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ACTIONS OF PESTICIDES AND OTHER DRUGS ON THE MALE REPRODUCTIVE SYSTEM

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by

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DDT administered to male mice caused significant reductions in the assimilation of androgens by sex accessory organs. DDT altered the metabolism of testosterone in the prostate gland and in the liver. DDT-^{3}H administration led to the detection of significant amounts of tritium in male reproductive organs.

Dieldrin caused significant alterations in the assimilation and metabolism of testosterone-1,2-^{3}H in sex accessory organs and in hepatic microsomes of rodents.

The herbicide 2,4,5 trichlorophenoxy acetic acid (2,4,5 T) was effective in altering the metabolism of androgens in male reproductive organs, but had little effect upon the hepatic microsomal metabolism of androgens.

Unlike the organochlorine-type pesticides, carbaryl administration failed to alter androgen metabolism. The administration of carbaryl-^{14}C led to detectable amounts of radioactivity in several organs of reproduction including the seminal vesicles, prostate gland and testes. Low concentrations of labeled carbaryl and/or its radiometabolites were detected in the seminal plasma of the male mouse.

Parathion administration did not produce any significant changes upon the uptake and/or the metabolism of androgens by sex accessory organs of the mouse.

The fungicide, thiophanate and thiophanate-methyl had no affect upon spermatogenesis or upon the metabolism of androgens. This agent did significantly increase the weights of the adrenal gland.

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SECTION I

CONCLUSIONS

ORGANOCHLORINES

DDT

Orally administered technical grade DDT (12.5, 25 or 50 mg/kg) was studied in intact male mice and in intact and ovariectomized female mice. Regardless of the dose of DDT, there was a significant reduction ($P \leq 0.05\%$) in the prostate gland's ability to assimilate radioactive testosterone. The mechanism(s) of inhibitory action of DDT upon male sex accessory glands did not appear to be due to its reported inherent estrogenicity. Single po doses of DDT-^{3}H revealed considerable amounts of radioactivity localized in several male reproductive organs. The prostate and the testes exhibited significant amounts as early as one and two hr post-administration. Epididymal fat pads retained amounts of radioactive pesticide as long as twelve days after DDT-^{3}H ingestion.

The 10-day oral administration of DDT (25 or 50 mg/kg) led to significant reductions in the accumulation of 1,2-^{3}H - testosterone and its principal metabolite 1,2-^{3}H - 5α-dihydrotestosterone by the anterior prostate gland of the mouse. However, the ratio of 1,2-^{3}H - testosterone to 1,2-^{3}H - 5α-dihydrotestosterone was not altered significantly. This would suggest that the uptake, but not the subsequent metabolism, of the labeled androgen was decreased. Hepatic formation of polar metabolites of 1,2-^{3}H testosterone was also reduced by DDT pretreatment. No significant changes were observed in accessory sex organ weights or prostate gland fructose concentration following pretreatment with this pesticide. The data suggest that DDT may in part alter the accumulation of prostatic androgens as a result of altered hepatic steroid hydroxylation. However, the results obtained do not rule out a direct effect of DDT on the uptake of 1,2-^{3}H - testosterone by the prostate gland.

Dieldrin

Dieldrin administration (1.25, 2.50, or 5.00 mg/kg daily x 5 p.o.) significantly reduced the total uptake and subsequent metabolism of

labeled androgens in the mouse anterior prostate gland. The in vivo metabolism of 1,2-^{3}H-testosterone to ^{3}H-dihydrotestosterone (^{3}H-DHT), ^{3}H-androstanediol or ^{3}H-androstenedione by the mouse prostate gland was lowered by pretreatment with dieldrin. Similarly, the in vitro metabolism of 1,2-^{3}H-testosterone to these aforementioned radiometabolites was reduced by dieldrin at a treatment level of 5 mg/kg (daily x 5 po). This highest dose regime also reduced the formation of the metabolites of testosterone in mouse hepatic microsomes. Varying concentrations of dieldrin (4×10^{-7}, 4×10^{-6}, or 2×10^{-5} M) in vitro effectively decreased the formation of H^{3}-DHT in the mouse anterior prostate gland and of ^{3}H-androstanediol in the rat ventral prostate gland.

The oral administration of varying doses (2.5 or 5 mg/kg daily x 10) of dieldrin led to significant reductions in the accumulation of radioactive androgen by the mouse prostate gland. This was reflected not only by a reduction in the total accumulation of tritiated steroid (^{3}H -T) by prostate gland, but also by a decrease in the concentration of dihydrotestosterone (^{3}H-DHT). The ratio of ^{3}H-T to ^{3}H-DHT remains, however, similar in treated and control groups. The doses of dieldrin used had little effect upon sex accessory organ weights or prostatic fructose concentration. Dieldrin administration failed to alter gonadal weights. There was no change in the hepatic formation of radioactive dihydrotestosterone, androstanediol or androstenedione from 1,2-^{3}H-testosterone in the dieldrin-treated animals, but dieldrin did produce increases in liver androgen hydroxylase activity. While the amounts of dieldrin used in these studies were quite high, the results, nevertheless, indicate that this organochloride could represent a potential deleterious chemical from the standpoint of the male reproductive system.

