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Environmental Exposure to *p,p'*-DDE and Human Fertility

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Organochlorine compounds have raised concern as possible environmental determinants of an increased incidence in male reproductive abnormalities in wildlife and of a supposed worldwide decrease in human sperm counts (Sharpe 1995, Sharpe and Skakkebaek 1993, Carlsen et al. 1992). More recently, *p,p'*-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p'*-DDE), the major and most persistent derivative of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl ethane) (DDT), has shown strong anti-androgenic properties in an experimental study on male rats (Keice et al. 1995), supporting the hypothesis of a link between environmental contamination from DDT derivatives and a decline in male fertility among humans. This paper tentatively addresses the hypothesis with an ecologic design using published data, considering also the effects of other covariates potentially associated with impaired human fertility.

MATERIALS AND METHODS

Data used for the present study include: 1) *p,p'*-DDE concentration in the tree bark of 27 world countries and in 17 U.S. states in 1992- 1995, expressed as *ng/g* of lipids, kindly provided by the authors of a recently published report (Simonich and Hites 1995). When more than one measurement was available for the same country or state, the median was selected for the purposes of this study. Data were log-transformed to approximate the normal distribution; 2) birthrate, percent urban population, *per capita* gross domestic product (GDP, in U.S. dollars), and percent fertile women using oral contraceptives by country in 1986-87 (World Atlas for multimedia IBM PC and compatibles 1993) and annual birth rate per 1,000 residents (*Br*), legal abortion rate per 1,000 live births (*Ar*), percent metropolitan population and average *per capita* income in 1987 by state in the United States (U.S. Bureau of the Census 1992). A pregnancy rate per 1,000 residents (*Pr*) was calculated for each U.S. state as $Pr = Br + Br*Ar/1{,}000$; and 3) international data on sperm counts (million cells/ml) in 1987-1990 (Carlsen et al. 1992) jointly available with tree bark *p,p'*-DDE for 9 countries. When sperm counts were reported more than once for the same country within the same time frame, a weighted average cells/ml for that country was calculated.

Multiple linear regression models were fitted separately on an international basis

and among U.S. states. On an international basis, birthrate and sperm counts were alternatively the outcome, while independent covariates included *per capita* GDP, percent urban population, percent fertile women using oral contraceptives, and tree bark *p,p* '-DDE. On an U.S. basis, pregnancy rate was modeled as a function of average annual *per capita* income, percent metropolitan population, and *p,p* '-DDE in the tree bark. The statistical significance of the regression coefficients (β) was calculated from the ratio of β and its standard error, which has a *t* distribution under the null hypothesis. The 95% confidence interval of β was derived from $\beta \pm 1.96\ se_{\beta}$. The analysis was conducted with the SYSTAT© software.

RESULTS AND DISCUSSION

Tree bark *p,p'*-DDE concentration was by far the highest in Romania (2647 ng/g), followed by India (495.25 *ng/g*) and Brazil (350 *ng/g*), and the lowest in Costa Rica (2.03 *ng/g*), United Kingdom (4.6 *ng/g* and Norway (5.1 *ng/g*). The range among U.S. states was as broad as among world countries, with extreme values of 0 and 2550.35 *ng/g,* respectively in Oregon and Arizona, and an average value of 29.183 *ng/g.* Elevated concentrations were also measured in New York state (833.25 *ng/g*), North Dakota (477.3 *ng/g,* and Texas (859.25 *ng/g*).

Table 1. Multiple regression model parameters predicting birthrate in 27 world countries, and pregnancy rate in 17 U.S. states.

Covariates States	Birth rate among world countries	Pregnancy rate in the United
Intercept	56.609 (47.596 - 64.621)	-2.635 (-15.691 - 10.691)
Percent metropolitan/ urban population	-0.181 (-0.387, 0.025)	0.013 (-0.082, 0.108)
Per capita GDP/ Average income	-0.455 (-0.929, 0.020)	1.394 (0.500, 2.288)
Percent use of oral contraceptives	-0.234 (-0.432, -0.036)	
p,p '-DDE	-1.049 (-2.396, 0.299)	0.193 (-0.387, 0.773)
R^2	0.859	0.573
p	< 0.001	< 0.01

On an international basis, birthrate declined with increasing use of oral contraceptives, increasing per capita GDP, increasing percent urban population,

and increasing tree bark *p,p'*-DDE (Table 1). However, the only significant result was observed for use of oral contraceptives. Although the small number of countries with complete information limited the possibility of inference, sperm counts also decreased with increasing *per-capita* GDP (β = -2.364; 95%C.I.= -4.342, -0.386) and increasing tree bark *p,p'*-DDE (β = -6.451; 95%C.I. = -15.436, 2.535). Among U.S. states, tree bark *p,p'*-DDE was not a negative predictor of pregnancy rate (Table 1), and average *per-capita* income showed a significantly positive regression coefficient.

This exercise used the 1992-1995 concentration of *p,p'*-DDE in the tree bark as a measure of DDT contamination in the environment of a number of world countries and U.S. states, which may be related to past local use of the pesticide, and/or to drift of volatile compounds through the atmosphere from warm regions, where the pesticide is still produced and used, to colder latitudes where volatile atmospheric contaminants more easily condense (Simonich and Hites 1995). Measures of DDT alone, as well as total DDT, including DDT, DDE, and dichloro-diphenyl-dichloroethane (TDE), were also available from the same source. However, *p,p'*-DDE is the major and most persistent DDT derivative, and it may better resume historic contamination, while total DDT and DDT alone would be more representative of contamination from recent uses of the pesticide (International Agency for Research on Cancer 1991). Besides, *p,p'*-DDE was the DDT derivative shown to be a potent anti-androgen in experimental animals (Keice et al. 1995). Finally, tree bark DDT readings gave null values in two-thirds of the measurements overall (58 out of 89) further pointing to *p,p'*-DDE as the most suitable indicator of DDT contamination. Still, concern in interpreting these results is required, as it is unknown to which extent tree bark *p,p* '-DDE is representative of the average exposure of the population in a given geographical area.

Overall, the present explorative study does not provide evidence of an impairment in human fertility in relation to environmental exposure to DDT derivatives. As the range of tree bark *p,p'*-DDE concentrations was approximately the same worldwide and among U.S. states, chance is the most likely explanation for the contradictory findings. However, outcomes of the two regression models were not exactly comparable, and both are crude indicators of human fertility, as they are influenced by many social and cultural factors, which contribute to their geographical variation. If other powerful determinants of reduced natality, such as use of oral contraceptives or other birth control procedures, were inversely related to environmental exposure to DDT derivatives among U.S. states, this could have masked a weak negative association between *p,p'*-DDE and pregnancy rate on a U.S. basis. Data by U.S. state were not available for the effect of these variables to be properly accounted for.

The ecologic study design has the advantages of low cost and quick execution, which are balanced by the so-called ecological fallacy (Morgenstern 1982), i.e. the dilution of effects resulting from assuming that the whole population of a given geographic area shares the same level of exposure to environmental contaminants. This adds to the previously described limitations in reducing the possibility of

inference from such an exercise. Nonetheless, the consistent, although not statistically significant, decrease in birthrate and sperm counts by increasing concentration of tree bark *p,p'*-DDE observed on an international basis, prompts more powerful analytic studies to test the hypothesis of a link between impaired human fertility and environmental exposure to DDT derivatives. These should be preferably conducted in countries where DDT use is still popular.

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