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Original Contribution

In Utero Exposure to the Antiandrogen 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) in Relation to Anogenital Distance in Male Newborns from Chiapas, México

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The insecticide 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) is still used for disease control in some areas, resulting in high levels of human exposure. The main degradation product of DDT is 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), an antiandrogen. In animal experiments, in utero exposure to DDE decreases anogenital distance in male offspring. In these models, anogenital distance serves as a measure of fetal androgen action. The authors designed the present study to examine the hypothesis that in utero exposure to DDE decreases anogenital distance in newborn human males. A cross-sectional study of 781 newly delivered male infants was conducted in 2002–2003 in Chiapas, México, where DDT had recently been used for malaria control. Measurements of anogenital distance and penile dimensions were taken, and a sample of the mother's blood was drawn. In this population, the range of serum DDE levels was large (0.8–398 μg/liter). The authors, using two-sided tests, found no evidence that exposure in utero to DDE was related to reduced androgen action as reflected by anogenital distance or penile dimensions at birth. If DDE has important antiandrogenic action in humans, it may be manifest only at higher levels of exposure or via effects on other outcomes.

androgens; DDT; developmental biology; dichlorodiphenyl dichloroethylene; endocrine system diseases; genitalia, male; prenatal exposure delayed effects

Abbreviations: DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene; DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane.

The insecticide 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane (DDT) is still used in some countries for disease-vector control, resulting in high levels of human exposure (1). However, the toxic effects of DDT and its degradation products have not been adequately characterized in humans (2), and additional data are needed to inform policy regarding use. 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), the main degradation product of DDT, has been reported to be a potent antiandrogen, and one of the effects seen in animal models is that in utero exposure decreases anogenital

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distance at birth (3). Among the potential clinical effects of human exposure to an antiandrogen early in life are cryptorchidism, hypospadias, and reduced fertility.

In animal experiments, anogenital distance is used as a measure of fetal androgen action (4–6). Anogenital distance usually tracks through life, varies by dose of antiandrogen, and can be predictive of other androgen-responsive outcomes (5, 7). In human males, testicular volume and penile dimensions have traditionally been used as indicators of androgenicity (8, 9), and use of anogenital distance as an outcome has been rare (4, 10). Recent human data suggest, however, that anogenital distance may be responsive to antiandrogenic exposures in utero (10), and it is measured more reliably than penile dimensions (11).

The present study was designed to examine the effect of in utero exposure to DDE on anogenital and penile dimensions in relatively highly exposed newborn males. DDT was used in the study area for agriculture until 1991 (12) and for malaria control until 2000 (13).

MATERIALS AND METHODS

A cross-sectional study of newly delivered male infants and their mothers was conducted in 2002–2003 in Tapachula, a city in the state of Chiapas, México. Women were recruited during the postpartum period at both of the city's hospitals, which also serve the surrounding area. Approximately 50 percent of births in Tapachula occur in these hospitals (14). Women who gave birth at the Social Security hospital were more frequently urban and had, on average, higher socioeconomic status and more education than women who gave birth at the general hospital (data not shown). If the eligibility criteria were met, the mothers were invited to participate and sign an informed consent form. The study protocol was approved by institutional review boards at the National Institute of Public Health in México and the National Institute of Environmental Health Sciences in the United States.

The eligibility criteria were chosen to exclude subjects for whom complicating medical conditions might have affected anogenital distance in male offspring or our ability to measure it. These criteria were determined a priori, before any data or determinants of anogenital distance were available. Exclusion criteria for the mother were age greater than 35 years; preeclampsia or pregnancy-related diabetes or hypertension; any seizure disorder requiring daily medication; history of repeated urinary tract infections; psychiatric, kidney, or cardiac disease; and being a nonspeaker of Spanish. Infants were excluded if they were female, if gestational age at delivery as estimated by the Capurro scale (15) or the medical record (based on the last menstrual period) was less than 36 weeks, if birth weight was less than 2,500 g, if the pregnancy was not singleton, if the Apgar score at 5 minutes was 6 or less, or if the child was admitted to the neonatal intensive care unit. Of the mothers who were invited to participate, 95 percent did so, resulting in the creation of 872 mother-infant pairs. Of these, the first 91 were enrolled when a preliminary anthropometric measurement protocol was in place. We excluded these pairs from the present analysis because their measurements were not comparable. This left us with 781 observations.