2,4,5-T

High doses of 2,4,5 trichlorophenoxy acetic acid (2,4,5 T) (6.25, 12.5, or 25 mg/kg daily x 10) were administered orally to mature male mice. The herbicide 2,4,5 T significantly reduced the assimilation of radioactive androgen by the prostate gland ($P \leq 0.05$). This was reflected not only in a reduction in the total accumulation of 1,2-^{3}H-testosterone by the prostate gland, but also in a decrease in the levels of its labeled metabolites. There was no change in the hepatic formation of either polar metabolites or of dihydrotestosterone, androstanediol, or androstenedione from ^{3}H-T in

the 2,4,5-T treated mice. This pesticide had little or no effect on the weight responses of either the testes or the sex accessory organs. Prostate gland fructose, a chemical indicator of androgenic activity, was not altered by 2,4,5-T treatment.

ORGANOPHOSPHATES

Parathion

The daily oral administration of parathion (1.3, 2.6 or 5.3 mg/kg) had no effect upon the uptake and subsequent metabolism of 1,2-^{3}H-testosterone by the mouse prostate gland. These dose schedules also had no effect upon the ability of the prostate gland to biotransform labeled testosterone to its principal radiometabolites. Hepatic microsomes obtained from mice previously treated with parathion failed to reveal any alterations in their capacity to hydroxylate 1,2-^{3}H-testosterone. Since the amounts of 6β, 7α or 16α-^{3}H hydroxy-testosterone were unchanged by parathion treatment, androgen hydroxylase activity was not affected by this organophosphate pesticide. Although these polar radiometabolites remained unchanged by parathion pretreatment, ^{3}H-androstanediol content was enhanced. ^{3}H-dihydrotestosterone (^{3}H-DHT) and ^{3}H-androstenedione formation from 1,2-^{3}H-testosterone by hepatic microsomes were not affected by parathion pretreatment. Various *in vitro* concentrations of parathion (4×10^{-7}, 4×10^{-6} or 2×10^{-5} M) significantly reduced the formation of ^{3}H-DHT in the mouse prostate gland, but not in the rat prostate gland. In the rat prostate, ^{3}H-androstenedione concentrations were significantly increased by parathion *in vitro*.

CARBAMATES

Carbaryl

Carbaryl (1-naphthyl-N-methylcarbamate), a carbamate pesticide, was investigated with regard to its effects on certain metabolic aspects of the male mouse reproductive system. A 5-day period of treatment with carbaryl had little effect on the ability of the anterior prostate gland to biotransform 1,2-^{3}H-testosterone to its major nonpolar

radiometabolites in vitro. This 5-day treatment period resulted in alterations in hepatic ^{3}H-hydroxytestosterone derivatives; carbaryl significantly increased 16α-^{3}H-hydroxytestosterone. The in vitro incubation of carbaryl with prostate tissue and 1,2-^{3}H-testosterone resulted in a stimulation of ^{3}H-dihydrotestosterone formation, suggesting a direct action of carbaryl on prostatic steroidogenesis.

A 5-day treatment period using varying doses of carbaryl (8.5, 17 or 34 mg/kg daily, p.o.) failed to alter significantly the ability of the prostate gland to assimilate 1,2-^{3}H-testosterone. Neither testicular nor sex accessory gland weights were affected by these regimens of carbaryl. A single oral dose of ^{14}C-carbaryl (24 μCi/kg equivalent to 0.9 mg/kg) led to detectable amounts of radioactivity in several organs or reproduction including the prostate gland, seminal vesicles and testes. Very low concentrations of labeled carbaryl and/or its radiometabolites were detected in the epididymal fat pads and in the seminal plasma.

FUNGICIDES

Thiophanate

The daily oral administration of thiophanate (295 mg/kg) or thiophanate-methyl (195 mg/kg) had no affect upon spermatogenesis or the ability of the prostate gland to assimilate 1,2-^{3}H-testosterone. Little change occurred in the weights of the sex accessory organs, though there were significant increases in the weight of the prostate gland. The weights of the adrenal glands also increased significantly in the treated mice.

SECTION II

RECOMMENDATIONS

The current series of studies encompassed the action of single pesticides with male reproductive systems.

It was found that the organochlorine pesticides are the principal class of pesticides that exert significant changes upon male reproductive systems. Although each of the representative compounds studied from this class of pesticides have the same basic effects upon the male reproductive system, the mechanism of their actions seems to be different. The present studies were not specifically designed to elucidate the mechanism of action of the various compounds. Future studies should certainly be devoted to examining some of these mechanisms.

Another recommendation to be considered is pesticide interactions. Pesticide synergism or interaction is an area in which remarkably little work has been done. Pesticide interactions are important since public exposure to pesticides is rarely to a single compound. Preliminary experiments involving pesticide interaction have been performed within this laboratory and have confirmed the interaction of more than one pesticide upon the endocrine system.

Limited parathion-dieldrin interaction studies have shown that the in vitro metabolism of Testosterone-H^3 to its principal metabolites by prostate glands from male mice were increased significantly by simultaneous or successive pre-treatment with dieldrin and parathion. Similar preliminary results were obtained when hepatic microsomal protein and cytochrome P-450 concentrations were investigated. Such studies require more extensive investigation.

A final recommendation is that toxicological and pharmacological examinations of pesticide products newly marketed should be expanded to assess their affects upon mammalian reproductive systems. It is necessary to obtain complete toxicological profiles on commercially available pesticides, singly or in combination, and to what extent the actions can alter endocrine function.

