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Original Contribution

Chlordecone Exposure, Length of Gestation, and Risk of Preterm Birth

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Persistent organic pollutants have not been conclusively associated with length of gestation or with preterm birth. Chlordecone is an organochlorine pesticide that has been extensively used to control the banana root borer population in the French West Indies. Data from the Timoun Mother–Child Cohort Study conducted in Guadeloupe between 2004 and 2007 were used to examine the associations of chlordecone concentrations in maternal plasma with the length of gestation and the rate preterm birth in 818 pregnant women. Data were analyzed using multivariate linear regression for length of gestation and a Cox model for preterm birth. The median plasma chlordecone concentration was 0.39 μg/L (interquartile range, 0.18–0.83). No correlation was observed with plasma concentrations of p,p′-dichlorodiphenyl dichloroethene ($\rho = 0.017$) or polychlorinated biphenyl 153 ($\rho = -0.016$), the other main organochlorine compounds detected. A 1-$\log_{10}$ increase in chlordecone concentration was associated with a decreased length of gestation (−0.27 weeks; 95% confidence interval: −0.50, −0.03) and an increased risk of preterm birth (60%; 95% confidence interval: 10, 130). These associations may result from the estrogen-like and progestin-like properties of chlordecone. These results are of public health relevance because of the prolonged persistence of chlordecone in the environment and the high background rate of preterm births in this population.

chlordecone; French West Indies; length of gestation; persistent organic pollutants; pesticides; preterm birth

Abbreviations: DDE, p,p′-dichlorodiphenyl dichloroethene; LOD, limit of detection.

Editor's note: *An invited commentary on this article appears on page 545, and the authors' response appears on page 548.*

Organochlorines are manmade chemicals that are persistent and are still present in the environment despite no longer being used. These chemicals are considered to pose a threat to human health, particularly during periods of increased sensitivity, such as gestation (1, 2). A number of studies have shown associations between maternal or cord blood concentrations of p,p′-dichlorodiphenyl dichloroethene (DDE), the main metabolite of dichlorodiphenyl trichloroethane, and decreased duration of gestation and/or increased risk of preterm birth. The largest study conducted to date included 2,380 children from an early pregnancy cohort set up in the United States in the 1960s, and it showed a dose-response relationship between the maternal blood concentration of DDE and preterm birth (3). More contemporary studies with fewer participants and lower DDE concentrations have had conflicting results: Some (4–6), but not all (7–9), showed associations between DDE exposure and adverse outcomes. Several of these studies investigated a number of other organochlorines simultaneously. Increased risks of preterm birth associated with hexachlorobenzene levels have been described in 2 studies (8, 10), and associations with hexachlorocyclohexane (mainly the β isomer) were described in 2 others (4, 8).

Chlordecone (kepone) is an organochlorine insecticide principally used for control of the banana root borer in Central and South America and the Caribbean, including Puerto Rico (11). It was initially manufactured in the United States, but production and use were banned there in 1976. Subsequently, it was produced in Brazil and intensively used in

banana fields in the French West Indies from 1981 to 1993. It is highly persistent in the environment; there is no significant biotic or abiotic degradation. Some soils in current and previous banana fields and some waterways are permanently polluted (12, 13). Currently, human exposure to chlordecone in the French West Indies results mainly from the consumption of contaminated food, especially seafood, root vegetables, and cucurbitaceae, as assessed by studies in the general population (14) and among pregnant women (15).

The toxicity of chlordecone to humans was discovered in 1975 after a poisoning episode in pesticide plant workers in the industrial city of Hopewell, Virginia. Male workers showed evidence of sustained toxicity involving the nervous system, liver, and testes (16–18). Additional studies on animals revealed that pregestational or gestational exposure of rats and mice to chlordecone affected embryo implantation and both prenatal and postnatal development (19). The mechanism of the toxic action of chlordecone is not completely understood. It has been suggested that its hormonal properties may be involved. Chlordecone is an endocrine disruptor with estrogen-like and progestin-like characteristics both in vitro and in vivo (20–24).

Experimental studies have documented the toxic effects of chlordecone exposure during gestation in animals, but there has been no epidemiologic study to determine whether chlordecone has similar consequences in humans at environmentally relevant exposure levels. The Timoun Mother–Child Cohort Study was established to investigate the impact on pregnancy and child development of prenatal exposure to the widespread chlordecone pollution in the French West Indies. Here, we report the relationships between maternal exposure to chlordecone and both the length of gestation and the risk of preterm birth.

