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Pesticides and Polychlorinated Biphenyls as Potential Risk Factors for Erectile Dysfunction

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Abstract

While it is biologically plausible that environmental chemicals such as pesticides and polychlorinated biphenyls (PCBs) with suspected hormone disrupting properties may have an impact on risk of erectile dysfunction (ED), few epidemiologic studies have assessed this potential association. In a clinic-based case-control study in Kingston, Ontario, consenting subjects completed a questionnaire and donated 15 mL of blood for analysis of organochlorines and lipids by gas chromatography. Exposures were compared for 101 cases with ED and 234 comparable control subjects. For most PCB congeners and organochlorine pesticides, geometric mean levels are similar for cases and controls. Multivariate logistic regression results do not show an increased or decreased risk of ED associated with levels of most detectable environmental substances after adjustment for age, total lipids, and confounders. Levels of 2 of the ubiquitous chlorinated pesticides, oxychlordane and *trans*-nonachlor, which are highly correlated, appear to associate with a reduced risk of ED, but the role of chance cannot be ruled out. To our knowledge, this study is the first to investigate the possible relationship between plasma levels of organochlorines and ED risk, and results do not provide evidence of an association.

Key words: Erectile function, environment, organochlorines, plasma, epidemiology

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While regarded as a benign condition, erectile dysfunction (ED) is a common problem with significant effects on the quality of life of aging males worldwide. This is attested to by the immediate and overwhelming demand that greeted the recent introduction of oral sildenafil therapy (Utiger, 1998) and the growing body of epidemiologic research on the causes of this problem (Feldman et al, 1994; Bacon et al, 2003). Indirect evidence of a potential effect of environmental contaminants of industrial and agricultural origin with suspected endocrine disrupting properties on ED risk comes from animal studies (Brien et al, 2000) and some epidemiologic studies reporting elevated risk among farm workers and pesticide applicators (Espir et al, 1970; Amr et al, 1997; Oliva et al, 2002). There has been intense scientific and societal concern regarding the potential adverse effects of environmental endocrine disrupters on male reproductive function and development (Skakkebaek et al, 2001; Toppari et al, 2002; Wetherill et al, 2005). However, very little attention to date has been paid to the effect of such agents on erectile function as a critical component of male reproductive function.

Ubiquitous environmental pollutants, such as polychlorinated biphenyls (PCBs) and chlorinated pesticides, with known or suspected endocrine-disrupting properties may modulate the normal functioning of endogenous hormones as agonists, as antagonists, or as mixed agonist-antagonist activity, particularly with respect to estrogen or testosterone activity (Toppari et al, 1996; Wolff et al, 1997). PCBs; *p,p*'-DDE, the most stable metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT); and other chlorinated pesticides belong to the class of organochlorines that are highly persistent lipophilic chlorine-containing compounds. PCBs have been manufactured commercially since 1929 for a variety of applications, including use as dielectrics in transformers and capacitors, whereas DDT has been one of the most widely used chemicals for insect control (Toppari et al, 1996; Moysich et al, 2002). Although banned from use and manufacture in the United States and Canada nearly 30 years ago (Longnecker et al, 1997), these chemicals persist in the environment, accumulating in the food chain. As a result, organochlorines are now detectable in most human plasma, adipose tissue, and breast milk (Charlier and Plomteux, 2002). In Western countries, major sources of organochlorine contaminants include foods, particularly meat, fish, and dairy products, as well as water, soil, and dust (Toppari et al, 1996; Paris-Pombo et al, 2003).

In recent decades, several reports have implicated exposure to pervasive estrogenic or antiandrogenic environmental contaminants in adverse effects on male reproductive function and development, such as a worldwide decline in sperm counts (Sharpe and Skakkebaek, 1993; Swan et al, 2000) and increased rates of male reproductive tract abnormalities (Paulozzi, 1999; Vrijheid et al, 2003) and testicular cancer (Adami et al, 1994). A recent report warns that environmental factors could have transgenerational effects through apparent reprogramming of the male germ line (Anway et al, 2005). To date, the role of such substances in male reproductive health remains controversial (Safe, 2005). While epidemiologic data, together with increased demand for clinical services to treat ED, indicate that sexual dysfunction in men is more prevalent than previously thought (Laumann, 1999), the impact of suspected endocrine disrupting substances on erectile function as a critical component of male reproductive function has been largely overlooked.