INTRODUCTION

Much literature exists pertaining to the effects of pesticides on both the vertebrate and the invertebrate animals. But little specific attention has been devoted to the actions of these compounds upon the endocrine system, and in particular their effects upon the male reproductive system. There is growing evidence that some of these compounds can adversely affect hormonal balance in mammals. Some of these pesticide-induced changes in hormonal balance can be mediated by alterations in hepatic microsomal enzyme systems (Hart and Fouts, 1963; Conney et al, 1967; Welch, et al, 1967; Abernathy et al, 1971). There also have been documented sex differences in the metabolism of pesticides (Wong and Terriere, 1965). Other pesticide-induced changes in hormonal balance can be ascribed to their direct actions upon such organs as the testes and the ovaries. They also produce changes in steroid-dependent organs such as the uterus and the prostate.

Reports have indicated that the organochlorines (e.g. DDT, Dieldrin, 2,4,5 T) can adversely affect the male reproductive function. Investigation with dieldrin suggests that it can affect androgen target organs such as the prostate gland (Thomas et al, 1973; Thomas and Schein, in press; Thomas and Lloyd, 1973). Wakeling et al (1972) showed that dieldrin significantly reduced both nuclear and cytoplasmic in vitro binding of dihydrotestosterone (DHT) to a prostatic protein fraction.

Relatively few studies have been concerned with the organophosphate pesticides. Swan et al (1958) reported that the acute toxicity of parathion was related to the sex of the animal and the sexual maturity gave added protection against the toxicity of parathion.

The carbamates, more specifically carbaryl, reportedly has an affect upon the adenohypophysial activity by increasing the synthesis and release of gonadotropin (Schtenberg & Rybakova, 1968). Little attention has been devoted to the actions of the carbamates on androgen metabolizing tissues such as the prostate or the liver. Carbaryl, like parathion, has been shown during this series of experiments to have no demonstrable effect upon the male reproductive system (Dieringer and Thomas, 1974).

Human male reproductive function also appears to be affected by exposure to pesticides as evidenced by the fact that impotence was reported by four out of five farm workers following exposure to several pesticides and herbicides (Espir et al, 1970).

The findings discussed in this report reveal the effects of the various pesticides upon the male sex accessory organs and upon the hepatic microsomal enzyme system involved in androgen metabolism.

More specifically these studies were designed to study the effects of pesticide exposure upon the in vivo and the in vitro assimilation of H^3-testosterone by the prostate gland. The prostate gland is a very representative organ insofar as male sex hormone responsiveness. Further, the in vivo and in vitro metabolism of the radiosteroid by the prostate gland, and upon the in vitro metabolism of radiosteroid by the hepatic microsomal enzyme system was clearly examined. The gravimetric responses of the testes and other sex accessory organs were investigated. Some studies were concerned with prostate gland fructose concentration since this parameter provides an additional index of androgenic activity.

The compounds investigated in this study were:

1. Organochlorines - DDT, Dieldrin, 2,4,5-T
2. Organophosphate - Parathion
3. Carbamate - Carbaryl
4. Fungicide - Thiophanate and Thiophanate-Methyl (per request of EPA)

EXPERIMENTAL DESIGN

Animal Techniques

Mature male Swiss-Webster mice weighing between 30 and 40 g were used in these experiments. All animals were obtained from Hilltop Lab Animals located in Scottdale, Pennsylvania. The animals were fed a standard diet of laboratory chow and water *ad libitum*. Some limited experiments used dogs.

Pesticide Dose Regimen

The pesticides and herbicides used for the *in vivo* studies were dissolved in corn oil and administered by gastric incubation in a volume of approximately 0.1 ml. Control animals received a similar volume of corn oil. The fungicides (viz. thiophanate and thiophanate-methyl) were suspended in a 1% Methocel® solution.

The pesticides were ordinarily administered over a period of 5 or 10 days (e.g. 1.25, 2.50 or 5.00 mg/kg dieldrin per day), and the animals were sacrificed 24 hours after the administration of the final dose. A no-effect level insofar as the weights of endocrine organs was frequently used to study subtle biochemical changes.

The *in vitro* studies examined the effects of varying concentrations of the compound being studied (4×10^{-7}, 4×10^{-6}, and 2×10^{-5} M) upon H^3-testosterone metabolism utilizing the prostate and the livers of the experimental animals. The pesticide solution was added (20 µl) directly into the incubating medium. Control groups received a 20 µl volume of corn oil.

Radiosteroid Accumulation By The Prostate In Pesticide-Treated Mice

Mouse anterior prostate glands (also called coagulating glands) were rapidly excised and frozen in liquid nitrogen five

minutes after a single intraperitoneal injection of 1,2-^{3}H testosterone (100 µCi/kg or 10 µg/kg) (spec. act. 43.5 µCi/mM) (New England Nuclear Co.). This 5 minute in vivo uptake of radioactive testosterone was studied 24 hours after administration of the final pesticide dose. In normal mice this uptake interval reveals significant androgen assimilation.

