 1,1-dichloro-2-p-chlorphenyl-2-o-chlorphenylethane on dog adrenal cortex. Science 136: 47. 1962.
14. Choudhury, B. and V. B. Robinson. Clinical and pathological effects produced in goats by injection of toxic amounts of chlordane and toxaphene. Am. J. vet. Res. 11: 50. 1950.

15. CLARKE, E. G. C. and M. L. CLARKE. Garner's Veterinary Toxicology. 3rd Edition. p. 210. Baltimore: The Williams & Wilkins Co. 1967.
16. CUETO, JR., C. and J. H. BROWN. Biological studies on an adrenocorticolytic agent and the isolation of the active components. Endocrinology. 62: 334. 1958.
17. CUETO, JR., C. and W. J. HAYES, JR. Effect of phenobarbital on the metabolism of dieldrin. Toxic. appl. Pharmac. 7: 481. (abst.) 1965.
18. DALE, W. E., T. B. GAINES and W. J. HAYES, JR. Poisoning by DDT: Relation between clinical signs and concentration in rat brain. Science 142: 1474. 1963.
19. DAVIDOW, B. and J. P. FRAWLEY. Tissue distribution, accumulation and elimination of the isomers of benzene hexachloride. Proc. Soc. exp. Biol. Med. 76: 780. 1951.
20. DAVIS, K. J. and O. G. FITZHUGH. Tumorigenic potential of aldrin and dieldrin for mice. Toxic. appl. Pharmac. 4: 187. 1962.
21. DINAMARCA, M. L., M. AGOSIN and A. NEGHME. The metabolic fate of C^{14}-DDT in *Triatoma infestans*. Expl Parasit. 12: 61. 1962.
22. DRAIZE, J. H., G. WOODARD, O. G. FITZHUGH, A. A. NELSON, R. B. SMITH, JR. and H. O. CALVERY. Summary of toxicological studies of the insecticide DDT. Chem. Engineering News 22: 1503. 1944.
23. DUNN, J. E., R. C. DUNN and B. S. SMITH. Skin sensitizing properties of DDT for the guinea pig. Publ. Hlth Rep., Wash. 61: 1614. 1946.
24. DURHAM, W. F., P. ORTEGA and W. J. HAYES, JR. The effect of various dietary levels of DDT on liver function, cell morphology, and DDT storage in the rhesus monkey. Archs int. Pharmacodyn. Thér. 141: 111. 1963.
25. ECOBICHON, D. J. and P. W. SASCHENBRECKER. Pharmacodynamic study of DDT in cockerels. Can. J. Physiol. Pharmac. 46: 785. 1968.
26. ECOBICHON, D. J. and P. W. SASCHENBRECKER. The redistribution of stored DDT in cockerels under the influence of food deprivation. Toxic. appl. Pharmac. 15: 420. 1969.
27. EDEN, W. G. Toxicity of dieldrin to chickens. J. econ. Ent. 44: 1013. 1951.
28. FINNEGAN, J. K., H. B. HAAG and P. S. LARSON. Tissue distribution and elimination of DDD and DDT following oral administration to dogs and rats. Proc. Soc. exp. Biol. Med. 72: 357. 1949.
29. FITZHUGH, O. G., A. A. NELSON and J. P. FRAWLEY. The chronic toxicities of technical benzene hexachloride and its alpha, beta and gamma isomers. J. Pharmac. exp. Ther. 100: 59. 1950.
30. FITZHUGH, O. G., A. A. NELSON and M. L. QUAIFE. Chronic oral toxicity of aldrin and dieldrin in rats and dogs. Fd Cosmet. Tox. 2: 551. 1964.
31. FRANK, P. A summary of work on aldrin and dieldrin toxicity at the Kettering Laboratory. Archs envir. Hlth 13: 195. 1966.
32. FREUNDT, K. J. and M. KIESE. Absorption of dieldrin fogs through the lungs. Arch. Tox. 19: 313. 1962.
33. GAINES, T. B. The acute toxicity of pesticides to rats. Toxic. appl. Pharmac. 2: 88. 1960.
34. GALLEY, R. A. E. Problems arising from the use of chemicals in food. The toxicity of residual agricultural chemicals. Chemy Ind. pp. 342–344. 1952.
35. GANNON, N. and G. C. DECKER. The excretion of dieldrin, DDT and heptachlor epoxide in milk of dairy cows fed on pastures treated with dieldrin DDT and heptachlor. J. econ. Ent. 53: 411. 1960.
36. GOODMAN, L. S. and A. GILMAN. The Pharmacological Basis of Therapeutics. 2nd Edition. New York: The MacMillan Co. 1960.