Given that the male erection is controlled by a complex interplay between neural, vascular, and hormonal factors (Melis et al, 1994; Lugg et al, 1995; Mills et al, 1996), it is plausible that organochlorine pesticides and various industrial chemicals with documented antiandrogenic or estrogenic properties (eg, DDT and its metabolites, PCBs) can interfere directly or indirectly with

the action of sex hormones, such as androgens, thus negatively impacting erectile function. A recent animal study showed that *p,p'*-DDE, the most persistent antiandrogenic metabolite of DDT, markedly interferes with erectile function in rats, producing long-term erectolytic effects from small concentrations (Brien et al, 2002). These data provide support to the global working hypothesis that environmental endocrine modulators are risk factors for ED.

Human adipose tissue, plasma, and breast milk have been found to have virtually equal distributions of persistent organochlorine compounds based on lipid content (Brown and Lawton, 1984), and therefore each may be used to estimate cumulative body burden (Laden et al, 1999; Moysich et al, 2002). Since the lipid content of blood is very low (<1%) (Woodruff et al, 1994), it is crucial that the method for detection of organochlorine levels be very sensitive. To evaluate the association between plasma concentrations of several persistent organochlorines and ED, a case-control study was conducted using sensitive measurement methods and adjusting for total lipids in blood.

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All men aged 50 to 80 years who visited a group of 5 urologists for various conditions from 1997 through 1999 in Kingston, Canada were potentially eligible if they had no previous history of prostate cancer and had a normal serum prostate-specific antigen (PSA) measurements and digital rectal exam (DRE) within 1 year of enrolment. Of 1288 men seen in clinic, 756 were ineligible and 56 refused to participate. In addition, 78 were excluded due to diagnosis of prostate intraepithelial neoplasia (n = 25), use of a hormonal medication (n = 18), or no blood taken (n = 35). Consequently, there were 408 study participants who completed a questionnaire on demographic, lifestyle, and medical factors. Patients with a diagnosis of incident prostate cancer were also excluded (n = 73) (Walker et al, 2005). Thus, there were 335 study participants with complete questionnaires and ascertainment of ED status.

Ascertainment of ED Status

Among the 335 eligible study participants, 101 had a clinical diagnosis of ED at the time of study enrollment and blood collection, and these comprised the case group. ED status was categorized into presence or absence of ED, and no assessment of severity was conducted. Controls comprised all other participants who were not suspected on a clinical basis to have ED (n = 234). Controls were diagnosed with a variety of benign urological conditions, including simple benign prostatic hyperplasia (BPH), prostatitis, hematuria, hematospermia, urinary obstruction/urgency/nocturia, renal calculi, Peyronie disease, and urinary tract infections.

Questionnaire

Following informed consent, all study subjects completed a standard questionnaire at home and were contacted by telephone a few days later to record results. The interview was conducted without subjects' knowledge of specific study objectives, and the interviewer was unaware of case/control status. The questionnaire included anthropometric, medical, sociodemographic, and lifestyle data. A subject was considered a smoker if he had smoked more than 1 cigarette per day for at least 6 months, an ex-smoker if he had stopped any amount of time before completing the questionnaire, and a nonsmoker if he had never smoked more than 1 cigarette per day for 6 months or more. Pack-years of smoking (the standard epidemiologic unit for cigarette smoking) were calculated according to the following formula: pack-years = (number of cigarettes per day/20) x years of smoking. Alcohol consumption was ascertained in the 1-year period 2 to 3 years prior to interview. One alcoholic

drink was defined as 12 oz of beer, 4 oz of wine, or 1.5 oz of liquor. Study participants reported whether they had ever had at least 1 drink per month for 6 months or more, and were further asked to indicate how many times, on average, they consumed each beverage per week, and these data were used to determine the total average weekly alcohol consumption. Diabetes history was reported as "ever having been informed by a physician of having diabetes." Current height and weight at age 40 (prior to ED) were used to calculate body mass index (BMI) for this study. Medication use was ascertained via questionnaire and clinical charts. Cardiovascular disease (CVD) medications were classified into a single group due to small numbers, and included the following drug classes: antihypertensive, antihyperlipidemics, and cardiac therapy.