After sacrifice the prostate glands were frozen, weighed, and homogenized in glass distilled water. The homogenates were rinsed 3 times with chloroform-ether (2:1) (efficiency of extraction was approximately 70%). The samples were subsequently shaken vigorously for 30 minutes and then allowed to stand overnight at 4°C in order to effect partition of the organic and aqueous layers. Aliquots of the organic phase of the samples were removed, evaporated to dryness under a stream of nitrogen, and resuspended in chloroform. A suitable scintillation cocktail was added to aliquots of the resuspension for subsequent measurement of radioactivity. Such measurements were provided an index of total radiosteroid (e.g. H^3-testosterone + H^3-DHT, etc.).

Twenty microliter aliquots of the resuspended prostate homogenates were spotted on Silica-Gel-G (Eastman Co.) thin layer chromatography (TLC) plates to examine the content of specific radiometabolites of H^3-testosterone. This TLC technique utilized a solvent system consisting of chloroform-ether (7:3). Visualization of radiosteroid metabolites was accomplished by iodine vapour. This particular TLC system effectively separates androstanediol (R_f=.507), androstenedione (R_f=.801), dihydrotestosterone (R_f=.680), and testosterone (R_f=.591). After visualization, the spots were scraped from the plates into scintillation vials for subsequent assessment of their radioactivity.

Some experiments isolated the polar metabolites of testosterone. Prostatic and hepatic androgen hydroxylase activity was examined following pesticide administration. Several hydroxytestosterone derivatives were separated (6β, 7α and 16α hydroxytestosterone).

Radioactivity (expressed as DPM/mg wet weight) was counted on a Packard tri-carb liquid scintillation spectrometer and was corrected for quenching and background.

Preparation Of Hepatic Microsomes From Mouse & Rat Livers

Liver samples (2 g) were rapidly excised and homogenized (Polytron®) in 2 volumes of ice cold 1.5% KCl. The homogenate was centrifuged (9000 x g) for 25 minutes at 4°C. The supernatant was decanted and subsequently re-centrifuged at 100,000 x g for 60 minutes at 4°C to guild a microsomal pellet. The microsomal pellet was resuspended in 3 volumes of ice cold phosphate buffer (pH 7.4) and adjusted so that 333 mg of fresh liver was equivalent to 20 mg of microsomal protein/ml. Proteins were measured using the Lowry technique. Aliquots (0.5 mls) of this adjusted microsomal fraction were used for in vitro incubation with 1,2-H^3-testosterone (3.4×10^{-8}M).

In Vitro Incubations

Hepatic microsomes or lobes of the prostate gland were incubated for 60 minutes at 37°C (or for 15 minutes in some of the experiments) in a Krebs-Ringer bicarbonate buffer (pH 7.4). This buffer system also contained 4mM NADP, 5mM glucose-6-phosphate, 5mM $MgCl_2$, 4µM nicotinamide, 5 I.U. glucose-6-phosphate dehydrogenase, and 1,2-H^3-testosterone. The total volume was 1 ml. Tissues were incubated aerobically in a Dubnoff Metabolic shaker. Reactions were terminated by addition of 2 ml of ice cold diethyl ether. The tissues (prostate) were subsequently removed from the incubation vials and frozen in liquid nitrogen. Tissue and/or medium radiosteroids were extracted, separated on TLC plates, and counted in a liquid scintillation system.

Radioactive Pesticide (And/Or Its Radiometabolites) Distribution Studies

The distribution of radioactivity following ^{14}C-carbaryl (24 µCi/kg or 0.9 mg/kg) (Mallinckrodt Radiochemicals) (spec. act. 5.2 mCi/m mol.) or ^3H-DDT (10 µCi/kg) (New England Nuclear) (spec. act. 51 Ci/mM) was examined following the single injection of either radioactive pesticide. Mice were sacrificed at varying intervals after the administration of the radioactive pesticide and various tissues (e.g. testes, prostate glands, epididymal fat, brain, etc.) were removed, weighed, digested in solubilizer (NCS) and counted in a Packard liquid scintillation spectrometer. No attempt was made to chemically identify the radioactivity.

Prostate Gland Fructose Determination

The anterior lobes of the mouse prostate glands were removed from mice killed by cervical dislocation 24 hours after the final dose of the pesticide treatment period, blotted, and weighed. Each gland was homogenized (4% W/V), precipitated with heavy metals (i.e. barium hydroxide and zinc sulfate), and the supernatant was examined for free fructose (Thomas *et al*, 1968). Fructose concentrations were expressed as mg/100 gm wet weight of the tissue.

Histological Sections

Testes were removed and were fixed in 5% formalin. They were sectioned (10 μ) and stained with hematoxylin and eosin.

Statistics

Experimental and control groups were chosen randomly. Age and weights were variables that were kept constant among the groups. Usually a minimum of six animals were used per group.

Tissue radioactivity DPM/mg or organ weights (*viz*. testes, prostate, etc.) obtained from appropriate controls were compared with the appropriate pesticide treated groups using either Student's *t*-test or one-way analysis of variance (Snedecor, 1956) depending on which was applicable.

SECTION V

EVALUATION OF RESULTS

Substantial amounts of radiosteroid were found in the mouse anterior prostate gland five minutes after i.p. injection of 1,2-H^3-testosterone (Table 1). However, pretreatment with varying doses of DDT (10 days) resulted in significant reductions in the labeled steroid concentration in this gland at the two highest doses (25 and 50 mg/kg). These reductions were reflected in decreases in both H^3-testosterone and its principal metabolite H^3-DHT.