METHODS

Study population

The present study was conducted in Guadeloupe (part of the French West Indies), an archipelago situated in the Caribbean Sea with a population of 450,000 inhabitants who are mostly of African descent. From December 2004 to December 2007, there were 1,068 women enrolled in a prospective epidemiologic mother-child cohort study. Women were enrolled during third-trimester check-up visits at public health centers (University Hospital of Pointe-à-Pitre, General Hospital of Basse-Terre, and antenatal care units). To be eligible, participants had to have resided in Guadeloupe for more than 3 years. The proportion of refusal was approximately 7%, and the most common reasons were refusal of the spouse, not wishing to participate in the follow-up, and not wishing to provide biological samples. The study was approved by the Guadeloupean Ethics Committee for studies involving human subjects, and detailed informed consent was obtained from each woman.

At enrollment, the participants answered a standardized questionnaire during a face-to-face interviews with trained midwives. The questionnaire covered sociodemographic characteristics, medical and obstetrical history, and lifestyle factors. Alcohol consumption during pregnancy was ascertained on 2 occasions: during the interview at enrollment and after delivery. After delivery, the medical history of the pregnancy and delivery information were collected from midwives, pediatricians, and hospital medical records. Cases involving multiple births ($n = 29$), terminations of pregnancy for fetal abnormality ($n = 2$), and stillbirths ($n = 4$) were excluded, resulting in a study sample of 1,033 singleton live births. From these eligible cases, maternal blood samples were obtained at delivery for 818 women.

Outcomes

Gestational age in weeks was estimated by the obstetricians in charge of follow-up. It was based on the first day of the last menstrual period and was confirmed or corrected by ultrasound. Data were available for 97% of the pregnancies. Preterm birth was defined as a birth before 37 completed weeks of gestation (25). We distinguished between spontaneous and medically induced births. Induced births included all cases of induced labor and of caesarean delivery before the onset of labor. Elective induced labor was not practiced at the delivery centers involved in this study.

Exposure assessment

Maternal blood samples were collected into spray-coated dipotassium ethylenediaminetetraacetic acid tubes. After centrifugation, plasma samples were stored at −20°C. Samples were identified using only a sample code. They were transferred by airmail on dry ice to Liege, Belgium, for organochlorine and lipid analysis.

Determination of chlordecone was done by the Center for Analytical and Research Technology at Liege University in Belgium. The preparation of samples and the quantification method have been previously described (26–28). Details are provided in Web Appendix 1, available at http://aje.oxfordjournals.org/. The limit of detection (LOD) was set at 3 times the background noise of the chromatogram and was thus 0.06 μg/L. Samples from a subgroup of 358 women who delivered after 37 weeks of gestation and whose children were enrolled for neurodevelopmental follow-up were also assayed to assess DDE and polychlorinated biphenyl 153 levels (26). The LODs for both compounds were 0.05 μg/L. Total cholesterol and triglyceride concentrations in plasma were determined using standard enzymatic procedures (DiaSys Diagnostic Systems GmbH, Holzheim, Germany), and total lipid concentrations were calculated as described previously (29).

Data and statistical analysis

Exposure was defined according to the chlordecone concentration in maternal plasma (modeled on a wet-weight basis) and was categorized in quintiles. A decimal log-transformed continuous exposure variable was also used. Multiple imputations were implemented to impute chlordecone concentrations below the LOD. The likelihood method was used (30) under the assumption that chlordecone is log-normally distributed. Five data sets with imputed concentrations below the LOD were generated. Modeling of associations with the length of gestation and the risk of preterm birth was performed within each set, and the results were combined

Table 1. Characteristics of Study Participants ($n = 818$), Length of Gestation, and Rate of Preterm Births ($n = 115$), Timoun Mother–Child Cohort Study, Guadeloupe, French West Indies, 2004–2007