Plasma PCB and Pesticide Measurements

Study participants donated 15 mL of blood for analysis of lipids and organochlorines. Plasma samples were analyzed by gas chromatography at the laboratory of the Centre de Toxicologie du Québec (CTQ). For determination of organochlorine total lipid level in plasma, 10 mL of blood was labeled only with an identification number and shipped on ice to CTQ and stored at −20 °C. Two mL of blood plasma were extracted and cleaned on Florisil columns, and fractions 1 and 2 were eluted. For gas chromatography, the fractions were evaporated and dissolved, and lipids were precipitated at −20 °C. After centrifugation, the fractions and the lipids were taken to a final volume of 100 µL and analyzed on an HP-5890 series II gas chromatograph with dual capillary columns and dual Ni-63 electron-capture detectors (Senefeld and Patterson, 1991). Peaks were identified by their relative retention times obtained in the 2 columns, using a computer program developed in-house. The identification window was ±0.001, and quantification was mainly done on the Ultra-1 column. Three calibration standards were used for each batch of samples. A hexane nonextracted standard containing PCB congeners and pesticides at 0.5 µg/L was used to check performance columns and sensitivity detectors. A water extract standard containing PCB congeners and pesticides other than *p,p*'-DDT at 0.5 µg/L was used to calculate the relative response factors for PCBs and pesticides other than aldrin, *p,p*'-DDT, ß-hexachlorocyclohexane (ß-HCH), and hexachlorobenzene (HCB).

Chemical analyses were done for 14 specific congeners of PCBs (IUPAC numbers: 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187, plus total PCBs as *Arochlor 1260*) and 13 chlorinated pesticides (aldrin, *cis*-chlordane, *trans*-chlordane, *p,p*'-DDE, *p,p*'-DDT, dieldrin, heptachlorepoxide, HCB, ß-HCH, mirex, *cis*-nonachlor, *trans*-nonachlor, and oxychordane). Most PCB congeners are mixed-type inducers that have been reported frequently in environmental samples (McFarland and Clark, 1989). The measurement unit (µg/L) was transformed to µg/kg lipid. Detection limits, based on 3 times the average standard deviation, were 4.0 µg/kg lipid for PCB congeners, 8.0 µg/kg lipid for *p,p*'-DDT and ß-HCH, 20 µg/kg for dieldrin and heptachloroepoxide, and 4.0 µg/kg for other pesticide compounds. The average percentage recoveries were greater than 95% for PCB congeners and ranged from 90% to 103% for pesticides. The between-day precision ranged from 3.3% to 7% and 5.5% to 14.2% for PCB congeners and pesticides, respectively. Total lipid in plasma was determined in 5 mL by a "summation" method in which total cholesterol, free cholesterol, triglycerides, and phospholipids were individually measured with an enzymatic method, then summed to obtain a total plasma lipid value (Akins et al, 1989).

Statistical Analysis

Distributions of characteristics of cases and controls are compared using the Pearson chi-square test for categorical variables, and the Student's *t* test or Wilcoxon rank sum test for continuous variables. Lipid-adjusted plasma organochlorine concentrations are used in all analyses. Levels of 5 PCB congeners (PCB28, PCB52, PCB101, PCB105, and PCB128), aldrin, alpha-chlordane, gamma-chlordane, *cis*-nonachlor, dieldrin, and heptachlorepoxide were nondetectable in more than 30% of the subjects