A questionnaire inquiring about sociodemographic characteristics, reproductive history, maternal health status, and various exposures was administered to the mothers. Maternal serum DDE and DDT levels were quantitated after solid phase extraction (C_{18} column purification), using gas chromatography and mass spectrometry (16, 17). For DDE, the limit of detection was 0.2 μg/liter; recovery was 97 percent; and the between-assay coefficient of variation at 10 μg/liter was 7 percent. For DDT, the limit of detection was 0.2 μg/liter; recovery was 97 percent; and the between-assay coefficient of variation at 2.5 μg/liter was 6 percent. Total serum lipid concentration was estimated on the basis of serum cholesterol and triglyceride levels (18), which were measured using standard enzymatic methods. Measurements of weight and height were performed on the mothers and newborns. In addition, we measured infant anogenital distance and penis size.

The technique for measurement of anogenital distance and penis size has been described in detail elsewhere (11) and is summarized briefly here. Three measures of anogenital distance were taken: the distance from the anterior base of the penis to the anus (anogenital distance 1), the distance from the posterior base of the penis to the anus (anogenital distance 2), and the distance from the posterior of the scrotum to the anus (anoscrotal distance) (see figure 1). In addition, we measured penis width and stretched penis length. The anogenital and penis width measurements were performed using Swiss Precision Cali Max Vernier calipers (Bel-Art Products, Pequannock, New Jersey). The calipers were read in increments of 1 mm. The penile measurements were done when the newborn's penis was flaccid. Each measurement was taken on two occasions; the first set of readings was recorded in the questionnaire, and after these were completed, the second set was taken and noted on a sheet that was attached to each subject's file. On each of these two

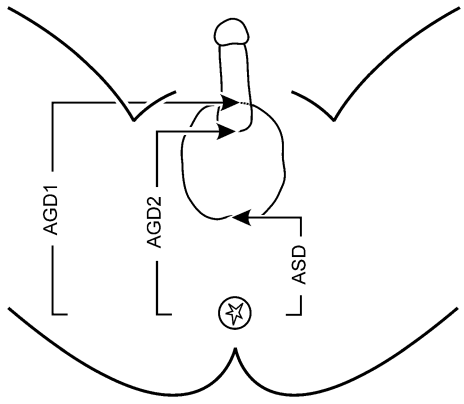

FIGURE 1. Diagram of the male genitalia showing the three anogenital distance measurements taken: anogenital distance 1 (AGD1), the distance from the anterior of the penis to the center of the anus; anogenital distance 2 (AGD2), the distance from the posterior of the penis to the center of the anus; and anoscrotal distance (ASD), the distance from the posterior of the scrotum to the center of the anus.

occasions, stretched penis length was usually measured in duplicate, yielding up to four recorded values. Over 80 percent of children were examined before they were 6 hours old. With one exception, all examinations were conducted before 34 hours of age; the remaining examination was conducted 7 days after birth. The anthropometrists received special training before measuring anogenital and penile dimensions, length, and weight, and they received periodic retraining during the study (the equipment used for length and weight measures has been described previously (11)). Twenty-two anthropometrists participated in the study. The reliabilities of the measurements (the fraction of the variability that is true variability rather than measurement variability) were as follows: anogenital distance 1, 0.91; anogenital distance 2, 0.88; anoscrotal distance, 0.85; penis width, 0.77; and stretched penis length, 0.76 (11). The small variations in measures among replicates and due to observers are described in detail elsewhere (11).

All 781 infants had measurements of each of the three anogenital distances taken; in all but two (anogenital distances 1 and 2) or three (anoscrotal distance) cases, duplicate measurements were taken. All infants also had data on penis width available (in duplicate in all but three cases). For 541 infants, all four stretched penis length measurements were available. Of the remainder, 43 infants had two measurements taken on the first occasion and one on the second occasion; 188 had two measurements taken on the first occasion and none on the second; three had one measurement taken on each occasion; five had only one taken on the first occasion; and one had no measurements taken.

Statistical analysis

The goal of the analysis was to test the hypothesis that maternal DDE concentration is associated with anogenital distances and penile measurements in newborn male infants. Significance tests were based on *F* tests in linear regression models, testing the hypotheses that the coefficient(s) were zero. All tests were two-sided.

Means of the replicates were used for all analyses. However, subjects were excluded from analyses of a particular anthropometric measurement if replicates differed by 30 percent or more; there were two such cases for anoscrotal distance, one for penis width, and three for stretched penis length. In the primary analysis, DDE level was expressed per gram of serum lipid concentration, and subjects were placed in categories of <3 μg/g, 3–<6 μg/g, 6–<9 μg/g, and ≥ 9 μg/g. These categories were chosen without examination of outcomes; the top category was chosen to contain a reasonable fraction of the children, with the remaining categories being of equal width. Finer categories (a width of 1 μg/g rather than 3 μg/g, with the top categories being collapsed to contain at least 20 children), were examined subsequently (see below). Analyses were also conducted with DDE concentration or logarithm of DDE concentration included as a linear term in the models.

