Reproduction in Female Rats Born to DDT-Treated Parents

by JOHN G. CLEMENT and ALLAN B. OKEY

Department of Biology
University of Windsor
Windsor, Ontario, Canada N9B 3P4

DDT intake by adult rodents can adversely affect their reproductive performance (BERNARD & GAERTNER 1964; CANNON & HOLCOMB 1968). Generally, however, mature animals must receive DDT in very high doses before their fertility is impaired (WARE & GOOD 1967; OTTOBONI 1969; DUBY et al. 1971). Low doses of technical grade DDT (ca. 80% p,p'-DDT/20% o,p'-DDT)may even prolong the reproductive life-span of the female rat (OTTOBONI 1972).

Sexual development and differentiation in the rat hypothalamus pass through a "critical period" in the early days of post-natal life (BARRACLOUGH & GORSKI 1962). During this period the hypothalamus is susceptible to damage by exogenous androgens or estrogens; in the female, hypothalamic damage can cause permanent sterility.

Reports that the o,p'-DDT isomer possessed estrogenic activity (BITMAN et al. 1968; WELCH et al. 1969) prompted HEINRICHS et al. (1971) to test the possibility that neonatal exposure to o,p'-DDT might alter subsequent reproduction in female rats. They found that injections of 1 mg of o,p'-DDT on days 2,3, and 4 of post-natal life induced a "persistent estrus" syndrome with polycystic ovaries and permanent sterility.

Our experience with o,p'-DDT administration to weanling rats indicates that when taken orally (in the diet) it produces a significant estrogenic effect only at very high doses (CLEMENT & OKEY 1972). DDT taken by the mother can, however, reach the fetus in utero (BÄCKSTRÖM et al. 1965; WOOLLEY & TALENS 1971) and DDT is excreted in rat milk (OTTOBONI & FERGUSON 1969; WOOLLEY & TALENS 1971). Thus, we tested reproductive performance of rats exposed to DDT isomers in utero and via the mother's milk to determine if these "natural" routes of exposure during critical developmental periods might produce reproductive disorders similar to those observed in rats injected with high doses of o,p'-DDT by HEINRICHS et al.

Bulletin of Environmental Contamination & Toxicology.
Vol. 12, No. 3 © 1974 by Springer-Verlag New York Inc.

METHODS

Male and female Wistar-strain rats, 80 to 100 days old were randomly assigned to diets containing either 0, 20, 200 or 1000 parts per million (ppm) of o,p'-DDT or to 0, 20, 200 or 500 ppm of p,p'-DDT*. The DDT was dissolved in 95% ethanol, then stirred with Purina Laboratory Chow in a mechanical mixer until the ethanol had evaporated and the mixture was homogeneous.

Male-female pairs given the same DDT treatment were caged together throughout a 6-month breeding period. DDT diets were continued during pregnancy and lactation. Upon parturition, litter size, weight and mortality were recorded. Offspring were weaned at 21 days of age, caged individually and fed control food (Purina Laboratory Chow) for the remainder of the experiment. At approximately 80 days of age vaginal smears were taken from the F_1 female progeny to ascertain whether or not they had normal estrus cycles. Female F_1 rats were mated with control rats at 105 days of age to determine if their reproductive performance had been altered by perinatal exposure to DDT isomers.

RESULTS

Viability and Growth

Growth was severely depressed in pups nursing on dams fed 200 or 500 ppm p,p'-DDT. All offspring born to dams fed 500 ppm p,p'-DDT were dead by 10 days after birth (Figure 1). The growth depression was reversible; pups surviving until weaning age (21 days postpartum) and then fed control chow were as large as control animals (of the same sex) at 105 days of age (data not shown).

Reproductive Performance of F_1 Progeny

Vaginal smears performed on female F_1 progeny at age 80 days showed that all females were cycling normally at that time. After mating with F_1 control-group males at 105 days of age, all females produced litters except those F_1 females originating from mothers fed 1000 ppm o,p'-DDT (Table 1). Of four o,p'-1000 female progeny mated, one produced a small live litter, one died during delivery and two did not become pregnant. Ovaries of the two sterile females contained cystic structures similar to those described by HEINRICHS *et al.* (1971).

---

* DDT isomers were obtained from the Aldrich Chemical Co. Milwaukee, Wisconsin. o,p'-DDT: 1,1,1-trichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane. p,p'-DDT: 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)ethane.

Figure I.

Growth Chart of Suckling Pups Exposed to DDT in Utero and Via the Mother's Milk.