37. GOWDEY, C. W., A. R. GRAHAM, J. J. SEGUIN and G. W. STAVRAKY. The pharmacological properties of the insecticide dieldrin. Can. J. Biochem. Physiol. 32: 498. 1954.
38. GOWDEY, C. W., A. R. GRAHAM, J. J. SEGUIN, G. W. STAVRAKY and R. A. WARD. A study of the pharmacological properties of the insecticide aldrin. Can. J. med. Sci. 30: 520. 1952.
39. GRADY, H. J., D. L. AZARNOFF, R. CREAGAR, D. H. HUFFMAN and J. NICHOLS. Specificity of enzyme inhibition by DDD. Proc. Soc. exp. Biol. Med. 119: 238. 1965.
40. HALBERSTRON, J. D. K., J. EICHORN and O. HACHTER. TPNH required for cholesterol side chain cleavage in adrenal cortex. Archs Biochem. Biophys. 85: 287. 1959.
41. HARADA, M., M. NAKAGAWA and S. O. ZAKI. Changes of bone tissues and endocrine glands in DDD (adrenocorticolytic drug) administered dogs and rats. Wakayama med. Rep. 3: 187. 1957.
42. HART, L. G., R. W. SHULTICE and J. R. FOUTS. Stimulatory effects of chlordane on hepatic microsomal drug metabolism in the rat. Toxic. appl. Pharmac. 5: 371. 1963.
43. HARVEY, J. M. Excretion of DDT by migratory birds. Can. J. Zool. 45: 629. 1967.
44. HATHWAY, D. E. and A. MALLINSON. Chemical studies in relation to convulsive conditions: Effect of telodrin on the liberation and utilization of ammonia in rat brain. Biochem. J. 90: 51. 1964.
45. HATHWAY, D. E., A. MALLINSON and D. A. A. AKINTONWA. Effects of dieldrin, picrotoxin and telodrin on the metabolism of ammonia in brain. Biochem. J. 94: 676. 1965.
46. HAYES, W. J., W. F. DURHAM and C. CUETO. The effect of known repeated oral doses of chlorophenothane (DDT) in man. J. Am. med. Ass. 162: 890. 1956.
47. HAYES, W. J. Review of the metabolism of chlorinated hydrocarbon insecticides especially in mammals. Ann. Rev. Pharmac. 5: 27. 1965.
48. HAYMAKER, W., A. M. GINZLER and R. L. FERGUSON. The toxic effects of prolonged ingestion of DDT on dogs with special reference to lesions in the brain. Am. J. med. Sci. 212: 423. 1946.

49. HODGE, H. C., A. M. BOYCE, W. B. DEICHMANN and H. F. KRAYBILL. Toxicology and no-effect levels of aldrin and dieldrin. Toxic. appl. Pharmac. 10: 613. 1967.
50. HUKUHARA, T. Distribution of DDT between brain and adipose tissue in experimental poisoning of rats and the behavior of DDT in stored fat during starvation. Archs exp. Path. Pharmac. 242: 522. 1962.
51. INGLE, L. Toxicity of chlordane to white rats. J. econ. Ent. 40: 264. 1947.
52. KAY, K. State of knowledge on human exposures and biological effects of economic poisons. Clin. Pharmac. Ther. 5: 737. 1964.
53. KIMBROUGH, R., T. B. GAINES and J. SHERMAN. Nutritional factors, long-term DDT intake and chloroleukemia in rats. J. natn. Cancer Inst. 33: 215. 1964.
54. KLEIN, A. K., E. P. LAUG, P. F. DATTA, J. O. WATTS and J. T. CHEN. Metabolites: Reproductive dechlorination of DDT to DDD and isomeric transformation of *o,p'*-DDT to *p,p*-DDT *in vivo*. J. Ass. off. analyt. Chem. 47: 1129. 1964.
55. KOEMAN, J. H., R. C. H. M. OUDEJANS and E. A. HUISMAN. Danger of chlorinated hydrocarbon insecticides in birds' eggs. Nature, Lond. 215: 1094. 1967.
56. KONST, H. and P. J. G. PLUMMER. Studies on the toxicity of DDT for domestic and laboratory animals. Can. J. comp. Med. 10: 128. 1946.
57. LILLIE, R. D. and M. I. SMITH. Pathology of experimental poisoning in cats, rabbits and rats with 2,2-bis (p-chlorophenyl) 1,1,1-trichoroethane. Publ. Hlth Rep., Wash. 59: 979. 1944.
58. LIPKE, H. and C. W. KEARNS. DDT dehydrochlorinase I. Isolation, chemical properties, and spectrophotomeric assay. J. biol. Chem. 234: 2123. 1959.