and thus were not considered in the analysis. Individuals with nondetectable organochlorine levels were assigned half the value of the detection limit, which is the standard practice (Haldane, 1955). These subjects are always in the baseline (first tertile) group for the analysis. Consistent with findings in other populations (Glynn et al, 2003; Ritchie et al, 2003), distributions of all organochlorine concentrations in plasma are positively skewed, and therefore were transformed to the log scale. Geometric means (GMs, corresponding to the median of the log-normal distribution) and associated 95% confidence intervals (CIs) were calculated for cases and controls. Associations among organochlorines were investigated by calculating the Pearson correlation coefficient (r) on log-transformed organochlorine concentrations, and Spearman correlation coefficients (r_s) were used to assess the associations between individual organochlorines with age, BMI, and pack-years of cumulative smoking among controls.

To estimate the ED risk associated with each substance, tertiles of chemical level were created based on the distribution among controls only, and these were used for the unconditional logistic regression analyses for 9 PCB congeners (99, 118, 138, 153, 156, 170, 180, 183, 187), total PCBs, and 7 chlorinated pesticides (*p,p*'-DDE, *p,p*'-DDT, *trans*-nonachlor, oxychlordane, HCB, ß-HCH and Mirex). Odds ratios (ORs) and corresponding 95% CIs were calculated using unconditional multivariate logistic regression (SAS Institute Inc, Cary, NC) to identify any association between each individual organochlorine substance and the presence of ED, always with control for age and total lipid level. In addition, covariates that were included in a model built by a backward selection procedure and were associated with ED risk at P less than .30 were further tested as potential confounders by modeling them with each organochlorine exposure variable separately. Covariates were considered to be confounding if their deletion from the model modified the estimate of the OR by more than 10% compared to the model saturated with all covariates (Rothman and Greenland, 1998). The covariates that were confounders in the analyses of each organochlorine are shown in the Appendix table.

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Table 1 provides summary descriptive information by case-control status. The mean age for all subjects is 64 years, and most were married, or living as married, and of British ancestry. Cases have a lower education level, higher levels of cumulative smoking, and a more frequent diagnosis of diabetes, whereas no difference in BMI at age 40 or pattern of alcohol consumption is observed. In terms of medications, use of cardiovascular or antidepressant medications does not differ between cases and controls, and mean total plasma lipid levels are virtually the same. Results of examining smoking, alcohol, diabetes, and medications as main effects have been published previously (Polsky et al, 2005), and these factors are considered as potential confounders in this study.

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Table 1. *Selected characteristics of cases and controls*

GMs for PCBs and chlorinated pesticides by case-control status are presented in Table 2. Plasma

levels of *p,p*'-DDE are highest among all individual substances analyzed (GM ~ 360 µg/kg of lipid). No difference is apparent between GMs for cases and controls for plasma concentrations of any organochlorine substance. Consistent with many previous studies of PCB levels among the general population (DeVoto et al, 1997; Glynn et al, 2000; Ritchie et al, 2003), higher chlorinated PCB congeners 138, 153, and 180 had the highest levels, in each instance with slightly higher concentrations among controls in this study. The GM for total PCBs is also slightly higher among controls. For most other PCB congeners, GM levels are virtually equal for cases and controls. Among the organochlorine pesticides, several concentrations (such as for *p,p*'-DDE and *trans*-nonachlor) are slightly higher among controls, while the GM for Mirex is slightly higher among cases.

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Table 2. *Geometric means and 95% confidence intervals for organochlorines in plasma by case-control status*

In terms of correlations, as expected, PCB concentrations are associated with age ($.18 \leq r_s \leq .29$), as are most pesticides ($.20 \leq r_s \leq .33$), with the exception of *p,p*'-DDT and Mirex. BMI at age 40 has a weak correlation with only 2 organochlorines—PCB 183 ($r_s = .16$) and ß-HCH ($r_s = .18$). Correlations between organochlorine levels and pack-years of smoking reveals a single weak correlation with *p,p*'-DDE ($r_s = .16$, $P = .01$).