	Births		Length of Gestation, weeks		Rate of Preterm Birth[a]	
	No.	%	Mean (SD)	*P* Value[b]	%	*P* Value[c]
Maternal age, years				0.01		0.25
<20	62	7.6	38.5 (1.4)		11.3	
20–24	118	14.4	38.5 (1.7)		14.4	
25–29	161	19.7	38.4 (1.8)		10.6	
30–34	214	26.2	38.4 (1.8)		13.5	
≥35	263	32.2	37.9 (2.0)		17.1	
Maternal place of birth				0.05		0.24
French West Indies[d]	634	77.5	38.2 (1.9)		15.0	
Other Caribbean Islands	90	11.0	38.4 (1.4)		11.1	
Europe	94	11.5	38.6 (1.7)		10.6	
Parity				0.10		0.76
0	301	36.8	38.4 (1.7)		13.0	
1	252	30.8	38.3 (1.9)		14.3	
≥2	265	32.4	38.1 (1.9)		15.1	
Marital status				0.09		0.12
Single	206	25.9	38.1 (2.0)		16.0	
Married or in a couple	429	53.8	38.4 (1.7)		11.7	
Living with own family	162	20.3	38.2 (1.9)		16.7	
Maternal education, years				0.69		0.96
<5	47	5.7	38.0 (1.7)		14.9	
5–12	573	70.1	38.3 (1.9)		13.8	
>12	198	24.2	38.3 (1.6)		14.7	
Body mass index[e]				0.02		0.20
<18.5	54	6.7	38.1 (1.4)		11.1	
18.5–24.9	421	52.5	38.5 (1.6)		11.6	
25–29.9	180	22.4	38.0 (2.2)		17.8	
≥30	147	18.3	38.2 (2.0)		15.7	
Smoking during pregnancy				0.23		0.25
Yes	47	5.8	38.6 (1.5)		10.6	
No	771	94.2	38.2 (1.8)		14.3	
Alcohol during pregnancy				0.37		0.88
Yes	23	2.9	38.6 (1.6)		13.0	
No	760	97.1	38.3 (1.7)		13.8	

Table continues

using the Proc MIANALYZE procedure in SAS (SAS Institute, Inc., Cary, North Carolina) according to the methodology described by Rubin (31) and Little and Rubin (32). Because the LOD was below the first quintile of the distribution, the multiple imputation exclusively applied to analyses based on the chlordecone concentration as a continuous predictor.

We collected information on socioeconomic and lifestyle characteristics, including maternal place of birth (French West Indies, other Caribbean islands, or Europe), enrollment site (university hospital (Pointe à Pitre), local hospital (Basse-Terre), or antenatal care units), age (<20, 20–24, 25–29, 30–34, or ≥35 years), years of education (<5, 5–12, or >12 years), smoking during pregnancy (yes or no), and alcohol consumption during pregnancy (yes, defined as at least 1 drink during preceding week or 1 binge drinking session during the previous 3 months reported at enrollment or after delivery, or no). We also collected information on marital status, which we then classified into 3 categories corresponding to family profiles common in the French West Indies: single, living with a partner, and single but living with family (an adult member of her family, typically mother, father, sister, or aunt). Medical and reproductive factors recorded included parity (defined as the number of previous viable pregnancies: 0, 1, or ≥2), number of prior preterm births

Table 1. Continued

	Births		Length of Gestation, weeks		Rate of Preterm Birth[a]	
	No.	%	Mean (SD)	*P* Value[b]	%	*P* Value[c]
Timing of first ultrasound				0.38		0.77
<15 gestational weeks	675	84.7	38.2 (1.8)		13.9	
≥15 gestational weeks	122	15.3	38.4 (2.0)		14.8	
High blood pressure during pregnancy				<0.001		<0.001
Yes	99	12.3	37.1 (2.4)		35.4	
No	705	87.7	38.4 (1.7)		11.1	
Gestational diabetes				0.003		0.06
Yes	74	9.3	37.7 (2.0)		18.9	
No	725	90.7	38.3 (1.8)		13.2	
Urinary tract infection				0.05		0.02
Yes	123	15.6	38.0 (1.9)		20.3	
No	667	84.4	38.3 (1.8)		12.4	
Prior preterm birth				0.01		0.04
Yes	80	9.9	37.7 (1.6)		22.5	
No	725	90.1	38.3 (1.8)		13.4	
Prior miscarriage				0.0001		0.02
Yes	212	25.9	37.8 (1.9)		19.3	
No	605	74.1	38.4 (1.8)		12.2	
Asthma				0.56		0.13
Yes	83	10.2	38.2 (1.9)		19.3	
No	732	89.8	38.3 (1.8)		13.5	
Enrollment site				0.06		0.07
University hospital	558	68.2	38.2 (1.9)		15.6	
Local hospital	186	22.7	38.5 (1.6)		9.7	
Local antenatal care clinic	74	9.1	38.3 (1.4)		13.5	
Sex of the newborn						
Female	404	49.4	38.4 (1.8)	0.05	12.4	0.20
Male	414	50.6	38.1 (1.9)		15.7	

