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Organochlorine pesticides and endometriosis

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Abstract

Limited study of persistent organochlorine pesticides (OCPs) and endometriosis has been conducted. One hundred women aged 18-40 years who were undergoing laparoscopy provided 20 cc of blood for toxicologic analysis and surgeons completed operative reports regarding the presence of endometriosis. Gas chromatography with electron-capture was used to quantify (ng/g serum) six OCPs. Logistic regression was utilized to estimate the adjusted odds ratios (aOR) and 95% confidence intervals (CI) for individual pesticides and groups based on chemical structure adjusting for current cigarette smoking and lipids. The highest tertile of aromatic fungicide was associated with a five-fold risk of endometriosis (aOR = 5.3; 95% CI, 1.2-23.6) compared to the lowest tertile. Similar results were found for t-nonachlor and HCB. These are the first such findings in a laproscopic cohort that suggest an association between OCP exposure and endometriosis. More prospective studies are necessary to ensure temporal ordering and confirm these findings.

Keywords

Endometriosis; Environment; Fecundity; Organochlorines; Pesticides; Reproductive toxicant

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1. Introduction

Endometriosis is a complex disease typically defined as an estrogen-dependent disease with an estimated incidence of 1.9/1,000 person-years [1]. Prevalence of endometriosis ranges from 20-65% among women seeking medical care [2-6]. Confirmation of the endometriosis diagnosis requires at a minimum the visual inspection of the pelvis for overt disease. This definition impacts the choice of study cohort since not all affected women are symptomatic, seek medical care, or undergo surgery.

Despite its etiology remaining speculative, increasing evidence supports a role of environmental chemicals in the development of endometriosis, particularly dioxin [7], polychlorinated dibenzodioxins and polychlorinated dibenzo furans [8], and polychlorinated biphenyls (PCBs) [9-11]. Of note, two other studies reported an association between higher concentrations of phthalates [12, 13], plasticizers frequently found in personal care products, and endometriosis. A case-control study in Atlanta aimed at measuring any potential association between serum dioxin levels as expressed by total toxic equivalence (TEQ) and serum total PCBs, as calculated by the sum of concentration of 36 congeners in women and endometriosis, found null results. The authors did not however examine the chemicals we examined in this study [14]. Limited attention has focused on persistent organochlorine pesticides (OCPs) and their association with endometriosis, despite their sharing a similar chemical structure with dioxins and PCBs and their ubiquitous presence in the environment. Organochlorine pesticides are persistent chemicals used to eliminate insects and have largely been banned in the U.S. These chemicals can bioaccumulate in fish, and diet is the main route of exposure for humans [9].

2. Materials and Methods

2.1 Study population

One hundred women, ages 18-40 years undergoing incident laparoscopy in 1999-2000 at one of two participating University-affiliated hospitals were approached for recruitment for study. Participating surgeons informed women about the study. Following consent, each woman was contacted by research personnel. Eighty-four women (84% response) participated in the study.

2.2 Data collection

The interview conducted in the woman's home prior to surgery via standardized questionnaire elicited information on the sociodemographic characteristics, reproductive and medical history and lifestyle and potential confounders: gravidity (number of pregnancies regardless of outcome), body mass index (BMI, weight in kilograms divided by height in meters squared), and current cigarette smoking based on recent findings [15, 16]. The research assistant conducting the interview was unaware of the woman's preoperative diagnosis, and the questionnaire was designed to elicit information on potential confounders in the association between environmental chemicals and disease. Approximately 20 cc of blood was obtained from all women, and 80 (95%) had sufficient sample for the OCP analysis after PCB analyses were completed. Blood was collected after the interview and

before surgery using venipuncture equipment determined by the participating toxicologic laboratory to be free of the contaminants under study.

Laparoscopic surgeons visually inspected the entire pelvis and recorded all pathology and the presence of endometriosis on standardized operative reports immediately following surgery. Severity of endometriosis was staged according to the American Fertility Society's revised definition as: Stage I (minimal); Stage II (mild); Stage III (moderate); and Stage IV (severe) [17, 18]. Full Institutional Review Board approval was obtained by the participating hospitals for the conduct of this study.