Examination of the relationships among individual organochlorines shows that the more highly chlorinated PCB congeners (138, 153, 156, 170, 180, 183, and 187) are highly correlated with each other ($.35 \leq r \leq .95$), as are the lower chlorinated PCB congeners (99 and 118; $r = .65$). Correlations among pesticides tend to be lower. Mirex is weakly correlated with *trans*-nonachlor, oxychlordane, and HCB ($.15 \leq r \leq .36$). Other Pearson correlation coefficients among pesticides range from .19 to .81, with the weakest correlation between *p,p*'-DDT and HCB, and the strongest ($r = .81$) between *trans*-nonachlor (component of the pesticide chlordane) and oxychlordane (a metabolite).

Risk estimates for the associations between PCB congeners and ED risk adjusted for confounders are presented in Table 3, and those for pesticides are presented in Table 4. The covariates that are confounders in the analyses of each organochlorine, in addition to age and blood lipid levels, are presented in the Appendix table. ORs for tertiles based on the distribution among controls for the association between ED and PCB congeners consistently reveal no statistically significant association or linear trend across individual PCB concentration categories, with all ORs slightly below or above 1.0 and with ORs usually decreasing from the middle to the highest concentration category (except for PCB99).

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Table 3. *Odds ratios and 95% confidence intervals for PCB congener concentration categories and erectile dysfunction*

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Table 4. *Odds ratios and 95% confidence intervals for chlorinated pesticide concentration categories and erectile dysfunction*

A similar picture is presented for the associations between ED and pesticides, with most ORs consistently below and a few slightly above 1.0. Decrease in risk is apparent for the highest concentration levels of *trans*-nonachlor (OR = 0.47, 95% CI 0.23–0.96) and oxychlordane (OR = 0.47, 95% CI 0.23–0.95) compared to the lowest concentration levels, with a decreasing linear trend (*P* = .04 for both). Concentrations of these 2 chemicals are highly correlated (*r* = .81), and therefore these results cannot be viewed as independent. All other results indicate associations close to the null or very slightly reduced ED risk.

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To our knowledge, this study is the first to investigate the possible relationship between plasma levels of organochlorines and ED risk, a hypothesis generated from both wildlife and occupational epidemiologic studies. Results here do not provide evidence of increased risk of ED associated with levels of most detectable environmental substances after adjustment for age, total lipids, and other relevant factors. Levels of 2 ubiquitous highly correlated pesticides, oxychlordane and *trans*-nonachlor, appear to be associated with a reduced risk of ED, but the role of chance cannot be ruled out, since multiple comparisons were undertaken.

In this study, to reflect total body burden, exposure to individual PCB congeners and chlorinated pesticides was assessed by measuring plasma levels of these compounds in a sample of 335 males aged 50–80 years. Serum/plasma levels of organochlorines can be used as surrogate measures of long-term exposure, since these compounds are lipophilic and highly resistant to metabolic breakdown (Phillips et al, 1989; Stellman et al, 1998). Concentrations of these substances are usually positively correlated with each other, likely due to common sources of exposure from diet, the primary exposure route for humans (Center for Disease Control, 2003). Strong correlations between serum/plasma concentrations of certain organochlorines are common findings in earlier studies (DeVoto et al, 1997; Gladen et al, 1999; Glynn et al, 2000), but because various PCB congeners and chlorinated pesticides have different biological activities, including estrogenic, antiestrogenic, and antiandrogenic effects (Toppari et al, 1996), individual PCBs were examined in this study.

The levels of organochlorines among controls in this study are consistent with the limited available research investigating levels of these substances in serum/plasma in the general population (Lebel et al, 1998; Glynn et al, 2000; Hauser et al, 2002; Center for Disease Control, 2003; Paris-Pombo et al, 2003; Ritchie et al, 2003). Thus, data from this study provide an opportunity to assess the possible association between ED and plasma organochlorine levels in the lower section of the exposure continuum. Consistent with other analyses, concentration of *p,p*'-DDE is highest among the pesticides in plasma, at about 14 to 50 times that of other measured substances; other highly detectable pesticides are *trans*-nonachlor, HCB, and oxychlordane. Among PCB congeners, PCB 153 has the highest level among the congeners, closely followed by other commonly detected congeners 180 and 138. Exposure to many of these chemicals, and particularly to PCB congeners, typically occurs from

mixtures rather than individual substances (Center for Disease Control, 2003), likely due to common sources of exposure from diet, confirmed by the high correlation among levels of these compounds in plasma found in this study.

