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Uterotropic Activity of DDT in Rats and Mink and Its Influence on Reproduction in the Rat

R. T. DUBY,[1] H. F. TRAVIS,[2] AND C. E. TERRILL[3]

Cornell University, and United States Department of Agriculture

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Uterotropic Activity of DDT in Rats and Mink and Its Influence on Reproduction in the Rat. DUBY, R. T., TRAVIS, H. F., and TERRILL, C. E. (1971). *Toxicol. Appl. Pharmacol.* **18**, 348–355. The injection of *o,p'*-DDT increased uterine weights in intact immature rats, and in intact and castrate immature mink. The *p,p'*-isomer had only slight activity while the uterotropic activity of technical DDT was dependent upon the level of the *o,p'*-isomer it contained. Chronic ingestion of these compounds by rats at levels of 1 to 15 ppm in the diet did not influence fertility or fecundity in 2 successive generations. The time of vaginal opening, growth rate, and litter size was not influenced. The injection of 90 or 900 μg of *p,p'*-DDT or *o,p'*-DDT on days 1, 2, and 3 of pregnancy did not influence the number of embryos surviving to day 10 of pregnancy in the rat. However, following castration of adult female rats raised on DDT-containing diets, uterine involution was accelerated in animals receiving 15 ppm technical DDT.

The effect of DDT on the reproductive function of birds and mammals is poorly understood. Although the widely used commercial grade of DDT (technical DDT) is a mixture of approximately 80% *p,p'*-DDT (2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane and 20% *o,p'*-DDT (2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-1,1,1-trichloroethane), the majority of the investigations on the effects of this pesticide on reproduction have been conducted with the *p,p'*-isomer. The results obtained indicate that reproduction in laboratory animals is not significantly influenced by 200 ppm or less. At higher levels the number of young weaned may be decreased (Treon *et al.*, 1954; Fitzhugh and Nelson, 1947; Deichmann and Keplinger, 1966; Bernard and Gaertner, 1964; Cannon and Holcomb, 1968). Investigations in this laboratory have shown that the feeding of up to 100 ppm *p,p'*-DDT to 2 successive generations of mink did not influence fertility (H. F. Travis, 1969, personal communication). In quail and pheasants, egg production and fertility are not generally decreased by 200–300 ppm of DDT, but at higher levels hatchability is decreased (Dewitt, 1955; Azevedo *et al.*, 1965; Schellenberger *et al.*, 1966). It is evident from the above observations that the *p,p'*-isomer of DDT does not directly influence reproduction except at unusually high levels.

Laboratory results are not in general agreement with observations in the field. Declines in reproduction in certain species of birds have been associated with the presence of DDT residues in their tissues and eggs (Wurster and Wingate, 1968). These observations are particularly pertinent to the raptores where sharp declines have been associated with a decrease in egg shell thickness (Hickey and Anderson, 1968). Similarly,

[1] Department of Animal Science, Cornell University, Ithaca, New York 14850.
Present address: Dept. of Vet. and An. Sci., Univ. of Massachusetts, Amherst, Mass. 01002.
[2] U. S. Fur Animal Experiment Station, Agricultural Research Service, Ithaca, New York 14850.
[3] Sheep and Fur Animal Research Branch, Agricultural Research Service, Beltsville, Maryland 20705.

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declines in reproduction were noted in ranch-raised mink (*Mustela vison*) fed fish containing DDT residues (Stephenson, 1966).

The recent observations of Welch *et al.* (1969) and Bitman *et al.* (1968) that the *o,p'*-isomer of DDT possesses uterotropic properties similar to those of estradiol-17β may help explain these discrepancies. It is known that the preimplantation stages of pregnancy are extremely sensitive to estrogens in laboratory animals (Greenwald, 1967), and reproduction in mink is inhibited by feeding low levels (10 μg/day) of diethylstilbestrol prior to and during the breeding season (Travis *et al.*, 1956; Shackelford and Cochrane, 1962). In light of these observations it was decided to reevaluate the effects of chronic ingestion of *p,p'*-DDT on reproduction in rats, and to compare the results with those obtained following feeding of technical DDT and the *o,p'*-isomer. The uterotropic activity of these compounds was also compared to that of estrone in intact immature rats, and in intact and castrate immature mink.