59. MARSDEN, S. J. and H. R. BIRD. Effects of DDT on growing turkey. Poult. Sci. 25: 3. 1947.
60. MESTITZOVA, M. On reproduction studies and the occurrence of cataracts in rats after long-term feeding of the insecticide heptachlor. Experientia 23: 1. 1967.
61. MORIN, E. W., A. ROBERTSON and M. BEAUREGARD. Endrin poisoning in chickens. Can. vet. J. 11: 74. 1970.
62. NELSON, A. A., J. H. DRAIZE, G. WOODARD, O. G. FITZHUGH, R. B. SMITH, JR. and H. O. CALVERY. Histopathological changes following administration of DDT to several species of animals. Publ. Hlth Rep., Wash. 59: 1009. 1944.
63. NICHOLS, J. and L. I. GARDNER. Production of insulin sensitivity with the adrenocorticolytic drug DDD 2,2-bis (p-chlorophenyl) 1,1-dichlorethane. J. Lab. clin. Med. 37: 229. 1951.
64. NICHOLS, J. and A. W. RICHARDSON. Effects of DDD on steroid response and blood flow through the adrenal after ACTH. Proc. Soc. exp. Biol. Med. 104: 539. 1960.
65. O'BRIEN, R. D. DDT: A new hypothesis of its mode of action. Science 146: 657. 1964.
66. O'BRIEN, R. D. DDT and related compounds. *In* Insecticides: Action and Metabolism. p. 108. New York & London: Academic Press. 1967.
67. OZBURN, G. W. and F. O. MORRISON. Development of DDT tolerant strain of laboratory mice. Nature, Lond. 196: 1009. 1962.
68. PEARSON, J. K. L., J. R. TODD and S. BAIRD. An outbreak of aldrin poisoning in suckling lambs. Vet. Rec. 70: 783. 1958.
69. PERRY, A. S. and W. M. HOSKIN. The detoxification of DDT by resistant house flies and inhibition of this process by piperonyl cyclonene. Science 111: 600. 1950.
70. PETERSON, J. E. and W. H. ROBINSON. Metabolic products of *p,p'*-DDT in the rat. Toxic. appl. Pharmac. 6: 321. 1964.
71. PHILIPS, F. S. and A. GILMAN. Studies on the pharmacology of DDT 2,2-bis (p-chlorophenyl)-1,1,1-trichloroethane. I. The acute toxicity of DDT following intravenous injection in mammals with observations on the treatment of acute DDT poisoning. J. Pharmac. exp. Ther. 86: 213. 1946.
72. PHILIPS, F. S., A. GILMAN and F. N. CRESCITELLI. Studies on the pharmacology of DDT [2,2-bis (p-chlorophenyl)-1,1,1-trichloroethane] II. The sensitization of the myocardium to sympathetic stimulation during acute DDT intoxication. J. Pharmac. exp. Ther. 86: 222. 1946.
73. PINTO, J. D., M. N. CAMIEN and M. S. DUNN. Metabolic fate of *p,p*-DDT [1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane] in rats. J. biol. Chem. 240: 2148. 1965.
74. QUASTEL, L. H. Acetylcholine distribution and synthesis in the central nervous system. *In* Neurochemistry. Ed. by K. A. C. Elliott and J. H. Quastel. p. 14. Springfield, Ill.: Charles C. Thomas. 1962.
75. RADELEFF, R. D. Veterinary Toxicology. p. 212. Philadelphia: Lea & Febiger. 1964.
76. RADELEFF, R. D., G. T. WOODARD, W. J. NICKERSON and R. C. BUSHLAND. U.S. Dept. Agric. Tech. Bull. No. 1122. 1955.
77. RADOMSKI, J. L. and B. DAVIDOW. The metabolite of heptachlor, its estimation, storage, and toxicity. J. Pharmac. exp. Ther. 107: 266. 1953.
78. RESSANG, A. A., I. TITUS, R. S. ANDAR and D. SOEDARMO. Aldrin, dieldrin and endrin intoxication in cats. Communicationes vet., Bogor 2: 71. 1958.
79. RICHTER, D. and R. M. C. DAWSON. The ammonia and glutamine content of the brain. J. biol. Chem. 176: 1199. 1968.
80. ROSENBERG, M. M. and H. E. ADLER. Comparative toxicity of DDT and chlordane to young chicks. Am. J. vet. Res. 11: 142. 1950.
81. ROSENBERG, M. M. and T. TANAKA. Toxicity of chlordane to growing chickens. Am. J. vet. Res. 11: 233. 1950.
82. ROSENBERG, M. M., T. TANAKA and H. E.

ADLER. Toxicity of chlordane to laying pullets. Am. J. vet. Res. 11: 236. 1950.