Abbreviation: SD, standard deviation.
[a] Birth before 37 complete weeks of gestation.
[b] Two-sided *P* value for differences between means (*t* test).
[c] Two-sided *P* value for differences between rates (χ^2 test).
[d] Guadeloupe and Martinique.
[e] Weight (kg)/height $(m)^2$.

(0, 1, or ≥2), number of prior miscarriages (0, 1, or ≥2), timing of first ultrasound (before 15 weeks of gestation or at 15 weeks or more), sex of the newborn (male or female), self-reported body mass index (weight (kg)/height $(m)^2$) before pregnancy, and presence of maternal disease (particularly high blood pressure) during pregnancy, including preeclampsia (yes or no), gestational diabetes (yes or no), urinary tract infection during pregnancy (yes or no), and asthma (yes or no). Body mass index was classified into 4 groups: underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (≥30). The rates of missing data for covariates varied from none to 2.6%.

Linear regression models were used to evaluate the relationship between chlordecone exposure and the length of gestation. The regression coefficient (β) represented a difference of 1 week in the length of gestation per chlordecone exposure category or per decimal log unit of the transformed plasma chlordecone concentration. To describe the shape of the dose-response relationship, we examined splines (restricted cubic spline functions with 3 knots at the quartiles of the distribution) using the SAS macro developed by Desquilbet and Mariotti (33). This approach allowed identification of the linear and/or nonlinear components of the relationship. Associations between maternal exposure and the risk of preterm birth were estimated by calculating a hazard ratio using a Cox model that accounted for the left truncation that is a possible consequence of inclusion of participants during late pregnancy (34).

Although many risk factors for preterm births have been clearly established, the potential link between chlordecone exposure and these risk factors has not been thoroughly studied; this is due in part to the very small number of studies of this exposure in humans. Using current knowledge on preterm birth risk factors and the relationship between chlordecone exposure and these factors (Web Table 1), we constructed a directed acyclic graph for preterm birth (Web Figure 1). History of preterm births was not considered as a confounder because it reflects an unmeasured degree of vulnerability and simultaneously may be a consequence of previous exposure (if any association exists); therefore, it appears as a collider. Our data provided no evidence of an association between parity and levels of chlordecone (Web Table 1). This is consistent with the pharmacokinetics of chlordecone: Unlike most other organochlorines, chlordecone is not significantly stored in fat tissues, and plasma levels are therefore not significantly affected by the lipid tissue redistribution that occurs during pregnancy and breastfeeding. The minimally sufficient set of adjustment variables based on the proposed directed acyclic graph included maternal enrollment site, place of birth, marital status, educational level, age, body mass index before pregnancy, and high blood pressure during pregnancy. We conducted sensitivity analyses that included additional adjustment of parity and analyses that included adjustment for gestational diabetes, as well as analyses in which we excluded blood pressure.

In the subgroup of 358 women in whom DDE and polychlorinated biphenyl 153 were measured, the Spearman's rank correlations coefficient between chlordecone and DDE was 0.017 ($P = 0.75$), and that between chlordecone and polychlorinated biphenyl 153 was −0.016 ($P = 0.76$). Therefore, DDE and polychlorinated biphenyl 153 were not considered to be confounders.

Lipophilic molecule concentrations are routinely expressed on a per-unit serum lipid basis, but this approach is prone to bias (35). Furthermore, a substantial portion of the chlordecone in blood is associated with proteins (mainly albumin) and high-density lipoproteins (36), whereas most other organochlorine compounds are associated with low-density lipoproteins and very high-density lipoproteins; consequently, expressing the chlordecone concentration on a per-unit serum lipid basis may be misleading. Nevertheless, to account for the residual chlordecone fraction transported by lipids, we considered total lipids in the adjusted models.

We also considered a possible interaction between chlordecone exposure and the sex of the newborn in relation to length of gestation and the risk of preterm birth. All statistical analyses were performed using SAS, version 9.3.