MATERIALS AND METHODS

The uterotropic activity of *p,p'*-DDT, *o,p'*-DDT, and technical DDT was compared to the activity of estrone in the 21-day-old rat (Sprague-Dawley, Blue Spruce Farms, Altamont, New York) and the immature (120- to 150-day-old) mink. Six-hour (Astwood, 1938) and 72-hr (Lauson *et al.*, 1939) assays were used in the rat experiments while only the 72-hr assay was used in the mink studies. The activity of each of the compounds was also determined 6 hours after 1, 2, or 3 daily injections in the rat. Acetone solutions of estrone or the pesticides were dissolved in corn oil and the acetone was evaporated under vacuum. Technical DDT (80%, *p,p'*-DDT and 20% *o,p'*-DDT) was prepared by combining the pure isomers. The hormone or pesticide was injected ip in 0.1 ml of sesame oil. Control animals were injected with an equal volume of sesame oil. At the termination of each experiment the uteri were removed and weighed after expressing the luminal fluids and trimming all adnexa.

Table 4 not much info 72 hrs

Two successive generations of rats were fed diets containing *p,p'*-DDT at 4 or 12 ppm, *o,p'*-DDT at 1 or 3 ppm, or technical DDT at 5 or 15 ppm to determine their effects on fertility and fecundity. The diets were prepared by mixing the desired amounts of pesticide dissolved in acetone to a commercial rat and mouse meal (Agway).[4] New portions of each diet were prepared at 3-week intervals. Weanling rats (21–25 days old) were purchased from Blue Spruce Farms, Altamont, New York, and immediately placed on their respective diets. The time of vaginal opening and body weights were recorded until the time of mating. Females mated to males of their respective groups were allowed to litter. Litter size was recorded on the day of birth and adjusted to 8 animals per female on day 5. Litter and dam weights were recorded on days 7, 14, and 21. Ten females and 5 males of the F_1 generation were randomly selected at day 25 and the experiment was repeated.

The influence of chronic ingestion (175 days) of DDT on uterine involution in ovariectomized rats was determined in females from the groups receiving the highest levels of the test compounds. These females were ovariectomized approximately 2 weeks following the weaning of their litters. At the time of necropsy, 14 days later, the uteri and pituitaries were removed and weighed.

Finally, the influence of injecting various isomers of DDT on early pregnancy in

[4] Agway, Incorporated, Syracuse, New York, 13200.

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adult rats was determined. Adult rats, maintained on a standard diet of rat and mouse pellets (Agway),[4] were mated and injected with either 90 or 900 μg of *o,p'*-DDT or *p,p'*-DDT on days 1, 2, and 3 of pregnancy. Oil-injected animals served as controls. The day sperm were observed in the vaginal smear was designated as day 1 of pregnancy. All animals were killed on day 10, the number of implantation sites counted, and ovarian weights obtained.

The data were analyzed by Analysis of Variance and Duncan's New Multiple Range test for equal and unequal subgroups (Steele and Torrie, 1960).

RESULTS

Rat uterine weights at 6 and 72 hr show that the *o,p'*-isomer of DDT possesses uterotropic properties. The *p,p'*-isomer was active in the rat only at the higher levels investigated (Tables 1 and 2). Histological examinations indicate that increases in uterine

TABLE 1

UTERINE WET WEIGHTS OF INTACT 21-DAY-OLD RATS 6 HR AFTER A SINGLE INJECTION OF ESTRONE OR DDT

Estrone (μg/rat)	0.0	0.25	0.5	1.0
Uterine weight (mg)[a]	26.2	39.4_a	37.9_a	42.5_a
SE[b]	2.5	1.4	2.4	2.2
o,p'-DDT (mg/rat)	0.0	1.0	2.0	4.0
Uterine weight (mg)	25.2	32.6_a	39.3_a	38.7_a
SE	1.9	2.1	2.4	1.9
p,p'-DDT (mg/rat)	0.0	1.0	2.0	4.0
Uterine weight (mg)	24.5	29.9 a	28.0	25.3
SE	1.3	2.6	1.8	2.1
Tech. DDT (mg/rat)	0.0	1.0	2.0	4.0
Uterine weight (mg)	27.6	32.0	33.5 a	37.2_a
SE	2.1	3.2	2.3	2.8

[a] Means with subscript are significantly different from all controls ($p < 0.05$).
[b] Standard error of mean.