83. SMITH, M. I. and E. F. STOHLMAN. The pharmacologic action of 2,2-bis (p-chlorophenyl) 1,1,1-trichlorethane and its estimation in the tissues and body fluids. Publ. Hlth Rep., Wash. 59: 984. 1944.
84. SMITH, M. I. and E. F. STOHLMAN. Further studies on the pharmacologic action of 2,2-bis (p-chlorophenyl) 1,1,1-trichlorethane (DDT). Publ. Hlth Rep., Wash. 60: 289. 1945.
85. SOLLMAN, T. A Manual of Pharmacology. 8th Edition. Philadelphia and London: W. B. Saunders Company. 1957.
86. STOHLMAN, E. F., W. T. S. THORP and M. I. SMITH. Toxic action of chlordane. Archs ind. Hyg. Occup. Med. 1: 13. 1950.
87. ST. OMER, V. V. E. The effects of some chlorinated hydrocarbon insecticides on biochemical changes in brains of female rats and cockerels. Ph.D. Thesis. Univ. Guelph, Guelph, Ont. Canada. 1969.
88. ST. OMER, V. V. E. Investigations into mechanisms responsible for seizures induced by chlorinated hydrocarbon insecticides: The role of brain ammonia and glutamine in convulsions in the rat and cockerel. In Press: J. Neurochem.
89. STREET, J. C. DDT antagonism to dieldrin storage in adipose tissue of rats. Science 146: 1580. 1964.
90. TAUBER, O. E. and A. B. HUGHES. Effect of DDT ingestion on total cholesterol content of ovaries of white rat. Proc. Soc. exp. Biol. Med. 75: 420. 1950.
91. TELFORD, H. S. and J. E. GUTHRI. Transmission of the toxicity of DDT through milk of white rats and goats. Science 102: 647. 1945.
92. THOMAS, J. W., P. E. HUBANKS, R. H. CARTER and L. A. MOORE. Feeding DDT and alfalfa sprayed with DDT to calves. J. Dairy Sci. 34: 203. 1951.
93. TINSLEY, I. J. DDT ingestion and liver glucose-6 phosphate dehydrogenase activity. Biochem. Pharmac. 14: 847. 1965.
94. TREON, J. F., F. E. SHAFFER, F. R. DURTA, J. CAPPEL, T. GAHEGAN and G. NEDDERMAN. The effects of repetitive exposure of animals to lindane vapor with some observations on the distribution of lindane in their tissue. Kettering Lab., Univ. Cincinatti. p. 16. 1951.
95. TSUKADA, Y., G. TAKAGAKI, S. SUGIMOTO and S. HIRANO. Changes in ammonia and glutamine content of the rat brain, induced by electric shock. J. Neurochem. 2: 295. 1958.
96. TULLNER, W. and R. HERTZ. Effect of intravenous *o,p'* DDD on plasma 17-hydroxycorticoid secretion in the dog. Endocrinology 66: 494. 1960.
97. TURK, R. D. and E. G. BATTE. Chlordane in the control of external parasites of dogs and cats. North Am. Vet. 29: 359. 1948.
98. VRBA, R. Significance of glutamic acid in metabolic processes in the rat brain during physical exertion. Nature, Lond. 176: 1258. 1955.
99. VRBA, R. A source of ammonia and changes of protein structure in the rat brain during physical exertion. Nature, Lond. 176: 117. 1955.
100. VRBA, R. Amide bonds in the rat brain after acute carbon disulphide poisoning. *In* Metabolism of the Nervous System. Ed. by D. Richter. p. 475. London: Pergamon Press. 1957.
101. WEBB, R. E. and F. HORSFALL, JR. Endrin resistance in the pine mouse. Science 156: 1762. 1967.
102. WHITE, W. C. and T. R. SWEENEY. The metabolism of DDT. I. A metabolite from rabbit urine. DDA: its isolation, identification and synthesis. Pub. Hlth Rep., Wash. 60: 66. 1945.
103. WINTERINGHAM, E. P. W. and J. M. BARNES. Comparative response of insects and mammals to certain halogenated hydrocarbons used as insecticides. Physiol. Rev. 35: 701. 1955.
104. WOODARD, G., B. DAVIDOW and A. NELSON. Effects observed in dogs following the prolonged feeding of DDT and its analogues. Fedn Proc. 7: 266. 1948.
105. WOODARD, G. and E. C. HAGAN. Toxicological studies on the isomers and mixtures of isomers of benzene hexachloride. Fedn Proc. 6: 386. 1947.
106. WOODARD, G., R. R. OFNER and C. M. MONTGOMERY. Accumulation of DDT in the body fat and its appearance in the milk of dogs. Science 102: 177. 1945.