2.3 Laboratory methods

Gas chromatography with electron-capture (GC-EC) was utilized in a blinded manner for quantifying six serum OCPs or their metabolites: aldrin, beta-benzene hexachloride (β -BHC); dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE); hexachlorobenzene (HCB), mirex, and *trans*-nonachlor (*t*-nonachlor). Briefly, to each serum sample surrogate standards of PCB IPAC isomer numbers 46 and 142 were added and allowed to equilibrate overnight. Methanol was added to precipitate serum protein and the sample mixture was then extracted with hexane at 50 rpm for 20 hours in a rotary extraction unit, followed by centrifugation and concentration to 2 ml under a stream of nitrogen. To separate lipids from PCBs, the mixture was passed through a deactivated Florisil column, eluted with hexane, and concentrated under a stream of nitrogen using 200 μ l of isooctane as a keeper solvent. Internal standards (congeners 30 and 204) were added to the extract prior to injection into an Agilent 6890 Gas Chromatograph equipped with an electron capture detector.

Chromatographic data were collected electronically and analyzed using Turbochrome chromatographic software. All chromatographic data were burned to compact discs for permanent data archiving. Serum specimens were run in batches of ten plus four quality control samples (i.e., reagent blank, matrix blank, matrix blank containing a mixed standard of 15 specific congeners at known values, and one duplicate participant sample). Matrix blanks consisted of sheep serum with low background levels of PCBs. Pesticide and PCB congener concentrations were calculated from standard curves for the 15 calibration standards, and the remaining congener concentrations were calculated from response factors that were generated for each congener in our laboratory. Each congener concentration was adjusted for surrogate recovery and subtraction of reagent blanks. The limit of detection was determined as three standard deviations of the mean of at least ten matrix blanks. We did not substitute values below the limits of detection nor did we automatically lipid-adjust concentrations to avoid biases associated with such practice [19, 20]. The limits of detection for β -BHC, DDE, HCB, mirex, *t*-nonachlor, and aldrin were as follows, respectively, 0.011, 0.022, 0.002, 0.020, 0.011, 0.017 ng/g serum.

Total serum lipids (TL) were determined using gravimetric procedures and quantified as the sum of total cholesterol (TC), free cholesterol (FC), triglycerides (TG), and phospholipids (PL) as follows: $TL = 1.677(TC-FC) + FC + TG + PL$ [21]. All lipids were expressed as mg/dl serum.

2.4 Statistical methods

Descriptive analyses were conducted to assess the missing data, the normality of OCP distributions and potential confounders for inclusion in unconditional logistic regression models. For analysis, OCP concentration was defined as the observed serum value for a particular pesticide corrected only for batch-specific recovery and blanks and expressed as nanograms per gram serum (ng/g), which translates to parts per billion (ppb).

All pesticides, except for aldrin and β -BHC, were categorized into tertiles for analyses, with the lowest tertile serving as the referent category in the logistic regression models. Since approximately 80% of women had values below the limits of detection (LOD) for aldrin and β -BHC, we undertook a series of analyses to assess the best way to correctly estimate their distributions relative to endometriosis diagnosis. Specifically, first we assumed that aldrin and β -BHC concentrations were log-normally distributed and then used the maximum likelihood ratio test for equivalence of distributions to determine if each compound discriminated women by endometriosis status. The corresponding likelihood functions were defined to be based on measurements subject to the detection limit [22]. Using this approach, aldrin differentially discriminated women by disease status as evidenced by the 2-log likelihood ratio test statistic ($18.57 > 5.9$; $p < 0.05$). To use the aldrin and β -BHC as explanatory exposures in logistic regression models considering the limit of detection issue, we then utilized maximum likelihood estimation procedures for obtaining the expected unobserved (conditional to $< \text{LOD}$) values [23]. The estimated values for aldrin and β -BHC were 0.00003 and 0.00007, respectively, and as such were substituted for all values $< \text{LOD}$ for these two compounds in logistic regression models.

All OCPs concentrations were log transformed by the formula $\ln(1 + \chi)$ except for DDE that was done through the Box-Cox transformation process to achieve normality. All transformed OCPs were included as continuous variables in the logistic regression models as covariates, and then finally categorized by chemical structural and target pest groupings – chlorinated insecticides (β -BHC and DDE), cyclodiene insecticides (aldrin, mirex, and *t*-nonachlor) and aromatic fungicides (HCB) – for inclusion in logistic regression models.