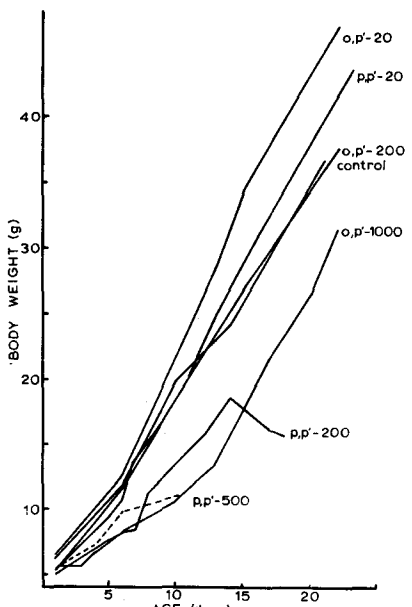

Table I. Reproductive Performance of F_1 Female Progeny Exposed to DDT "In Utero" and Through the Maternal Milk

Treatment Given to Mother	Number of F_1 Female Progeny Bred	Number Producing Litters	Mean Litter Size
Control	14	14	13.6
o,p'-DDT, 20 ppm	1	1	16.0
o,p'-DDT, 200 ppm	4	4	13.8
o,p'-DDT, 1000 ppm	4	1*	3.0
p,p'-DDT, 20 ppm	4	4	13.8
p,p'-DDT, 200 ppm	2	2	15.0
p,p'-DDT, 500 ppm	0 (no F_1 progeny survived to weaning)		

* Significantly different from control group
p = 0.0005 by Fisher Exact Probability Test
(SIEGEL 1956)

DISCUSSION

In the present study "natural" routes of perinatal exposure to DDT (across the placenta and via the milk) produced sterility of the type described by HEINRICHS et al. for neonatal rats injected with large doses of o,p'-DDT.

It is unlikely, however, that early exposure to o,p'-DDT poses a hazard to successful reproduction in rodents. Although we examined only small numbers of perinatally exposed rats, we believe that it is reasonable to conclude that the polycystic ovary syndrome is inducible only by o,p'-DDT doses far in excess of those available in the biosphere. o,p'-DDT levels in the diet must be above 500 ppm before an estrogenic (uterotrophic) response is elicited in immature female rats (CLEMENT & OKEY 1972). Even in biological samples containing more than 100 ppm total DDT residues, the o,p'-DDT content rarely exceeds 1 ppm (BAETCKE et al. 1972). The p,p'-DDT isomer is excreted in high concentration in the milk of rats fed technical grade DDT; o,p'-DDT, however, is excreted in concentrations several-fold less than its concentration in the mother's diet (OTTOBONI & FERGUSON 1969). The reason for this low excretion probably is rapid conversion of o,p'-DDT into methoxy and hydroxy derivatives (FEIL et al. 1971). Thus, lactating females would have to ingest enormous quantities of o,p'-DDT before it would effectively reach the nursing offspring during their critical developmental period.

In this study as in several previous reports (see review by CONNEY & BURNS 1972) DDT reduced fertility only at doses approaching the acutely toxic levels in rodents. Overall, reduction in the reproductive capacity of small rodents exposed to DDT seems to be achieved largely by increased neonatal mortality rather than by a single specific effect at one point in the reproductive cycle.

ACKNOWLEDGEMENT

Supported by a grant from the National Research Council of Canada.

REFERENCES

BÄCKSTRÖM, J., E. HANSSON and S. ULLBERG: Toxicol. Appl. Pharmacol. 7, 90 (1965).

BAETCKE, K.P., J.D. CAIN and W.E. POE: Pesticides Monitoring J. 6, 14 (1972).

BARRACLOUGH, C.A. and R.A. GORSKI: J. Endocrinology 25, 175 (1962).

BERNARD, R.F. and R.A. GAERTNER: J. Mammal. 45, 273 (1964).

BITMAN, J., H. CECIL, S.J. HARRIS and G.F. FRIES: Science 162, 371 (1968).

CANNON, M.S. and L.C. HOLCOMB: Ohio J. Sci 68, 19 (1968).
CLEMENT, J.G. and A.B. OKEY: Can. J. Physiol. Pharmacol. 50, 971 (1972).
CONNEY, A.H. and J.J. BURNS: Science 178, 576 (1972).
DUBY, R.T., H.F. TRAVIS and C.E. TERRILL: Toxicol. Appl. Pharmacol. 18, 348 (1971).
FEIL, V.J., E.J. THACKER, R.G. ZAYLSKIE, G.H. LAMOUREAUX and E. STYROVOKY: Am. Chem. Soc. 162nd Meet. Sept. (1971; abstract).
HEINRICHS, W.L., R.J. GELLERT, J.L. BAKKE and N.L. LAWRENCE: Science 173, 642 (1971).
OTTOBONI, A.: Toxicol. Appl. Pharmacol. 14, 74 (1969).
OTTOBONI, A.: Toxicol. Appl. Pharmacol. 22, 497 (1972).
OTTOBONI, A. and J.I. FERGUSON: Toxicol. Appl. Pharmacol. 15, 56 (1969).
SIEGEL, S.: Nonparametric Statistics for the Behavioral Sciences. New York: McGraw-Hill 1956.
WARE, G.W. and E.E. GOOD: Toxicol. Appl. Pharmacol. 10, 54 (1967).
WELCH, R.M., W. LEVIN and A.H. CONNEY: Toxicol. Appl. Pharmacol. 14, 358 (1969).
WOOLLEY, D.E. and G.M. TALENS: Toxicol. Appl. Pharmacol. 18, 907 (1971).