

ARTICLES

Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth

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Summary

Background DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane) is highly effective against most malaria-transmitting mosquitoes and is being widely used in malaria-endemic areas. The metabolite, DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene), has been linked to preterm birth in small studies, but these findings are inconclusive. Our aim was to investigate the association between DDE exposure and preterm birth.

Methods Our study was based on the US Collaborative Perinatal Project (CPP). From this study we selected a subset of more than 44 000 eligible children born between 1959 and 1966 and measured the DDE concentration in their mothers' serum samples stored during pregnancy. Complete data were available for 2380 children, of whom 361 were born preterm and 221 were small-for-gestational age.

Findings The median maternal DDE concentration was 25 µg/L (range 3–178)—several fold higher than current US concentrations. The adjusted odds ratios (OR) of preterm birth increased steadily with increasing concentrations of serum DDE (ORs=1, 1.5, 1.6, 2.5, 3.1; trend p<0.0001). Adjusted odds of small-for-gestational-age also increased, but less consistently (ORs=1, 1.9, 1.7, 1.6, 2.6; trend p=0.04). After excluding preterm births, the association of DDE with small-for-gestational-age remained.

Interpretation The findings strongly suggest that DDT use increases preterm births, which is a major contributor to infant mortality. If this association is causal, it should be included in any assessment of the costs and benefits of vector control with DDT.

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Introduction

DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane) was banned or restricted in industrialised countries in the 1970s but it is still widely used against malaria-transmitting mosquitoes in many countries.¹ DDT is fairly inexpensive, the concentrations to which human beings are exposed during mosquito control are thought to have no serious toxic effects,² and the benefits of the decrease in malaria are substantial.^{3,4} International debate continues about the urgency of eliminating its use.⁵

DDT is a well established reproductive toxin in certain bird species. Although mammals are less susceptible to its effects than are birds,⁶ large doses of DDT produce premature delivery in rabbits,⁷ and might have the same effect on Californian sea lions.⁸ In man, DDT exposure has been associated with preterm birth and spontaneous abortion.^{9–12} However, studies are small and have not received much attention. Overall, the effects of DDT on reproduction in man are unclear and understudied.

We have measured concentrations of p,p'-DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene), a persistent metabolite of DDT, in 2613 maternal serum samples from the US Collaborative Perinatal Project (CPP). Most mothers were enrolled in the early 1960s, when DDT use in the USA was at a peak.¹³ Thus, we were able to examine the association between DDE exposure and preterm birth with greater statistical power than previously, and with adjustment for potentially confounding factors.

Methods

Study participants

The CPP was a prospective study of the cause of neurological disorders and other conditions in US children.¹⁴ Pregnant women were enrolled between 1959 and 1966 when they presented for prenatal care at any of 11 university hospital clinics or at one group of private practices. Researchers selected these mothers on the basis of centre-specific methods, such as the last digit of the patient's hospital number. Mothers lived in urban areas, and had a median socioeconomic index 7% below the USA value. Workers took samples of the mothers' non-fasting blood about every 8 weeks before delivery, at delivery, and at 6 weeks' postpartum. Serum samples were stored in glass at -20°C, with no recorded thaws. Researchers enrolled about 42 000 women, who gave birth to 55 000 babies. These infants were systematically assessed for neurodevelopmental defects and other outcomes until the age of 7 years. In our study we measured serum organochlorine concentrations in a subset of CPP mothers. Mothers were eligible if they had an available 3 mL serum sample taken in the third trimester, and had a singleton livebirth, and had all data required for our sampling methods. 44 075 mothers and their corresponding children met the eligibility criteria. We used three sampling methods to select children for inclusion in our study. First, we took a simple random sample (n=1200). Second, we selected boys with cryptorchidism, hypospadias, or polythelia (n=232, 213, 185, respectively).

A third group of 993 children was selected according to outcomes of their tests of neonatal tone, neonatal reflexes, Bayley scale of infant development at 8 months, intelligence quotient on the Weschler intelligence scale for children (WISC) at age 7 years, and audiogram results at age 7 years. Our sampling methods increased our statistical power so that we could test hypotheses about in-utero organochlorine exposure in relation to the specific outcomes listed. The sampling was done independently and the 71 children selected for more than one type of sampling method were included only once in the analysis.