RESULTS

Most of the women in our study were born on Caribbean islands (primarily the French West Indies) where most inhabitants are of African descent, and most were multiparous (Table 1). Approximately two thirds were enrolled into the study at the University Hospital, and approximately two fifths were overweight or obese before pregnancy. Very few women reported smoking (5.8%) or alcohol consumption (2.9%) during pregnancy. The mean duration of gestation was 38.3 weeks, and 14.1% of the children ($n = 115$) were born preterm. Among the preterm births, 55 (47.8%) were spontaneous preterm births and 59 (51.3%) were medically induced preterm births; for 1 woman, the type of preterm birth could not be traced. Gestational age at enrollment (mean, 27.2 weeks) did not differ between spontaneous and induced preterm births and term births. Rates of detection and concentrations of organochlorine compounds in the plasma of a subsample of the study population are presented in Table 2.

We studied the shape of the dose-response relationship using splines. It appeared that the shape of the curve presented a significant decreasing linear component ($P = 0.03$), with the nonlinear component not being significant ($P = 0.39$) (Web Figure 2).

Table 3 shows the results of linear regression analysis for maternal chlordecone levels in relation to length of gestation. In the adjusted model, there was a statistically significant shorter length of gestation in the 2 highest quintiles of exposure. When studying exposure as a continuous variable, we found that higher maternal chlordecone levels were statistically significantly associated with a shorter length of gestation in adjusted models.

Table 2. Detection and Concentration of Organochlorine Compounds in Maternal Plasma Among Timoun Mother–Child Cohort Study Participants, Guadeloupe, French West Indies, 2004–2007

Type of Organochlorine by Group	No. of Births	Detection Frequency, %	Geometric Mean, µg/L	Minimum, µg/L	Percentile, µg/L					Maximum, µg/L
					5th	25th	50th	75th	95th	
All women										
Chlordecone	818	88.4	0.35	<LOD	<LOD	0.18	0.39	0.83	2.50	19.7
Subgroup[a]										
Chlordecone	358	92.2	0.34	<LOD	<LOD	0.19	0.40	0.88	2.42	19.3
DDE	358	86.0	0.63	<LOD	<LOD	0.22	0.59	1.26	4.10	24.5
PCB 153	358	87.7	0.18	<LOD	<LOD	0.09	0.18	0.34	0.94	1.95

Abbreviations: DDE, p,p′-dichlorodiphenyl dichloroethene; LOD, limit of detection; PCB 153, polychlorinated biphenyl 153.

[a] Subgroup of 358 women who delivered after 37 weeks of gestation and whose children were enrolled for neurodevelopmental follow-up.

Table 3. Crude and Adjusted Regression Coefficients for Length of Gestation According to Chlordecone Concentration in Maternal Blood Among Timoun Mother–Child Cohort Study Participants, Guadeloupe, French West Indies, 2004–2007

Chlordecone Level, μg/L	No. of Births	Crude		Adjusted[a]	
		β	95% CI	β	95% CI
<0.14	163	0.0	Referent	0.00	Referent
0.14–0.28	165	−0.10	−0.50, 0.30	−0.26	−0.66, 0.13
0.29–0.51	162	−0.10	−0.50, 0.30	−0.23	−0.62, 0.16
0.52–0.97	165	−0.31	−0.71, 0.30	−0.60	−0.99, −0.20
>0.98	163	−0.25	−0.65, 0.15	−0.48	−0.88, −0.07
Log_{10} chlordecone	818	−0.11	−0.34, 0.11	−0.27	−0.50, −0.03

Abbreviation: CI, confidence interval.

[a] The covariates for which we adjusted were maternal age, place of birth, enrollment site, marital status, educational level, body mass index, high blood pressure during pregnancy, and total plasma lipid level (g/L). The analysis was conducted on 767 complete cases.

When all births were considered, the adjusted hazard ratio of preterm birth appeared to be statistically significantly increased for the fourth (hazard ratio = 3.1, 95% confidence interval: 1.6, 6.0) and fifth (hazard ratio = 2.2, 95% confidence interval: 1.1, 4.5) quintiles (Table 4). Expressing exposure as a continuous variable led to maternal chlordecone levels being statistically significantly associated with a higher hazard ratio for preterm birth in the adjusted model. Similar associations were observed when the analyses were done according to the mode of onset of labor (Table 4).