TABLE 2

UTERINE WET WEIGHTS OF INTACT 21-DAY-OLD RATS AFTER 3 DAILY INJECTIONS OF ESTRONE OR DDT

Estrone (μg/rat/day)	0	0.25	0.50	1.0
Uterine weight (mg)[a]	32.0	56.2_a	53.0_a	49.8_a
SE[b]	2.9	1.7	2.9	1.8
o,p'-DDT (mg/rat/day)	0	1.0	2.0	4.0
Uterine weight (mg)	29.5	42.6_a b	47.4_a c	48.5_a c
SE	1.4	1.8	4.5	2.7
p,p'-DDT (mg/rat/day)	0	1.0	2.0	4.0
Uterine weight (mg)	31.2	33.2	30.8	41.0_a
SE	3.9	1.8	2.5	2.0
Tech. DDT (mg/rat/day)	0	1.0	2.0	4.0
Uterine weight (mg)	27.1	34.4 b	37.5_a b	48.4_a c
SE	1.3	3.2	1.8	2.4

[a] Means with subscript are significantly different from all controls ($p < 0.05$).
[b] Standard error of mean.

weight 6 hr after a single injection are due to endometrial edema. At 72 hr the weight changes are primarily due to endometrial and myometrial hypertrophy, hyperplasia, and, to a lesser extent, interstitial edema. The response of the uterus to these compounds is similar at 30 hr, while at 54 hr uterine weights in *o,p'*-DDT-treated animals were 71% greater than those treated with estrone (Table 3).

TABLE 3

UTERINE WET WEIGHTS OF 21-DAY-OLD RATS[a] 6 HR AFTER 1, 2, OR 3 DAILY INJECTIONS OF 4 MG OF DDT OR 1 μG OF ESTRONE

Time after 1st injection (hr)	Control	Estrone	*p,p'*-DDT	Tech. DDT	*o-p'*-DDT
6	26.2[b] (2.49)$_a$	42.5 (2.20)$_b$	25.3 (2.09)$_a$	37.2 (2.77)$_{ab}$	38.7 (1.93)$_{ab}$
30	30.0 (3.30)$_a$	51.3 (3.92)$_{bc}$	39.3 (3.86)$_{ab}$	37.5 (1.65)$_{ab}$	58.6 (1.53)$_c$
54	33.7 (3.71)$_a$	53.2 (5.88)$_{bc}$	45.9 (3.98)$_{ab}$	48.4 (3.20)$_{bc}$	91.3 (3.47)$_d$
72	29.5 (1.35)$_a$	49.8 (1.84)$_{bc}$	41.0 (1.95)$_b$	48.4 (2.41)$_{bc}$	48.5 (2.67)$_{bc}$

[a] Uterine wet weights (mg) expressed as mean of 6 rats per group with SE ( ).
[b] Means with different subscripts are significantly different ($p < 0.05$).