Adjusted odds of an endometriosis diagnosis (aOR) and corresponding 95% confidence intervals (CI) were estimated using SAS (SAS Institute, 2006) and also adjusted for current cigarette smoking (yes/no) and serum lipids (mg/dl serum). We did not adjust for gravidity or parity, given that either may be in the causal pathway for endometriosis.

3. Results

Thirty-two (38%) women were reported to have endometriosis while 52 (62%) did not. Of those diagnosed with endometriosis, 20 women were diagnosed as having Stage I or II (minimal-mild) endometriosis, while 12 women were diagnosed as having Stage III or IV (moderate-severe). Women with endometriosis were more likely to have higher educational attainments and household incomes than unaffected women; conversely, they were less likely to be current smokers or ever pregnant than women without disease (Table 1) [15][5]. A previously published report on this same data discusses the findings with regard to body size and figure and demonstrates that women diagnosed with endometriosis were found to

have a lower BMI both at the time of diagnosis and historically than women without endometriosis [16].

Adjusted odds of an endometriosis diagnosis were elevated for women whose OCP serum concentrations were in the highest tertiles for HCB (aOR = 6.4; 95% CI, 1.0 - 42.8) *t*-nonachlor (aOR = 4.6; 95% CI, 0.5 - 41.6) compared with women in the lowest category when simultaneously considering all other OCPs in the models (Table 2). Elevated adjusted odds were observed for women whose serum concentrations were above the LOD for aldrin and β -BHC, as well. These associations persisted and were often stronger in the models when the concentrations of the chemicals were transformed and examined in a continuous fashion. The adjusted odds for endometriosis among women for a per unit log transformed increase in HCB was 1.4 (95% CI, 0.5, 3.9) and 5.0 (95% CI, 0.7 - 35.8) per unit log transformed increase in *t*-nonachlor. Of added note is the increase in some of the odds ratios after adjusting for total serum lipids (mg/dl serum) and current smoking (yes/no) behavior, although most confidence intervals included unity. We did not include infertility or menstrual cycle characteristics in the models as they may be in the pathway to disease. We included all compounds in the first two models to reflect the mixture of chemicals to which women are most likely exposed. We also ran the models without adjusting for the other compounds. Pearson correlation coefficients were calculated for the correlation between each of the chemicals and only four were significant at the $p < 0.05$ level ranging from 0.198 for HCB and mirex to 0.669 for β -BHC and aldrin. The ORs were slightly higher (Table 2) for endometriosis comparing women who were in the higher tertiles of each of the exposures compared to those in the lowest tertile when the other chemicals were not considered in the model. The confidence intervals remained wide making these results difficult to interpret with regard to the adjusted models. We believe that the models including the other compounds more accurately reflect the probable chemical mixture found in women.

We further inspected our data to see if choice of comparison group affected the results, by dividing women without endometriosis into a group in whom other gynecologic pathology (but not endometriosis, $n=30$) was observed and a group of women in whom no gynecologic pathology was noted (i.e., tubal sterilizations without pathology, $n = 22$). Overall, the odds ratios were stable and consistent with the findings when the comparison groups were combined, except for aldrin and HCB for which a large percentage of the women had concentrations below the LOD (data not shown).

When OCP concentrations were left in their original unit but grouped by structure, significantly elevated aORs were observed for the highest tertile of aromatic fungicides (aOR = 5.3; 95% CI, 1.2 - 23.6) and elevated but not statistically significant aORs were observed for cyclodiene insecticides (aOR = 2.7; 95% CI, 0.8 - 9.5), as well as the mid-range tertile for chlorinated insecticides (aOR = 1.6; 95% CI, 0.5 - 5.3) (Table 3).

4. Discussion

OCPs were associated with an elevated adjusted odds of having a laparoscopically-confirmed endometriosis diagnosis, however many of the confidence intervals were wide and included unity. For the pesticides HCB and *t*-nonachlor, the data were suggestive of

increasing risk by tertile. The effect estimates for aldrin, β -BHC and mirex also suggested higher odds ratios, although these observations were based on extremely limited numbers of women with concentrations above the LOD and, thereby, need cautious interpretation. We included all OCP concentrations simultaneously in the model irrespective of the percent of concentrations above the LOD in an attempt to more closely model the chemicals mixture to which women are exposed. The magnitude of observed effects increased for most OCPs after adjusting for serum lipids and current smoking status, denoting their possible importance in the development of endometriosis. However, most confidence intervals included one necessitating caution when interpreting the results.