This investigation was a clinic-based case-control study in Kingston, Canada. Eligibility criteria included normal PSA and DRE within a year prior to study enrollment. Thus, in the current study, all controls were confirmed to be free of prostate cancer at enrollment. Further, an advantage of using hospital-based subjects is that cases and controls were likely to have been influenced by the same selection factors that resulted in their attendance at urology clinics. Men undergoing PSA/DRE screening are a more health-conscious group, and comparisons are most valid within this group, as was done in this study. Although bias is unlikely, if any urological conditions common among controls such as BPH are related to the same risk factors as for ED, then the observed risk would be diluted towards no effect. This could be one explanation for the null results observed in this study; however, current knowledge is not at the point where we know if and how these risk factors differ.

Information bias or differential recall bias was minimized by the study design, since blood was the primary exposure medium. Data on lifestyle and medical factors were collected via self-report and without participants' knowledge of the specific outcome under study (stated as "prostate conditions"), reducing the likelihood of recall bias, although some degree of nondifferential misclassification may have occurred (equally for cases and controls). The ED case definition used in this study was based on clinical diagnosis alone, and while decreasing the analytic resolution, it does not impact on the essential diagnostic dichotomy of ED "yes" or "no." The main limitation of this study is the small sample size, reflected in the relatively wide confidence intervals. If these environmental chemicals are affecting risk of ED, the magnitude of the risk may be quite low, and therefore future studies must be larger to detect these risks.

Research in the area of male sexual function and environmental contaminants is limited. Because this study is the first of its kind, we are unable to compare these findings directly to existing research. As a result, this discussion is limited to animal studies and human epidemiologic studies involving occupational exposure to pesticides and other industrial chemicals. Kelce et al (1995) showed that *p,p*'-DDE possesses antiandrogenic and estrogenic properties, and may affect erectile function through its antiandrogenic activity. In an investigation using a rat model, Brien et al (2000) showed that this endocrine disrupter markedly interferes with erectile function in rats and demonstrates persistence after a single dose. The main purported mechanism of this observed effect was described as prolonged androgen receptor blockade, while further studies are needed for full elucidation of this mechanism. Given that the male erection is at least partially androgen-dependent (Lugg et al, 1995), this finding lends substance to the hypothesis that environmental endocrine disrupting substances can negatively impact erectile function in humans by modulating the normal functioning of endogenous hormones.

A few studies of farmers and pesticide applicators show increased risk of ED associated with apparent higher exposure to environmental chemicals, although no study measured chemicals in blood. In a recent study by Oliva et al (2002), a sample of 199 Argentinean males who sought help for ED at andrology units underwent laboratory explorations to assess nocturnal erectile activity, and exposure to environmental agents was assessed via a detailed interview. Although this could not identify specific compounds or their exposure conditions (ie, frequency and intensity), general exposure to pesticides or solvents in various industries was reported to be associated with an increased risk of an abnormal nocturnal erectile pattern. However, these methods are subject to recall and misclassification biases, and another limitation is the lack of a biomarker of exposure,

as was used in this study.

In conclusion, while there is some speculation on the potential association between organochlorines and ED coming from occupational and animal studies, levels of these contaminants in this study population were low and were not associated with increased ED risk. While no association of ED risk with plasma measurements of ambient levels of organochlorine substances was seen in our study, further studies in larger populations using biomarkers of exposure are warranted to rule out a potential relationship. Given the prevalence and impact of sexual dysfunction in the aging population, investigation into the causes of ED, including the potential effect of environmental chemicals, should be pursued.

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Appendix. *Covariates included in the confounder models*†

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Footnotes

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