The effects of a 10-day p.o. regimen of DDT on the hepatic biotransformation of H^3-testosterone to various metabolites is shown in Table 2. Substantial reductions were found in the in vitro formation of 6β, 7α, and 16α by liver microsomal preparations from animals pretreated with the two highest dose levels of DDT.

Pretreatment with dieldrin can significantly decrease the amount of radiosteroid accumulated by the prostate gland (Table 3). The highest dose level led to a 40% reduction in the levels of prostate gland radiosteroid. Dieldrin failed to produce any marked changes in the relative proportion of the radiometabolite formed from 1,2-H^3-testosterone; marked changes were found in the absolute amounts of the specific radiometabolites compared to control values. Dieldrin enhanced hepatic androgen hydroxylase activity (Table 4). While the amounts of 6β and 7α were slightly increased by dieldrin pretreatment, the 16α derivative was significantly increased. This effect has been found in both the 5 day and the 10 day dieldrin pre-treatment studies.

Because of these observed effects (i.e. Table 4), it was of interest to examine the in vitro accumulation of radiosteroids by the mouse prostate gland following a 10-day dieldrin pretreatment period (Table 5). There was a marked increase in the accumulation of labeled testosterone that took place and the relative proportion of these androgens was not altered.

Table 6 indicated that a 10-day period of administration of 2,4,5-T also significantly reduced the assimilation of radioactive steroid by the mouse prostate gland. The effect of this herbicide on the relative degree of steroid biotransformation is also shown. No changes were detected in the relative proportion of the radiometabolites of 1,2-H^3-testosterone, although marked alterations were found in the absolute levels of radiometabolites.

Table 7 shows the effect of a 10-day regimen of 12.5 mg/kg of 2,4,5-T on the hepatic biotransformation of 1,2-H^3-testosterone. No significant changes were found.

While the assimilation of androgens was reduced by treatment with the organochlorines, no significant alterations were observed in the gravimetric responses of either the seminal vesicles or the prostate glands (Table 8). Similarly, fructose levels in the prostate glands of DDT and 2,4,5-T were not significantly reduced. Prostate gland fructose concentrations in the dieldrin-treated animals, although not significantly reduced, showed a trend toward reduction. Testicular weights also remained unchanged.

Table 9 shows that varying doses of parathion had little gravimetric effect upon the reproductive organs of the mouse. Neither the testicular weights nor the prostate gland weights were affected. The uptake of tritiated testosterone was not affected by pretreatment with parathion. Similarly, radiometabolites were not affected by parathion. Regardless of the dose of parathion, no changes in the pattern of radiosteroids were detected. Parathion pretreatment likewise failed to effect any demonstrable changes in the hydroxylation of 1,2-H^3-testosterone by the hepatic microsomal enzyme system (Table 10).

Carbaryl pretreatment led to slight enhancement in the ability of the prostate to assimilate injected 1,2-H^3-testosterone, but no statistical elevations were noted (Table 11). Gravimetric responses of the sex accessory organs remained unaffected. Although not shown, limited studies have demonstrated that pretreatment with carbaryl significantly enhanced the 16α-hydroxylation of 1,2-H^3-testosterone by the hepatic microsomal enzyme system.

The assimilation of labeled testosterone by mice pretreated with thiophanate or thiophanate-methyl (daily x 5 po) was not affected (Table 12). This fungicide had no effect upon the gravimetric responses of sex accessory organs, but it did cause a significant increase in the weight of the adrenal gland. The histological sections of the testes revealed that neither thiophanate nor thiophanate-methyl affected spermatogenesis. No sterile tubules were observed and the interstitial cells appeared normal.

TABLE 1

Accumulation of Radioactive Steroid in Mouse Anterior Prostate Glands Following Oral Administration of DDT (daily x 10).

Daily Dose (mg/kg)	H^3-Testosterone (T^3-H)[a]	H^3 5α-dihydro-testosterone	Total Steroid
Control	3594 ± 268	2453 ± 294	8180 ± 816
12.5	3252 ± 224	1904 ± 179	7298 ± 990
25	2305 ± 179[b]	1816 ± 161[b]	5787 ± 619[b]
50	2028 ± 116[b]	1837 ± 152[b]	5508 ± 717[b]

[a] Mean ± S.E.M. of 6 animals expressed as dpm/

[b] Significantly Different from control $P < 0.05$

TABLE 2

Accumulation of Radioactivity as Various Hydroxylated Metabolites of Testosterone Following a 15 Minute Incubation of Liver Microsomes With 1,2-H^3-Testosterone.