When grouped by chemical structure and intended use, only the aromatic fungicides were associated with a significant and approximately five-fold increase in the odds of an endometriosis diagnosis. HCB has been reported to adversely affect hormonal processes via the neuroendocrine axis [24].

We further inspected our data to see if choice of comparison group affected the results, by dividing women without endometriosis into groups in whom other gynecologic pathology was observed and one in whom no gynecologic pathology was noted. The fact that the odds ratios were relatively consistent suggests that OCP exposures may be associated with an increased odds of developing endometriosis, specifically, and not gynecologic disease more generally.

Combined, our findings do not rule out a possible etiologic role of OCPs and diagnosis of endometriosis, especially the aromatic fungicides. Our findings are strengthened by the use of a population-based laparoscopic sampling framework involving two hospitals, a high participation rate, measurement of serum concentrations and relevant covariates in advance of surgery, and use of a standardized operative protocol for inspecting the pelvis for diagnosis and staging endometriosis [17, 18]. The change in magnitude of the odds ratio by choice of model underscores the relative fragility of all models, largely given our limited cohort size and the skewed distributions toward the LOD for some OCPs.

Interpreting our findings in the context of past research is limited in that we were only able to find a few published reports. One recent study offers the suggestion that exposure to OCPs may play a role in the occurrence of endometriosis. A case-control study in Italy with 80 cases and 78 controls found an increased risk for women exposed to the highest tertile of DDE compared to the lowest (OR=2.14; 95% CI, 0.93-4.93), while no association was seen for HCB [25]. Lebel et al. [14] in 1998 reported no differences in the mean plasma concentration for eleven chlorinated pesticides, including aldrin, *p,p'*-DDE, HCB, mirex, and *t*-nonachlor considered in our analyses. One possible explanation for their negative finding could be the authors' matching on indication for laparoscopy which may have inadvertently matched on disease status [26]. A second negative study conducted by Tsukino et al. [30] in 2005 compared serum concentrations of thirteen chlorinated pesticides/metabolites, including the pesticides assessed in our study, among infertile women undergoing laparoscopy. Women were categorized into two groups with the 'control' group comprising infertile women with Stage 0 or Stage I and the 'case' group comprising women with Stages II, III or IV endometriosis, and risk of endometriosis was adjusted for menstrual

regularity and average cycle length [27]. Interpretation of this study is difficult given the absence of a comparison group without infertility or endometriosis and the possible over-adjustment of models for menstrual cycle characteristics that may be a manifestation of endometriosis or in the causal pathway.

The most recent report from the CDC on human exposure to environmental chemicals (2003-2004) indicates that the geometric means for serum levels of exposure for the OCPs examined were comparable between the women in the NHANES survey and the serum levels for women we saw in our data [28].

To the best of our knowledge, our findings are the first to suggest a possible association between OCPs other than DDE and endometriosis, particularly the aromatic fungicides. The findings add to the existing literature that suggests other hormonally active environmental chemicals such as PCBs [10] and dioxin [7] may affect likelihood of endometriosis. These preliminary findings await further corroboration before more definitive conclusions may be reached about the etiology of OCPs in the development of endometriosis. Also, if corroborated, this finding underscores the importance of choice of comparison group when assessing the effects of persistent environmental chemicals and endometriosis.

Our findings also need to be interpreted in relation to the study's limitations consistent with the observational design of this study. Given the relatively short interval between blood collection and surgery, we cannot establish the temporal ordering of OCP exposure and disease. Other important considerations include factors that impact a woman's decision to seek gynecologic care and undergo laparoscopy. Our finding might be consistent with reverse causality as well in that women with endometriosis tend to have lower parity and, thereby, fewer opportunities to breastfeed. Since breastfeeding is reported to lower women's serum concentrations of OCPs [29, 30], higher concentrations may simply reflect less breastfeeding and not causality, *per se*. We purposefully did not include gravidity or parity in the model, since they are likely to be in the endometriosis pathway. To this end, women with higher concentrations may have lower fecundity as reported for other persistent chemicals [31, 32] ultimately leading to a greater risk for developing endometriosis. Delineating the causal ordering of exposure, fecundity and gynecologic disorders remains a research priority.