Laboratory assays

We measured serum concentrations of *p,p'*-DDT and *p,p'*-DDE at the US Centers for Disease Control and Prevention between 1997 and 1999 after solid-phase extraction, clean-up, and dual-column gas chromatography with electron-capture detection.¹⁵ The results shown are not adjusted for recovery. 87% of serum batches included a sample from a single large pool, which we used to calculate the between-assay coefficient of variation. We measured serum cholesterol and triglycerides with standard enzymatic methods and serum sodium by inductively coupled plasma-atomic emission spectroscopy.

We measured DDE concentrations in serum from the third trimester because these samples were the most complete. We selected 67 women from the CPP study at random to assess the variability of DDE concentrations in the first and third trimester.

Outcome measures

Our primary outcomes were the proportion of preterm and small-for-gestational-age babies. We measured the length of gestation as the date of delivery minus the date of last menstrual period. We classified a birth as preterm if delivery occurred before 37 completed weeks' gestation, and as small-for-gestational-age if birthweight was less than the tenth percentile at each week of gestation, with the mothers selected for our study as the standard.

Statistical analysis

We examined DDE concentrations in relation to odds of preterm birth and small-for-gestational-age birth with logistic regression models. To divide individuals into categories based on DDE concentrations, we used a set of four equally spaced cutpoints that gave at least 50 mothers per category, on the basis of the distribution of controls in the simple random sample of 1200 children selected by our first sampling method. We adjusted for study centre in all multivariate models. Because serum DDE concentration is determined in part by the concentration of serum lipids, we included serum triglycerides and cholesterol as continuous variables in all multivariate models. We thought a priori that infant ethnic origin and sex, mothers' age, height, body mass index before pregnancy, rate of weight gain during pregnancy, parity, socioeconomic index, and smoking during pregnancy would potentially confound the relations of interest and, therefore, we included them in all multivariate models. Additionally, we assessed whether use of oestrogen during pregnancy, use of progesterone during pregnancy, season of birth, marital status, education, and index of adequacy of prenatal care use had further influence on the effect estimates.¹⁶ We examined potential confounding by these factors by comparing the coefficient for DDE from models, including study centre, lipids, and the other a priori confounders with the coefficient from a model with each additional factor, one at a time.

DDE was modelled as a categorical variable and as a corresponding ordinal variable. For the assessment of confounding in models in which DDE was represented as a categorical variable we used only the coefficient for the highest category of DDE. If adjustment for a variable altered the DDE coefficient by 10% or more for either premature or small-for-gestational-age deliveries, we retained the variable in the final set of covariates, which was the same for both outcomes. Adjustment for prenatal care index was the only additional variable that met the criteria. The findings were similar when the analysis was restricted to those in the simple random sample, and results were homogeneous across the nine subject categories sampled (not shown). Because of missing data on covariates, 233 infants were excluded from the analysis of preterm birth. One additional baby was excluded from the small-for-gestational-age analysis because of missing data on birthweight. Thus, we included 361 preterm and 221 small-for-gestational-age infants in the final logistic analysis.

Results

Of the mothers and infants included in the analysis (table 1), the excess of male babies compared with the CPP overall was due to our selection design, which

	Overall (n=2380)*	Preterm (n=361)	SGA (n=221)
Children			
Boys	1473 (62%)	241 (16%)	110 (8%)
Girls	907 (38%)	120 (13%)	111 (12%)
Ethnic origin			
White	1033 (43%)	104 (10%)	70 (7%)
Black	1223 (51%)	235 (19%)	138 (11%)
Other	124 (5%)	22 (18%)	13 (11%)
Mother's age (years)			
Mean (SD)	24.2 (6.1)
≤16	131 (6%)	30 (23%)	10 (9%)
>16	2249 (94%)	331 (15%)	211 (9%)
Height (m)			
Mean (SD)	1.61 (0.07)		
≤1.6	847 (36%)	144 (17%)	88 (10%)
>1.6	1533 (64%)	217 (14%)	133 (9%)
BMI before pregnancy (kg/m²)			
Mean (SD)	22.9 (4.4)		
≤21	904 (38%)	171 (19%)	111 (12%)
>21	1476 (62%)	190 (13%)	110 (8%)
Weight gain during pregnancy (g per week)			
≤250	1064 (45%)	184 (17%)	133 (13%)
>250	1316 (55%)	177 (13%)	88 (7%)
Previous pregnancies			
None	745 (31%)	111 (15%)	79 (11%)
One or more	1635 (69%)	250 (15%)	142 (9%)
Socioeconomic index			
≤5%	1476 (62%)	267 (18%)	153 (10%)
>5%	904 (38%)	94 (10%)	68 (8%)
Smoking status			
Nonsmoker	1328 (55%)	187 (14%)	86 (7%)
Smoker	1052 (44%)	174 (17%)	135 (13%)
DDE serum concentration (mg/L)			
≤15	409 (17%)	34 (8%)	20 (5%)
15–29	1097 (46%)	153 (14%)	106 (10%)
30–44	483 (20%)	80 (17%)	47 (10%)
45–59	226 (10%)	50 (22%)	22 (10%)
≥60	165 (7%)	44 (27%)	26 (16%)