	DDT (mg/kg x 10 day, po)			
	Control[a]	12.5	25	50
6B-Hydroxytestosterone	850 ± 69	841 ± 110	609 ± 138[b]	516 ± 146
7	835 ± 191	685 ± 86	331 ± 53[b]	253 ± 34
16	776 ± 222	845 ± 39	300 ± 68[b]	427 ± 88

[a] Mean ± SEM of 6 animals expressed as dpm/167 mg equivalents of liver tissue

[b] Significantly different from control $P < 0.05$

TABLE 3

Effects of Orally Administered Dieldrin (daily x 10) on the Accumulation and Metabolism of 1,2-H^3-Testosterone by the Mouse Anterior Prostate Gland.[a]

Dose (mg/kg)	Androstanediol		Testosterone		DHT		Androstenedione		Total % Reduction of Total	
	% Total	% Change	%Total	%Change	%Total	%Change	%Total	% Change		
Control	15	--	44	--	30	--	11	--	--	3
1.25	14	-30	41	-30	31	-23	14	1	-24	2
2.50	17	-24	41	-38	28	-38	14	-15	-33	2
5.00	18	-35	41	-46	27	-48	14	-25	-43	1

[a] Mice were sacrificed 5 minutes after ip injection of H^3-Testosterone

[b] Mean ± SEM of 12 organs

[c] Significantly different from control ($P < 0.05$)

TABLE 4

Effects of Dieldrin (2.5 mg/kg, daily x 10) on the In Vitro Metabolism of 1,2-H^3-Testosterone by Liver Homogenates Obtained From Male Mice.

Radiosteroid	(dpm/mg) Control	(dpm/mg) Dieldrin
Testosterone	1000 ± 169	866 ± 140
6β-hydroxytestosterone	1154 ± 61	1346 ± 91
7α-hydroxytestosterone	915 ± 61	1058 ± 80
16α-hydroxytestosterone	3291 ± 86	6515 ± 95[b]

[a] Mean ± S.E.M. of 6 animals

[b] Significantly different from control $P < 0.05$

TABLE 5

In Vitro Metabolism of H^3-Testosterone by Mouse Anterior Prostate[a]

Daily Dose	Testosterone		DHT		Androstenedione		% Increa Total Ra Steroid
	%Total	% Change	% Total	% Change	%Total	%Change	% Total	% Change	
Control	23[b]	--	34	--	36	--	7	--	--
2.50	19	46	36	166	38	89	8	123	108

[a] Mice were treated po for 10 days with 2.50 mg/kg of dieldrin

[b] Values are means for 7 observations

TABLE 6

Effects of Orally Administered 2,4,5 T (daily x 10) on the Accumulation and Metabolism of H^3-Testosterone by the Mouse Anterior Prostate Gland.[a]

Daily Dose (mg/kg)	Androstanediol		Testosterone		Dihydrotestosterone		Androstenedione		Total % Reduc.
	%Total	%Change	%Total	%Change	%Total	% Change	% Total	% Change	
Control[b]	15	--	44	--	30	--	11	--	--
6.25	15	-4	44	-13	28	-23	13	1	14
12.50	15	-19	42	-22	28	-24	13	-4	19
25.0	15	-37	40	-40	31	-33	14	-14	35

[a] Mice were killed 5 minutes after ip injection of H^3-testosterone

[b] Mean of 6 or more animals

[c] Significantly different from control $P < 0.05$

TABLE 7

Effects of 2,4,5-T Pretreatment (12.5 mg/kg, daily x 10) Upon *In Vitro* Hepatic Hydroxylation of H^3-Testosterone.

Radiometabolite	Control	2,4,5-T
6β Hydroxytestosterone	1084 ± 94[a]	956 ± 199
7 α	825 ± 155	1065 ± 286
16α	3364 ± 117	3911 ± 811

[a] Mean ± SEM of six samples expressed as DPM/167 mg liver tissue

TABLE 8

Effects of Orally Administered Organochlorides (daily x 10) on Reproductive Organ and Sex Accessory Tissue in the Mature Male Mouse.

(mg/kg) Treatment	Organ Weights (mg/kg body wt.)[a] Testes	Sem. Ves.	Prostate	Prostatic Fructose[b] mg/100 gm wet wt.
Control	8.1±0.3	2.8 ± 0.5	.61 ± .03	.19 ± .02
DDT (50)	7.2 ± 0.8	2.6 ± 0.1	.72 ± .05	.20 ± .01
2,4,5-T(25)	7.3 ± 0.3	3.2 ± 0.1	.56 ± .02	.19 ± .02
Dieldrin (5)	7.2 ± 0.4	2.6 ± 0.1	.71 ± .05	.14 ± .01

[a] Mean ± SEM of at least 6 organs

[b] Mean ± SEM of at least 12 organs

TABLE 9

Effects of Varying Doses of Parathion on Reproductive Organs of Male Mice and on the Five Minute Accumulation and Metabolism of H^3-Testosterone by the Anterior Prostate Gland of the Mouse.

Daily Dose (mg/kg)	Testes wt. (mg)	Prostate wt. (mg)	Total Prostate Radioactive (dpm/mg)	H^3-T	H^3-DHT	H^3-di
0	268 ± 8[a]	31 ± 1	495 ± 96	239 ± 37[b]	85 ± 21	14 ±
1.3	249 ± 8	32 ± 2	532 ± 78	260 ± 38	83 ± 14	19 ± 0.
2.6	269 ± 12	34 ± 1	755 ± 33	471 ± 51	87 ± 6	12 ±
5.3	268 ± 16	32 ± 1	692 ± 84	421 ± 87	86 ± 6	14 ±

[a] Mean ± SEM of 6 or more animals

[b] dpm/mg

[c] Testosterone-H^3

[d] Dihydrotestosterone-H^3

[e] Androstenediol-H^3

TABLE 10

Effects of Parathion (daily x 5 po) on the *In Vitro* Biotransformation of H^3-Testosterone by Hepatic Microsome of the Mouse.[a]