In sum, our data are consistent with a possible relation between OCPs and endometriosis but the findings must await corroboration. Further efforts to clarify the impact of choice of comparison group or mixture of OCPs in the context of other environmental chemicals and lifestyle will be important for delineating the causal pathway.

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List of Abbreviations

PCB	polychlorinated biphenyl
OCP	organochlorine pesticide
β-BHC	beta-benzene hexachloride
HCB	hexachlorobenzene
DDE	dichlor-diphenyl-dichloroethylene
t-nonachlor	<i>trans</i> -nonachlor
GC-EC	gas chromatography with electron capture
TL	total serum lipids
TC	total cholesterol
FC	free cholesterol
TG	triglyceride
PL	phospholipids
ppb	parts per billion
LOD	limit of detection
OR	odds ratio
aOR	adjusted odds ratio
CI	confidence interval
BMI	body mass index

Table 1
Characteristics of women by laparoscopic endometriosis diagnosis

Characteristic	Endometriosis n=29		No Endometriosis n=51		OR (95% CI)
	n	(%)	N	(%)	
Education (years)					
12	4	(14)	23	(45)	1.0 (<i>referent</i>)
13-16	17	(59)	23	(47)	4.3 (1.2- 14.6)
>16	8	(27)	5	(10)	9.2 (2.0- 43.0)
Household income (in dollars)					
<15,000	1	(3)	10	(20)	1.0 (<i>referent</i>)
15,000-59,999	13	(45)	23	(45)	5.7 (0.6- 49.3)
60,000	15	(52)	18	(35)	8.3 (1.0- 72.8)
Current cigarette smoking					
Yes	4	(14)	24	(47)	0.2 (0.1- 0.6)
No	25	(86)	27	(53)	1.0 (<i>referent</i>)
Mean number cigarettes $\pm$ SD ^a	9	(6)	15	(6)	
BMI (kg/m²)					
<18.	1	(4)	1	(2)	1.0 (0.1- 16.2)
18.5-24.9	24	(83)	23	(45)	1.0 (<i>referent</i>)
25.0-29.9	1	(4)	13	(26)	0.1 (0.1- 6.0)
30	3	(10)	14	(28)	0.2 (0.1- 0.8)
Mean $\pm$ SD	23	(3)	27	(6)	
Age (years)					
20-29	7	(24)	18	(35)	1.0 (<i>referent</i>)
30-34	11	(38)	19	(37)	1.5 (0.5- 4.7)
35	11	(48)	14	(28)	2.0 (0.6- 6.6)
Mean $\pm$ SD	32	(4)	31	(5)	
Ever pregnant					
Yes	9	(31)	32	(63)	0.3 (0.1- 0.7)
No	20	(69)	19	(37)	1.0 (<i>referent</i>)

BMI, weight in kilograms/height in meters squared.

OR, odds ratio; 95% CI, 95% confidence interval;
^a Among women who reported smoking

Table 2
Serum organochlorine pesticide concentrations and odds of an endometriosis diagnosis