Values are numbers (%) unless otherwise indicated. Total is number of individuals with complete data for all variables listed in table and for whom premature delivery status was known. BMI=body mass index. SGA=small-for-gestational-age.

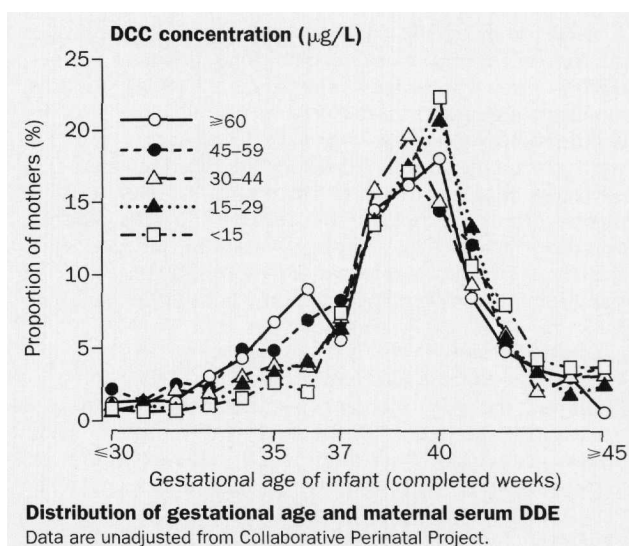
Table 1: Characteristics of mothers and children, and frequency of preterm and small-for-gestational-age birth

included boys with cryptorchidism, hypospadias, and polythelia. Similarly, the slightly higher proportion of black mothers was due to the high frequency of polythelia in this ethnic group. The median age of the mothers was 23 years (IQR 20–28). Most mothers did not complete formal education and were non-smokers. The median concentration of serum DDE was 25 µg/L (17–37, range 3–178). The median concentrations of serum cholesterol, triglycerides, and sodium were 6.0 mmol/L, 2.2 mmol/L, and 129 mmol/L, respectively. These values were close to those expected for pregnant women.

We recovered an average of 70% of DDE in every sample. Of the 2823 mothers, we obtained an acceptable measurement for DDE serum concentration in 2613 (93%) but not in 210 (7%), mainly because the measured value did not meet the quality control standards for acceptance.¹⁵ Mothers without an acceptable DDE concentration did not differ from those who did with respect to concentration of serum triglycerides, cholesterol, or sodium, study centre, or frequency of preterm or being small for gestational age. Of the 2613 women with a measured DDE concentration the distributions of age, race, smoking status, socioeconomic index, and study centre were essentially the same as for all CPP mothers (data not shown). All mothers had serum DDE of more than 0.61 µg/L (greater than our assay detection limit). The between-assay coefficient of variation was 19% at 29 µg DDE per L (n=291).

Maternal serum DDE was stable throughout pregnancy. For the 67 women who we selected at random from the CPP, the Pearson's correlation coefficient between lipid-adjusted DDE concentrations measured in first and third trimesters was 0.86.¹⁷ DDE crosses the placenta and concentrations in the mother's serum at delivery and the child's cord serum were highly correlated at $r=0.79$ in a US study.¹⁸

The proportion of preterm birth was fairly high (table 1). We recorded a greater frequency of preterm birth in males, blacks, mothers with a lower socioeconomic index, and those who smoked. Mothers who were young, had short stature, low body-mass index before pregnancy, or low rate of weight gain in pregnancy had a higher



frequency of preterm births than those who did not have these characteristics.