TABLE 4

INFLUENCE OF ESTRONE AND DDT ON UTERINE WET WEIGHTS OF INTACT AND CASTRATE IMMATURE MINK

	Uterine wet weight (mg) (mean ± SE)[a]		
	Estrone (μg/kg)		
Treatment	0	12.5	25.0
Intact	101.5 ± 9.8$_a$ (10)[b]	288.3 ± 22.6$_c$ (10)	340.6 ± 21.9$_d$ (10)
Ovariectomized	105.4 ± 10.2$_a$ (6)	242.0 ± 17.6$_{bc}$ (6)	348.8 ± 35.6$_d$ (6)
	DDT (mg/kg)		
	1.0	10.0	
Intact, *o,p'*-DDT	97.7 ± 7.1$_a$ (8)	260.7 ± 18.9$_{bc}$ (8)	
Ovariectomized, *o,p*-DDT	—	228.8 ± 12.7$_b$ (8)	
Intact, *p,p'*-DDT	99.6 ± 10.0$_a$ (8)	100.5 ± 9.51$_a$ (8)	

[a] Means with different subscripts are significantly different ($P < 0.05$).
[b] Number of observations in group.

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The responses of intact and ovariectomized mink to similar doses of estrone were not significantly different (Table 4), thereby permitting a comparison of the effects of DDT in both the intact and ovariectomized animal. The injection of 10 mg/kg of body weight of the *o,p'*-isomer significantly increased uterine weights in intact and castrate animals. The *p,p'*-isomer was completely inactive at these levels when assayed in the intact animal (Table 4). At 1.0 mg/kg body weight neither isomer increased uterine weight, but *o,p'*-DDT did increase mitotic activity of the endometrium.

The chronic ingestion of *o,p'*-DDT, *p,p'*-DDT, or technical DDT did not influence growth patterns, time of vaginal opening, fertility, or fecundity in two successive generations of rats. No differences were noted in litter sizes at birth or litter weights at day 21. Similarly, no effects were noted on testicular maturation or fertility in the male rats in this study.

The ingestion of *o,p'*-DDT at 3 ppm or *p,p'*-DDT at 12 ppm for up to 175 days did not maintain uterine weights in adult female castrate rats. On the other hand, technical DDT at 15 ppm significantly decreased uterine weights. None of the above treatments influenced pituitary weights (Table 5).

TABLE 5

UTERINE INVOLUTION AND PITUITARY WEIGHT AFTER OVARIECTOMY IN RATS FED DDT FOR 175 DAYS

	Control	*o,p'*-DDT 3 ppm	*p'p*-DDT 12 ppm	Tech. DDT 15 ppm
No. of animals	6	7	7	9
Body weight (g)	281.0 (8.84)[a]	290.7 (7.48)	283.4 (13.81)	268.1 (5.7)
Uterine weight (mg), 14 days post-ovex	149.5 (7.67)	151.1 (6.78)	149.0 (8.15)	124.4 (4.82)[b]
Pituitary weight (mg), 14 days post-ovex	11.35 (0.43)	11.88 (0.36)	12.21 (0.63)	11.42 (0.41)

[a] Standard error of mean.
[b] Significantly different from controls ($P < 0.05$).

The injection of 90 or 900 μg of either *o,p'*-DDT or *p,p'*-DDT on days 1 through 3 of pregnancy failed to influence the number of deciduomata present on day 10. No differences were observed in the number of corpora lutea, their size and color, or ovarian weights.

DISCUSSION

The results of this investigation confirm the reports of Welch *et al.* (1969) and Bitman *et al.* (1968) that *o,p'*-DDT possesses uterotropic properties and extends this observation to mink. The maintenance of the uterotropic properties of *o,p'*-DDT in castrate mink indicates that its action is directly on the uterus rather than indirect by stimulating endogenous release of estrogens. Welch *et al.* (1969) reported similar observations in the immature castrate rat. They also reported that pretreatment of rats with carbon

tetrachloride inhibited the estrogenic response of the uterus to *o,p'*-DDT suggesting that an unknown metabolite may be the active agent.

Although *o,p'*-DDT mimics the uterotropic property of estrone its mode of action may be different. Unlike estrone, *o,p'*-DDT elicits a significant uptake of water by uterine tissues within 6 hours after the last of 3 daily injections. Since uterine weights decrease to values comparable to estrone 24 hr later, this is a transient process. These data suggest that *o,p'*-DDT alters capillary permeability to a greater extent than does estrone. The failure of the *p,p'*-isomer to promote a similar increase in uterine weight may be due to its structure which alters its binding to uterine receptors.