Organochlorine Pesticide (ng/g serum)	OR (95%CI) ^a	aOR (95%CI) ^b	aOR (95%CI) ^c
Aldrin			
Above LOD	1.3 (0.2- 8.2)	1.2 (0.2- 8.1)	1.8 (0.5-7.5)
Below LOD	<i>referent</i>	<i>referent</i>	<i>referent</i>
β-BHC			
Above LOD	3.6 (0.5-27.4)	2.0 (0.3-15.8)	1.7 (0.4-6.7)
Below LOD	<i>referent</i>	<i>referent</i>	<i>referent</i>
DDE			
<0.63	<i>referent</i>	<i>referent</i>	<i>referent</i>
0.63-0.94	1.0 (0.3- 4.0)	1.0 (0.2- 4.4)	2.2 (0.6-7.3)
>0.94	0.2 (0.02- 0.9)	0.1 (0.02- 0.8)	0.8 (0.2-3.0)
Continuous	0.8 (0.2- 2.4)	0.5 (0.1- 1.7)	1.4 (0.6-3.6)
HCB			
<0.02	<i>referent</i>	<i>referent</i>	<i>referent</i>
0.02-0.04	2.0 (0.5- 8.1)	2.2 (0.5- 10.5)	1.6 (0.4-6.2)
>0.04	4.5 (0.8- 23.7)	6.6 (1.0- 42.8)	4.5 (1.1-18.1)
Continuous	1.2 (0.5- 3.0)	1.4 (0.5- 3.9)	2.1 (1.0-4.5)
Mirex			
<0.008	<i>referent</i>	<i>referent</i>	<i>referent</i>
0.008-0.17	1.0 (0.3- 3.6)	1.1 (0.3- 4.8)	1.4 (0.4-4.7)
>0.17	1.2 (0.3- 4.9)	1.1 (0.2- 5.3)	1.4 (0.4-4.8)
Continuous	1.0 (0.6- 1.6)	0.9 (0.5- 1.6)	1.2 (0.8-1.9)
<i>t</i>-nonachlor			
<0.05	<i>referent</i>	<i>referent</i>	<i>referent</i>
0.05-0.07	2.4 (0.5- 12.0)	3.0 (0.5- 18.3)	2.8 (0.8-10.3)
>0.07	3.9 (0.5- 31.4)	4.6 (0.5- 41.6)	2.8 (0.8-10.5)
Continuous	3.0 (0.9- 16.9)	5.0 (0.7- 35.8)	2.3 (0.8-6.1)

NOTE: Continuous serum concentrations were all log transformed; DDE concentrations were Box-Cox transformed.

β-BHC, beta-benzene hexachloride

DDE, dichloro-diphenyl-dichloroethylene

HCB, hexachlorobenzene

OR, odds ratio; 95% CI, 95% confidence interval

aOR, adjusted odds ratio

^aModel includes all other OCPs

^baOR odds ratios adjusted for total serum lipids (mg/dl serum), current smoking (yes/no), and other OCPs; four women (3 with and 1 without endometriosis) had insufficient serum remaining for lipid measurement

^codds ratios adjusted for total serum lipids (mg/dl serum), current smoking (yes/no)

Table 3
Serum organochlorine pesticides tertiles grouped by chemical structure and odds of an endometriosis diagnosis

Organochlorine Pesticide Groupings (ng/g serum)	Endometriosis n	No Endometriosis n	OR (95%CI)	aOR (95% CI) ^a
Aromatic fungicides^b				
> 0.04	14	13	3.8 (1.2-12.3)	5.3 (1.2-23.6)
0.02-0.04	9	17	1.9 (0.5-6.2)	1.9 (0.5-7.3)
<0.02	6	20	<i>referent</i>	<i>referent</i>
<i>Mean ± SD</i>	<i>0.04 (±0.03)</i>	<i>0.03(±0.03)</i>		
Chlorinated insecticides^c				
>0.093	9	18	1.1 (0.3-3.4)	1.0 (0.3-3.7)
0.062-0.093	12	15	1.7 (0.5-5.3)	1.6 (0.5-5.3)
<0.062	8	17	<i>referent</i>	<i>referent</i>
<i>Mean ± SD</i>	<i>1.23 (±1.50)</i>	<i>0.83 (±0.41)</i>		
Cyclodiene insecticides^d				
>0.100	12	15	2.8 (0.9- 9.1)	2.7 (0.8- 9.5)
0.065-0.100	11	15	2.6 (0.8- 8.5)	2.2 (0.6- 7.8)
<0.065	6	21	<i>referent</i>	<i>referent</i>
<i>Mean ± SD</i>	<i>0.10 (±0.06)</i>	<i>0.09 (±0.07)</i>		

OR, odds ratio; 95% CI, 95% confidence interval; SD, standard deviation

^a aOR, odds ratio adjusted for total serum lipids (mg/dl serum) and current smoking (yes/no)

^b Includes hexachlorobenzene (HCB)

^c Includes aldrin, mirex and *t*-nonachlor

^d Includes β-BHC and dichloro-diphenyl-dichloroethylene (DDE)