There was a greater frequency of small-for-gestational-age female than male infants (table 1). Mothers who were black, short, slim, and had a low rate of weight gain in pregnancy, or were nulliparous, or smokers had a high proportion of small-for-gestational-age babies.

The distribution of gestational age for those who had mothers in the higher DDE exposure categories was less peaked (figure) than for those who had mothers in the lowest exposure categories. With increasing concentration of serum DDE, the unadjusted frequencies of preterm and small-for-gestational-age birth increased (tables 1 and 2). The odds ratios were reduced by multivariate adjustment. For preterm births the change from the unadjusted to adjusted odds ratio was nearly all due to confounding by study centre; for small-for-gestational-age births no one factor accounted for most of the effect of adjustment. Further adjustment for weeks of gestation at the time blood samples were taken, or for serum sodium had no material effect on the results (data not shown).

The adjusted odds ratios for preterm birth increased steadily with increasing concentration of DDE (trend

	Serum DDE (μg/L)					
	<15	15–29	30–44	45–59	≥60	β (SE)
Preterm birth						
Number of cases	34	153	80	50	44	..
Number of controls	375	944	404	176	120	..
Odds ratio (95% CI)						
Unadjusted	1	1.8 (1.2–2.7)	2.2 (1.4–3.4)	3.1 (2.0–5.1)	4.0 (2.5–6.7)	0.31 (0.05)
Adjusted	1	1.5 (1.0–2.3)	1.6 (1.0–2.6)	2.5 (1.5–4.2)	3.1 (1.8–5.4)	0.26 (0.06)
Male infants	1	1.8 (1.1–3.2)	2.0 (1.1–3.7)	3.2 (1.6–6.3)	3.4 (1.7–7.2)	0.27 (0.07)
Female infants	1	1.1 (0.6–2.2)	1.2 (0.6–2.5)	1.6 (0.7–4.0)	2.2 (0.9–5.5)	0.20 (0.10)
White infants	1	1.4 (0.8–2.6)	1.6 (0.7–3.4)	1.9 (0.6–5.6)	3.7 (0.9–13.0)	0.26 (0.13)
Black infants	1	1.5 (0.8–2.9)	1.5 (0.8–2.9)	2.5 (1.3–5.2)	2.8 (1.4–5.9)	0.24 (0.07)
Small-for-gestational-age						
Number of cases	20	106	47	22	26	..
Number of controls	389	991	436	204	138	..
Odds ratio (95% CI)						
Unadjusted	1	2.1 (1.3–3.5)	2.1 (1.2–3.7)	2.1 (1.1–4.0)	3.7 (2.0–6.8)	0.21 (0.06)
Adjusted	1	1.9 (1.3–3.5)	1.7 (0.9–3.0)	1.6 (0.8–3.3)	2.6 (1.3–5.2)	0.13 (0.07)
Male infants	1	2.0 (1.0–4.2)	1.3 (0.6–3.2)	2.2 (0.9–5.5)	2.8 (1.0–7.4)	0.15 (0.10)
Female infants	1	1.8 (0.9–3.9)	1.9 (0.8–4.4)	1.0 (0.3–3.0)	2.4 (0.9–6.6)	0.10 (0.11)
White infants	1	1.3 (0.7–2.7)	1.0 (0.4–2.6)	3.9 (1.3–11.2)	4.4 (1.0–17.1)	0.34 (0.15)
Black infants	1	2.6 (1.2–6.6)	2.2 (1.0–5.7)	1.7 (0.7–4.9)	3.3 (1.3–9.3)	0.10 (0.09)

Data from Collaborative Perinatal Project. Adjusted for study centre, sex, smoking habit, maternal height (m), maternal BMI before pregnancy (kg/m²), maternal pregnancy weight gain (g per week), maternal age (years), socioeconomic index, parity, total cholesterol (mmol/L), triglycerides (mmol/L), and index of prenatal care (four categories). Results for mothers and infants of other race not shown due to small numbers. SE=standard error.