The uterotropic activity of *o,p'*-DDT may be related to its structural similarity to diethylstilbestrol, a potent nonsteroidal estrogen. Fisher *et al.* (1952) have suggested that *p,p'*-DDT is devoid of this activity because of the presence of chlorine in the para positions. This precludes the presence of an active hydrogen group at this location, which is thought to be required for estrogenic activity. That this may be the case is demonstrated by the work of Welch *et al.* (1969) and Bitman *et al.* (1968), who reported that pretreatment of animals with *o,p'*-DDT inhibited the uptake of tritiated estradiol-17β by the rat uterus. Pretreatment with *p,p'*-DDT was without influence on estradiol-17β uptake. These observations suggest that *o,p'*-DDT, or a metabolite, binds to the estrogen receptors in the uterus to exert its uterotropic influence.

The failure of *p,p'*-DDT or technical DDT to alter fertility in 2 successive generations of rats is consistent with the reports of Fitzhugh and Nelson (1947), Treon *et al.* (1954), and Ottoboni (1969). However, Treon *et al.* (1954) noted that in some cases neonatal mortality was increased by the feeding of 50 ppm DDT. In the present investigation no differences were noted in growth rates or survival of offspring in any of the treatments. This agrees with the work of Ottoboni and Ferguson (1969) who reported that feeding 20 ppm technical grade DDT did not influence neonatal survival despite the transmission of considerable quantities of *p,p'*-DDT or *o,p'*-DDT and their metabolites to the young through the milk. These observations indicate that survival of newborn rats is not influenced by the feeding of up to 20 ppm of technical DDT.

Deichmann and Keplinger (1966) noted that the feeding of technical DDT to mice reduced the number of litters produced per pair and delayed the time required to the first successful mating. Our observation that the time of vaginal opening or testicular maturation was not influenced by the feeding of DDT suggests that the time of puberty was not influenced. These results are in contrast to those obtained by Burlington and Lindeman (1950), who noted that testicular growth and the subsequent development of the secondary sex characteristics of cockerels were inhibited by the feeding of "purified DDT." A delay in ovulation in the finch was also noted following the feeding of DDT (Jefferies, 1967). These observations suggest that DDT may be capable of controlling the reproductive activity of an animal by influencing the release of gonadotropic hormones from the pituitary. The failure to observe such an inhibition in the current investigation may have been due to the levels fed or species differences.

The failure of ip injections of *o,p'*-DDT to inhibit pregnancy in the rat is not consistent with the results obtained following the injection of estrone (Duby, 1965; Greenwald, 1967). The preimplantation stages of pregnancy are extremely sensitive to estrogens and as little as 20 μg of estrone will completely inhibit pregnancy or significantly reduce litter size in the rat. Yet when 900 μg (3.6 mg/kg) of *o,p'*-DDT was injected on

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each of the first 3 days of pregnancy, no effect on fertility or fecundity was noted. These data suggest that, although *o,p'*-DDT may elicit uterotropic responses, it does not possess the antifertility properties of estrone, at least at the levels used in this study.

The failure of chronic ingestion of *o,p'*-DDT to maintain uterine weights in mature ovariectomized rats suggests that the amount of pesticide at the target tissue was below the threshold required for estrogenic activity. On the other hand, the observation that the feeding of technical DDT at 15 ppm significantly reduced uterine weights in castrate rats suggests that circulating uterotropic steroids may have been reduced by increased catabolism induced by stimulation of hepatic microsomal enzymes (Conney *et al.*, 1967). Kinoshita *et al.* (1966) have shown that when more than 5 ppm of technical DDT are fed to rats there is a significant induction of hepatic drug-metabolizing enzymes. This activity reaches its peak in about 3 weeks and is then maintained for at least 23 weeks. These enzymes (hydroxylases) are also involved in the catabolism of the steroid hormones, and Peakall (1967) has shown that orally administered DDT increases the catabolism of estradiol-17β in the chicken. However, it remains to be seen whether this change in metabolism has an influence on circulating steroid concentrations or steroid production by endocrine glands.

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