The findings remained unchanged when parity or gestational diabetes was included in the full model (Web Table 2). However, the strength of the associations decreased when high blood pressure was excluded from the model (Web Table 2). Women with high blood pressure during pregnancy appeared to have lower chlordecone blood concentrations than did other women (Web Table 1).

Women for whom we were not able to measure chlordecone concentration ($n = 215$) were more often recruited in the local hospital of Basse-Terre, which is in the most contaminated area in Guadeloupe. They tended to have shorter lengths of gestation (38.0 weeks vs. 38.3 weeks; $P = 0.04$) and a higher prevalence of preterm births (19.1% vs. 14.1%; $P = 0.07$) than did women for whom blood samples were available. Sensitivity analyses imputing expected median values of chlordecone according to major determinants of chlordecone exposure had only small impact on risk estimates (Web Table 3). Despite the interaction between chlordecone exposure and the sex of the newborn not being statistically significant ($P > 0.2$) in relation to length of gestation and the risk of preterm birth, the stratified results suggest a higher level of association among girls than boys (Web Table 4).

DISCUSSION

We examined the association between levels of chlordecone in maternal plasma and the duration of pregnancy in a population of pregnant women in Guadeloupe. We observed that greater maternal exposure to chlordecone was associated with shorter gestation. In addition, higher levels of exposure were associated with an increased risk of preterm birth in a dose-response–type association for all preterm births and for all modes of labor.

The present epidemiologic study is one of the few in which the association between chlordecone at environmentally relevant exposure levels and human health was examined (27, 37, 38). Local soil pollution by chlordecone (20% of agricultural lands) caused by its use in banana plantations between 1973 and 1993 has led to the contamination of root and cucurbit vegetables and of livestock and poultry that graze on these contaminated areas; costal fish and seafood are also contaminated. These contaminated foodstuffs represent only a fraction of what is consumed in the French West Indies, but they explain the chronic contamination of the population. Regulatory measures to restrict commercialization of those food products that exceed threshold limit values of contamination have been implemented to reduce human exposure, but these measures only apply to licensed farms and fishermen. Indeed, there is an extensive informal network of production, distribution, and sale of foodstuffs, as well as families and individuals who produce food for their own consumption. These chains of supply are not adequately controlled.

Chlordecone has not been measured in populations other than those in the French West Indies (27, 37, 38) and Hopewell, Virginia (16, 17). The poisoning episode that affected pesticide plant workers in Hopewell (most of whom were men) during the mid-1970s led to a very high exposure rate, resulting in blood concentrations 100 to 1,000 times greater than those currently observed in the population of the French West Indies. Chlordecone exposure was also measured in adult Hopewell residents during the mid-1970s, and the serum concentrations in subjects with detectable values (at that time the LOD was around 1.5 μg/L) was between 5–32 μg/L (16), a range similar to those currently observed in the population of the French West Indies.

The strengths of the present study include its prospective design, the evaluation of exposure based on determinations of the chlordecone concentration in maternal plasma, and the consideration of co-exposures to other organochlorine compounds (DDE and polychlorinated biphenyl 153). Single

Table 4. Crude and Adjusted Hazard Ratios for Risk of Preterm Birth According to Chlordecone Concentration in Maternal Blood and Mode of Onset of Labor, Timoun Mother–Child Cohort Study, Guadeloupe, French West Indies, 2004–2007

Chlordecone Level by Birth Category, μg/L	No. of Births	No. of PTB[b]	Crude		Adjusted[a]	
			HR	95% CI	HR	95% CI
All births						
<0.14	163	16	1.0	Referent	1.0	Referent
0.14–0.28	165	21	1.5	0.8, 2.8	1.5	0.7, 3.1
0.29–0.51	162	23	1.6	0.8, 3.0	1.6	0.8, 3.1
0.52–0.97	165	30	2.1	1.1, 4.0	3.1	1.6, 6.0
>0.98	163	25	1.7	0.9, 3.3	2.2	1.1, 4.5
Log_{10} chlordecone	818	115	1.3	0.9, 1.9	1.6	1.1, 2.3
Spontaneous preterm and term births						
<0.14	154	7	1.0	Referent	1.0	Referent
0.14–0.28	151	10	1.5	0.6, 4.1	1.4	0.5, 4.0
0.29–0.51	145	6	1.0	0.3, 2.9	1.1	0.3, 3.5
0.52–0.97	154	16	2.6	1.1, 6.6	3.5	1.3, 9.8
>0.98	154	16	2.6	1.1, 6.6	2.7	0.9, 7.8
Log_{10} chlordecone	758	55	1.7	1.1, 2.8	1.8	1.0, 3.3
Induced preterm and term births						
<0.14	147	8	1.0	Referent	1.0	Referent
0.14–0.28	149	11	1.7	0.7, 4.3	2.2	0.7, 6.2
0.29–0.51	156	17	2.3	1.0, 5.6	2.6	1.0, 6.5
0.52–0.97	155	14	2.1	0.9, 5.2	3.3	1.3, 8.7
>0.98	155	9	1.3	0.5, 3.6	2.2	0.8, 6.4
Log10 chlordecone	762	59	1.1	0.7, 1.8	1.5	0.9, 2.6