Table 2: Maternal serum DDE concentration in relation to odds of preterm or small-for-gestational-age birth

$p < 0.0001$). Quadratic spline models with the same covariates (not shown) showed that the odds of preterm birth began to increase at a DDE concentration of 10 $\mu\text{g/L}$. These odds ratios were greater for male than for female infants, but the statistical test for interaction did not lend support to this difference. The odds ratios for preterm white and black infants were not different.

The adjusted odds ratio for small-for-gestational-age birth was largest for mothers in the highest category of DDE exposure (trend $p = 0.04$). Again, spline models showed that these odds increased at concentrations greater than 10 $\mu\text{g/L}$. As with preterm birth, the odds ratios were usually greater for male than for female infants but the difference was not significant. The odds of small-for-gestational-age birth with increasing concentrations of DDE in white compared with black mothers was not statistically different (interaction $p > 0.10$). When the analysis for all ethnic origins was repeated after exclusion of infants born before 37 weeks of gestation, the adjusted DDE and small-for-gestational-age association was slightly stronger than that shown in table 2.

We also examined the odds of a birthweight less than 2500 g in relation to DDE concentration. For categories of DDE (<15 $\mu\text{g/L}$, 15–29 $\mu\text{g/L}$, 30–44 $\mu\text{g/L}$, 45–59 $\mu\text{g/L}$, and 60 $\mu\text{g/L}$) the adjusted odds ratios were: 1, 2.0, 2.3, 2.9, and 4.1, respectively, with all CIs excluding 1 (trend $p < 0.0001$). The association of DDE with preterm and small-for-gestational-age birth was statistically homogeneous across every study centre (all $p > 0.35$). Of the 238 mothers excluded from the analysis because of missing data on covariates, 165 were excluded because of missing maternal height measurements. However, adjustment for height (or body-mass index) had little effect on the results, and when these mothers were included in the analysis (without adjustment for height or body mass index) the results were essentially the same as shown in table 2. Because length of gestation was estimated from last menstrual period, DDE-induced menstrual irregularities could account for an association of DDE with length of gestation or preterm birth. However, the median length of time between menstrual periods was 4.3 weeks for mothers in all five categories of serum DDE. Furthermore, vaginal bleeding during pregnancy was unrelated to concentration of DDE.

In a model of birthweight as a continuous variable, the adjusted mean birthweight in the lowest DDE category was 3230 g and in the highest was 3080 g (trend $p = 0.01$; adjustment as in table 2). In a similar model of weeks' gestation the adjusted mean gestation in the lowest DDE category was 39.5 weeks and in the highest was 38.6 weeks (trend $p = 0.002$). When the birthweight analyses were repeated in infants born after 37 or more weeks' gestation, the associations were reduced: the lowest and highest category means were 3270 g and 3210 g, respectively (trend $p = 0.25$). These findings were less striking than for the small-for-gestational-age analysis in term births because the birthweight distribution in the highest DDE exposure group was less peaked. The odds of giving birth after more than 42 weeks' gestation fell with increasing DDE category (data not shown). In models of length and of head circumference at birth, DDE concentration was unrelated after adjustment for birthweight and the other factors, as in table 2 (data not shown).

Our selection of individuals was such that only 1521 infants in the analysis could have died anytime during the neonatal period (0–28 days after birth). The remaining babies had to have survived long enough to have a neurodevelopmental test result. Of these 1521, 11 neonatal deaths occurred (0.7% neonatal mortality rate), of which

only one was from a mother who had less than 15 $\mu\text{g/L}$ serum DDE (ie, too few deaths for an informative analysis). We examined the association of DDT with preterm and small-for-gestational-age birth with models such as those shown in table 2. DDT concentrations were not independently associated with either outcome, nor did the ratio of DDT/DDE improve the fit of the models.

Discussion

Our finding of a high frequency of preterm births in male and black infants, in mothers who had a low socioeconomic index, and those who were smokers are in accordance with previous reports.¹⁹ The high frequency of preterm birth in mothers who were young, of short stature, had a low body-mass index before pregnancy, and had a low rate of weight gain during pregnancy has also been reported but less consistently.¹⁹ The greater proportion of small-for-gestational-age births in girls was expected because birthweight percentiles were calculated for both sexes combined. Characteristics of mothers who had small-for-gestational-age births have been noted previously.²⁰

Maternal serum concentration of DDE was associated with increased odds of premature birth, and independently, with increased odds of small-for-gestational age birth. Compared with most recognised risk factors for these types of birth,^{19,20} the size of the associations we recorded were fairly large. For preterm birth the odds ratio increased steadily with DDE concentration.