	Polar Metabolites		
(mg/kg) Daily Dose	16α Hg	7α Hg	6β Hg
0	163 ± 12[b]	57 ± 3	34 ± 3
1.3	144 ± 8	63 ± 6	36 ± 2
2.6	137 ± 13	67 ± 6	30 ± 2
5.3	152 ± 9	57 ± 5	40 ± 3

[a] Microsome Incubated for 60 minutes at 37°C

[b] Mean ± SEM of six animals

TABLE 11

Effects of Varying Doses of Carbaryl (daily x 5, po) on Reproductive Organs of Mature Male Mice

Daily Dose (mg/kg)	Testes Weight (mg/g)	Prostate Weight (mg/g)	Prostate Radioactivity (dpm/mg)[a]
0	7.0 ± 0.5[b]	0.70 ± 0.09	235 ± 65
8.5	7.1 ± 0.2	0.67 ± 0.08	442 ± 90
17	7.2 ± 0.4	0.80 ± 0.11	406 ± 91
34	7.8 ± 0.2	0.72 ± 0.11	367 ± 88

TABLE 12

Effects of Thiophanate and Thiophanate-Methyl on Organ Weights and on the five Minute Assimilation of H^3-Testosterone by the Prostate Gland of Mature Male Mice.

Group	Body Weight (g)	Testes (mg)	Prostate (mg)	Sem. Ves. (mg)	Adrenal (mg)	Total Radioac
Control	37.0 ± 1.2[a]	236 ± 10	26 ± 2	157 ± 16	9.3 ± 0.8	304 ±
Thiophanate (275 mg/kg)	35.2 ± 1.2	268 ± 10	31 ± 3	133 ± 10	13.6 ± 1.1[c]	311 ±
Thiophanate-Methyl (192 mg/kg)	35.4 ± 0.8	271 ± 11	33 ± 1[c]	146 ± 5	18.0 ± 0.6[c]	294 ±

[a] Mean ± SEM of eight animals

[b] DPM/mg

[c] Significantly different from control ($P < 0.05$)

DISCUSSION OF RESULTS

These studies demonstrate that DDT (12.5, 25 and 50 mg/kg) can result in a decrease in the five minutes in vivo accumulation of labeled ^{3}H-testosterone and its principal metabolite ^{3}H-DHT by male organs of reproduction. The ratio of ^{3}H-testosterone to ^{3}H-DHT, however, did not change significantly, suggesting that the uptake, and not the metabolism of ^{3}H-testosterone was altered by pre-treatment with DDT. Several organochlorine pesticides including DDT have a well documented affect on hepatic steroid hydroxylase enzyme systems (Conney, et al, 1967; Hart and Fouts, 1965). Because of reported species differences with regard to the effect of DDT on liver hydroxylating enzymes, it seemed important to examine the action of this pesticide upon both hepatic and prostatic steroid metabolizing enzymes. A ten-day oral pre-treatment of mice with DDT which resulted in a decrease in accumulation of radioactive steroid by the prostate gland caused substantial reductions in the ability of the liver to form radioactive polar metabolites. Since polar metabolites of testosterone catabolism are more readily excreted, it would not be surprising that such changes could contribute to altered endocrine states in DDT-treated animals. It is possible that DDT transiently increased circulating levels of hormone available to the prostate gland thus rendering the prostatic receptor sites less available for the injected H^{3}-testosterone. A similar mechanism has been suggested by Blend and Visek (1972) to explain their observations that dieldrin decreased the effectiveness of chlormadinone to reduce canine prostatic secretions. It should be noted however that if endogenous concentrations of androgen were elevated by prior DDT treatment, the elevations were not great enough and/or not high enough to alter sex accessory weights in prostate gland fructose concentrations. Future studies should investigate endogenous levels of circulating male sex hormones. Wakeling et al (1973) has reported that DDT, as well as dieldrin, inhibit the in vitro binding of ^{3}H-DHT to a specific receptor. Distribution studies from this laboratory using H^{3}- revealed elevated levels of radioactivity localized in male gonads, anterior lobes of the prostate gland and seminal plasma of mice 2 hours after i.p. administration. This indicates that DDT has the potential to be transmitted to the female with the concomitant possibility of genetic alterations occurring.

The dieldrin studies demonstrated that a 5 or 10 day pre-treatment causes a marked reduction in the accumulation of

1,2-H^3-testosterone by the mouse prostate gland without affecting the relative proportions of the radiometabolites as compared to the control animals. This would suggest that the decrease in the accumulation of radiosteroids by the prostate gland was the result of altered uptake rather than a change in the bioconversion of testosterone. Such findings warranted studying the effects of dieldrin pretreatment upon the hepatic microsomal hydroxylation system. Dieldrin pretreatment resulted in a significant increase in the 16 -hydroxylation of testosterone. Since these polar metabolites of testosterone are more readily excreted, it would be expected that there would be an alteration in the endocrine status of the dieldrin pretreated animal. It is possible that dieldrin decreased the amount of circulating hormones available to the prostate gland. A reduction of circulating androgens is suggested by the trend toward a decrease in prostate gland fructose concentration. The increased incorporation of labeled steroid observed in the prostate glands of dieldrin pretreated animals incubated in vitro with 1,2-H^3-testosterone further supports the idea of reduced circulating androgens.