Abbreviations: CI, confidence interval; HR, hazard ratio; PTB, preterm birth.

[a] The covariates for which we adjusted were maternal age, place of birth, enrollment site, marital status, educational level, body mass index, high blood pressure during pregnancy, and total plasma lipid level (g/L). The analysis was conducted on 750 complete cases for all births, 694 spontaneous preterm births, and 703 induced preterm births.

[b] For one woman, the type of preterm birth was unknown.

determinations of plasma chlordecone concentration provide an accurate reflection of the load of this compound in the body (17, 39). Its half-life in blood is approximately 6 months (17), so a single measure at the end of pregnancy can be considered to be reasonably representative of exposure throughout the pregnancy.

Our study also has some limitations. The prevalence of preterm birth in our study population was 14.1%, consistent with the high rate of preterm births among populations of African descent irrespective of their geographic location (40, 41). Nevertheless, we may have overestimated this rate because recruitment was mainly at the University Hospital, and this favors inclusion of pregnant women at risk of preterm birth. This also explains the high proportion of induced preterm births compared with spontaneous preterm births. However, any such oversampling should not impair internal comparisons. Also, the models for linear and logistic regression were adjusted for site of enrollment. There were small differences in some population descriptors between the subgroups with and without plasma chlordecone determinations, but sensitivity analyses indicated that these missing data were only weakly associated with risk (Web Table 3). In our study population, high blood pressure during pregnancy is associated with lower chlordecone blood concentrations, and we have no immediate explanation for this finding. The mechanisms through which chlordecone may lower the risk of high blood pressure during pregnancy, the possible influence of high blood pressure on chlordecone concentration in blood, or the influence of unknown confounders in this association remain to be studied. Inclusion of high blood pressure during pregnancy as a variable in the adjusted model reinforces the association between chlordecone exposure and risk of preterm birth.

We are aware that estimates of gestational age based on first trimester ultrasound may be biased if environmental exposure affects early fetal growth (42), although in practice the consequences of this problem are generally limited (43). Moreover, toxicological studies in rats and mice have indicated that chlordecone exposure during gestation, at doses that do not cause maternal toxicity, was not associated with low fetal growth (44).

Parturition is triggered by the shortening and dilatation of the cervix associated with uterine contractions. Progesterone plays a key role in maintaining pregnancy. In humans,

progesterone-receptor–dependent events, rather than circulating progesterone levels, appear to be critical (45). For example, treatment of pregnant women with progesterone-receptor antagonists induces labor at any stage of pregnancy (46). Chlordecone binds estrogen receptors α and β, acting as an agonist of estrogen receptor α and an antagonist of estrogen receptor β (47, 48). It also stimulates the synthesis of the progesterone receptors in rat uterine tissues in vivo (21), and this process is mediated by estrogen receptors. Chlordecone can inhibit the binding of the progestin agonist R5020 to the form A of the progesterone receptor in vitro (22). These observations suggest that the observed associations between exposure to chlordecone and both decreased gestational length and increased risk of preterm birth are due to the estrogenic and/or progestin activities of chlordecone.

In summary, the data that we report provide some evidence that chlordecone, a chemical with well-established estrogen-like and progestin-like properties, may affect the duration of gestation (with gestation at least 3 days shorter for the 40% of women with blood chlordecone levels >0.52 μg/L) and thus increase the risk of preterm birth. These findings were observed in a population with a high baseline risk of preterm birth. The association was detectable even though the concentrations of chlordecone in the blood were in the order of magnitude of 1 part per billion. Further efforts are required to protect pregnant women against exposure to chlordecone, particularly from its major dietary sources.

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