In tropical countries, where DDT is used for malaria control,^{1,3,5} blood concentrations of DDE can greatly exceed the range observed in the CPP.²¹ If DDE causes premature birth, it is likely to cause increased infant mortality.²² In the USA and elsewhere, alternative agents, such as pyrethroids and malathion, are used for mosquito control,²³ although their reproductive toxicity might also need assessment.

Average serum DDE concentrations in the US population are now substantially less than 15 $\mu\text{g/L}$.²⁴ Because our spline results suggested essentially no relation of DDE with either preterm or small-for-gestational-age births at concentrations less than 10 $\mu\text{g/L}$, US studies done now would be unlikely to detect the associations that we recorded. Consistent with this possibility is the finding of a median DDE in women in New York City, USA, of about 1.4 $\mu\text{g/L}$, and lack of an association between DDE and preterm delivery.²⁵

DDE hampers the binding of androgen to its receptor,²⁶ and therefore could cause androgen insensitivity. In female mice bred to have androgen insensitivity, mean litter size and duration of reproductive life were reduced;²⁷ measures of gestational length or birthweight were not noted. DDE also affects the binding of progesterone to its receptor;²⁸ by blocking progesterone DDE could cause both shorter gestation and small-for-gestational-age birth. Diethylstilbestrol (a powerful oestrogen) is a strong risk factor for preterm and small-for-gestational-age birth.²⁹ *o,p'*-DDT,³⁰ a minor component of DDT, is weakly oestrogenic and quickly metabolised. Because our study was originally designed to focus on the potentially androgen-blocking effects of *p,p'*-DDE, we did not measure serum *o,p'*-DDT. However, at the time the data were obtained concentrations of *p,p'*-DDE might have correlated with exposure to *o,p'*-DDT. Lundholm and Bartonek³¹ suggested that the adverse effect of DDT on reproduction in birds is due to inhibition of prostaglandin synthesis by DDE, but drugs that inhibit prostaglandin synthesis do not have adverse effects on human pregnancy.³² DDT is toxic to insects because it delays closing of sodium channels in

neurons.³³ Human placental tissue contains sodium channels,^{34, 35} and compared with other tissues outside the nervous system, the placenta is unusually susceptible to neurotoxins. Thus a neurotoxic effect of DDE on the placenta could account for its adverse effects on reproduction. However, we did not record any obvious associations between DDE concentration and abruptio placenta, placenta praevia, or pre-eclampsia. There is no evidence that favours a specific mechanism for a DDE effect on preterm and small-for-gestational-age births.

If DDE increases premature birth and thus infant mortality, our strategy of selecting for analysis those infants who survived might have caused us to underestimate a DDE effect. Another potential difficulty was that, as with many biomarkers of chemical exposure, tissue concentrations might be associated with factors other than cumulative exposure. Recent data suggest that most serum DDE is associated with serum albumin.³⁶ If high serum albumin was associated with premature and small-for-gestational-age birth, our results could have been confounded. We measured albumin in too few people ($n=200$) to assess albumin as a potential confounder.

Despite the widely-held view that DDE resists degradation in most situations,³⁷ few data exist on DDE stability in serum during frozen storage. However, pooled breastmilk samples from Swedish mothers, stored in 1972 at -20°C , were analysed for DDE after 15 and 25 years; DDE concentrations showed no decline over this time.^{38, 39}

Our findings suggest that DDT use increases preterm births, and, by inference, infant mortality. Benefits of vector control with DDT might need to be reassessed in the context of this adverse effect on human beings and the availability of alternative methods of vector management.

Contributors

M P Longnecker had the original idea for the study, designed the main features of the study, analysed the data, and wrote the report. M A Klebanoff and H Zhou participated in the study design. H Zhou also helped with data analysis. J W Brock established and supervised the serum organochlorine assays. M A Klebanoff, H Zhou, and J W Brock provided critical comments on the manuscript draft.

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