Studies with 2,4,5-T, like that of DDT and dieldrin, also revealed a reduction of 1,2-H^3-testosterone assimilation by the mouse prostate gland. 2,4,5-T did not affect the relative proportions of the radiometabolites. Although pretreatment with 2,4,5-T caused a significant reduction of the accumulation of 1,2-H^3-testosterone, no affect could be detected on the hepatic formation of labeled hydroxylated androgens. Endogenous levels of blood androgen levels appear not to be affected by the administration of 2,4,5-T since there were no alterations in either sex accessory weights or prostatic fructose concentrations. These results indicate, therefore, that 2,4,5-T may exert a direct affect upon the prostate gland such as that reported to exist for dieldrin and DDT. Only additional studies will reveal if 2,4,5-T inhibits androgen binding in target tissues.

The organophosphate studies indicated that unlike the organochlorine, parathion did not produce significant alterations in either uptake or biotransformation of 1,2-H^3-testosterone. No significant changes were noted in the formation of polar metabolites by hepatic microsomal fraction from parathion-pretreated mice, although Kuntzman et al (1966) showed that several of the organophosphate pesticides produce significant reductions in the formation of polar metabolites from testosterone by rat liver fractions.

The carbamates, like the organophosphates, did not appear to exert any demonstrable effect upon the male reproductive system. Early studies by Ware and Good (1967) observed no detectable differences in reproductive success of mice when pretreated with different carbamate pesticides. Guthrie et al (1971) reported similar findings. Carbaryl was found to have no effect on the assimilation of radioactive testosterone by the mouse prostate gland or upon the in vivo metabolism of testosterone by the prostate gland (Thomas et al, 1973). However, carbaryl does seem to have the ability to enhance the production of 16 hydroxylated testosterone metabolites in liver microsome fraction. Although carbaryl can increase 16 -hydroxylase activity of the liver, circulating androgen levels did not seem to be affected as evidenced by the lack of significant changes in the prostate gland weights and the gonadal weights.

The thiophanate and thiophanate-methyl assays were ancillary to the objectives and primary goals of the present series of experiments. Extensive studies could not be performed with these compounds due to the limited available quantities of these fungicides. Neither fungicide affected spermatogenesis. The ability of the prostate to assimilate H^3-testosterone was not affected by either thiophanate or thiophanate-methyl. There were no important changes in absolute sex accessory organ weights, although thiophanate-methyl caused significant increases in prostate gland weight. This may be rated to the significant increases in adrenal weights. It is possible that these were stress-producing agents.

In summary, therefore, this series of studies has demonstrated that the carbamates alone or the organophosphates alone exerted little effect upon the endocrine balance in the male reproductive system of the mouse. However, all three organochlorine compounds (viz. DDT, dieldrin and 2,4,5-T) employed in this series of investigation substantially reduced the uptake of radioactive testosterone by androgen dependent organs. No common site of action is as yet clearly evident. Changes in hepatic steroid hydroxylase enzyme activity may, in part, explain the actions of DDT and dieldrin. Further, although all three compounds may be exerting an inhibitory action at the level of endocrine target organs (e.g. testosterone or DHT-binding and/or transport), it seems unlikely that reported inherent estrogenicity (in the case of technical grade DDT) accounts for their actions. Further experiments may fully resolve their molecular mechanism(s) upon the reproductive system.

SECTION VII

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SECTION IX

GLOSSARY

DDT - (1,1-bis [p-chlorophenyl] -2,2,2-trichloroethane)

Dieldrin - (1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-exo-1,4:5,8-dimethanonaphthalene)

2,4,5-T - (2,4,5-trichlorophenoxy acetic acid)

Parathion - (0,0-diethyl-0- [p-nitrophenyl] ester phosphorothioic acid

Carbaryl - (1-naphthyl-N-methyl carbamate)

Thiophanate - [1,2-bis-(3-ethoxycarbonyl-thiourendo)-benzene]

Thiophanate-methyl - [dimethyl-4,4'-o-phenylene-bis-(3 thioallophanate)]

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DDT or dieldrin or 2,4,5 T administered to male mice caused significant reductions in the assimilation of androgens by sex accessory organs. DDT or dieldrin altered the metabolism of testosterone in the prostate gland and in the liver. DDT-^{3}H administration led to the detection of significant amounts of tritium in male reproductive organs. Unlike the organochlorine-type pesticides, neither carbaryl nor parathion administration altered androgen metabolism. The administration of carbaryl-^{14}C led to detectable amounts of radioactivity in several organs of reproduction including the seminal vesicles, prostate gland and testes. The fungicide thiophanate and thiophanate-methyl had no affect upon spermatogenesis or upon the metabolism of androgens.

17. Key Words and Document Analysis. 17a. Descriptors

pesticides
male reproductive organs
DDT
Dieldrin
2,4,5 T
testosterone metabolism
prostate gland
hepatic microsomes
parathion
carbaryl
thiophanate
steroidogenesis
spermatogenesis

17b. Identifiers/Open-Ended Terms

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- localization of DDT in reproductive organs
- Dieldrin and DDT effects on testosterone uptake
- parathion and androgen metabolism
- parathion and androgen metabolism

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