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p,p'-DDT is an Estrogenic Compound

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DDT (1,1,1-trichloro-2,2-bis [chlorophenyl] ethane is an insecticide still indiscriminately used in several Third World countries (Metcalf 1973). Of the two isomers, p,p'-DDT is considered the least toxic and therefore the more appropriate for use. The wide use of DDT is known to contaminate the environment, including food. This contamination makes important the investigation of its toxic effects in mammals (Albert 1981). o,p'-DDT has been reported to exert estrogen-like activity (Foster et al. 1975; Kupfer 1975; Kupfer and Bulger 1976). It binds to cytosol estrogen receptors (Kupfer and Bulger 1977) and induces several estrogenic responses, such as increases in rat uterine wet and dry weight, protein and glycogen concentrations (McBlain 1987) and increase in thymidine incorporation into uterine DNA (Galand et al. 1987; McBlain 1987). In contrast to o,p'-DDT, its p,p'-isomer was reported to display a much lower or unexistent estrogenic activity (Foster et al. 1975; Galand et al. 1987; Nelson 1974; Robinson et al. 1984; Stancel et al. 1980).

The responses to estrogen in the uterus can be classified into separate groups that are mediated by different kind of estrogen receptors through independent mechanisms (Tchernitchin 1983; Tchernitchin et al. 1985). This independence between mechanisms allows the dissociation between the various estrogenic responses; i.e., their selective stimulation or inhibition (Tchernitchin et al. 1985). Further, there exist estrogenic compounds (estriol, equilin, nafoxidine, diethylstilbestrol) that selectively induce responses mediated by one of these mechanisms but not others, because of their differential affinity for receptors involved in these responses (Galand et al. 1984; Grunert et al.

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1986; Tchernitchin 1972; Tchernitchin et al. 1975, 1985). Taking above into consideration, it is possible that p,p'-DDT may selectively induce estrogenic responses in some cell-types but not in others, and that these effects might remain undetected by the classical biochemical techniques that do not discriminate among the various uterine cell-types (Grunert et al. 1986; Tchernitchin et al. 1985). The present study investigated the estrogenic responses of p,p'-DDT action separately in the different uterine cell-types.

MATERIALS AND METHODS

Four groups of immature female Sprague-Dawley rats, of 40 to 49 g body wt., were used in the present study; 5 to 8 animals comprised each group. The two experimental groups were intravenously injected with 0.5 mg p,p'-DDT in 0.1 ml dimethyl sulfoxide (DMSO); the control groups were injected with equal amounts of vehicle. The uteri were excised under ether anesthesia 6 or 24 h after treatment, fixed in 10% neutral formalin, and histologically processed for further studies (Tchernitchin and Galand 1983). The following estrogenic responses were investigated: myometrial hypertrophy, measured as increase in the reciprocal value of cell density (RVCD) in circular myometrium, and edema in deep and in superficial endometrial stroma, measured as increases in RVCD in these histological locations (Grunert et al. 1986).

The Least Significant Difference (LSD) *a posteriori* test was used for comparison between experimentals and controls and between 6 and 24 h of treatment. The common variance needed for this test was estimated from a one-way unbalanced analysis of variance (ANOVA).

RESULTS AND DISCUSSION

The data on the effect of an intravenous injection of 0.5 mg p,p'-DDT on RVCD in circular myometrium, deep endometrial stroma and superficial endometrial stroma, 6 or 24 h after treatment, is shown in Figure 1. It can be observed that the insecticide induces a hypertrophic response in circular myometrium and an edematous response in deep and in superficial endometrium, at 24 h after treatment. These responses were not detected at 6 h after treatment.

The present results show that p,p'-DDT, considered as the least toxic DDT isomer and therefore the most appropriate for use, displays estrogenic activity inducing both myometrial hypertrophy and endometrial edema. It is well documented that myometrial hypertrophy is a genomic response to estrogen (Grunert et al. 1984) that

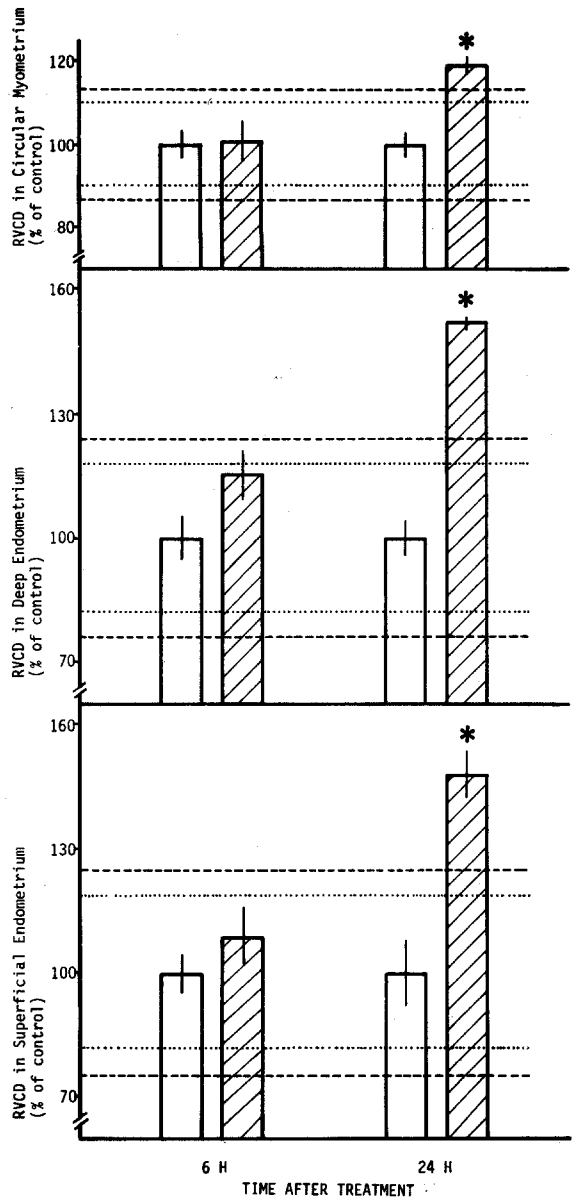

Figure 1. Effect of p,p'-DDT on the reciprocal value of cell density (RVCD) in deep and in superficial endometrial stroma and in circular myometrium. In comparisons between DDT-treated rats (hatched bars) and controls (open bars), the limits of significance at the levels of p=0.05 and p=0.01 are shown by the horizontal dotted and broken lines respectively. *p<0.001 in comparisons between 6 and 24 h of treatment.

is mediated by the cytosol-nuclear receptors, and that endometrial edema is a non-genomic response to estrogen (Tchernitchin and Galand 1982) mediated by estrogen receptors located in the eosinophils (Tchernitchin 1983). The effects of the pesticide suggest its interaction with both kind of estrogen receptors in the rat uterus: the cytosol-nuclear receptors and the eosinophil estrogen receptors.

Taking into consideration (a) the prolonged half life of DDT, (b) the potentially carcinogenic effect of various estrogens on the genital tract of the elderly, and (c) the potentially dangerous permanent effects of various estrogenic compounds on women that were exposed in utero to them, as it has been shown in offspring of pregnant women exposed to diethylstilbestrol (Iguchi et al. 1986). the present results should alert regulatory officials of the potential danger of the indiscriminate use of DDT.

Therefore, based on the present results and on previously reported data, we alert authorities about the need to control the use and abuse of DDT to avoid unwanted side effects in the population. This consideration is important in Third World countries such as Chile, where at present this compound is used almost freely without any efficient control at all.

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