When evaluating the relations of anogenital and penile dimensions to DDE, we examined both crude and adjusted relations. Adjustment factors were those items that had previously been shown to be related to the anthropometric measurements in these data (11); potential predictors examined included infant birth weight and length, gestational age, maternal height, prepregnancy body mass index (weight (kg)/height $(m)^2$), maternal age, parity, maternal education, maternal marital status, household income per capita, urban versus rural residence, and hospital. Those variables that were significant at $p < 0.20$ in models including all non-DDE predictors were included in the present models (19). For anogenital distances, these factors were birth weight (included as a linear term (g)), gestational age (categorized as 36–37, 38, 39, 40, and ≥ 41 weeks), urban versus rural residence, and hospital. For penile measurements, they were birth weight (linear (g)), maternal age (linear (years)), maternal height (linear (cm)), and parity (categorized as 1, 2–3, and ≥ 4). In both cases, we also adjusted for anthropometrist as a random effect, to account for interobserver variability. Linear regression models were fitted using the MIXED procedure in SAS, version 9.00 (SAS Institute, Inc., Cary, North Carolina). All categorical variables were modeled with indicator variables.

Levels of DDT and DDE were highly correlated (Spearman $r = 0.84$), so we avoided fitting models that included both terms. However, we also conducted analyses for DDT similar to those described above. In addition, we examined models that included DDE and the ratio of DDT to DDE.

RESULTS

The mothers in the study were relatively young (table 1), and the median height (152.4 cm) was close to the national median (153.0 cm) for women of reproductive age (20). Median body mass index (23.1 kg/m^2) was below the national median (25.0 kg/m^2) (20). Most of the mothers had had children previously. They were about evenly split between the two hospitals. More than half lived in urban areas, primarily Tapachula, with the remainder living in surrounding villages. Only 32 percent had gone beyond the ninth grade in school (not shown). Twenty-nine percent reported living in houses that had been sprayed with DDT. Given the eligibility criteria, which excluded infants under 2,500 g or born before 36 weeks' gestation, the range of birth weights among the babies was as expected. The Spearman correlation of DDE (lipid basis) with gestational age was 0.00, the correlation with birth weight was 0.03, and the correlation with birth length was 0.05.

The range of serum DDE levels among the mothers was large (table 2); the median was approximately 10-fold greater than recent measures taken among women in the United States (0.26 μg/g lipid) (21). The relatively low ratio of DDT to DDE reflects the fact that the study was carried out several years after DDT had last been used. The median level of DDT was more than 15 times greater than US median levels (<0.02 μg/g lipid (21)). The major determinant of DDE concentration was rural residence (median DDE values were 4.0 μg/g for rural residence and 2.1 μg/g for urban residence). Conditional on residence, reported spraying of the individual home had much less influence (among

TABLE 1. Characteristics (%) of newly delivered male infants ($n = 781$) and their mothers according to maternal serum 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) level, Chiapas, México, 2002–2003

Characteristic	DDE level (μg/g lipid)				
	Total	<3	3–<6	6–<9	≥9
Mother					
Age (years)					
15–19	23.8	22.8	25.6	27.4	22.4
20–24	35.6	39.7	32.0	26.0	31.8
25–29	27.9	27.7	25.7	28.8	31.8
30–35	12.7	9.9	16.6	17.8	14.0
Height (cm)					
133–149	34.4	32.9	37.1	37.0	34.6
150–159	54.4	56.1	53.1	49.3	53.3
160–169	11.1	11.0	9.7	13.7	12.2
Prepregnancy body mass index*,†					
12–19	17.1	19.0	14.0	18.8	13.2
20–24	48.3	47.7	47.7	49.3	50.9
25–29	24.3	24.3	26.2	24.6	20.8
30–39	10.4	8.9	12.2	7.3	15.1
Parity					
1	41.1	35.5	45.7	49.3	50.5
2–3	53.9	58.2	50.3	46.6	47.7
4–6	5.0	6.3	4.0	4.1	1.2
Hospital					
Social Security hospital	47.0	46.5	52.0	53.4	36.5
General hospital	53.0	53.5	48.0	46.6	63.6
Residence					
Rural	40.6	28.6	46.3	56.2	68.2
Urban	59.4	71.4	53.7	43.8	31.8
House sprayed with DDT‡ for malaria control§					
Yes	29.3	25.6	31.3	26.5	42.9
No	70.7	74.4	68.7	73.5	57.1
Infant					
Gestational age (weeks)					
36–37	3.5	3.3	2.9	2.7	5.6
38–39	40.1	41.1	35.4	39.7	43.9
40	51.3	50.5	55.4	54.5	45.8
41–43	5.1	5.2	6.3	2.7	4.7
Birth weight (g)					
2,500–2,999	21.5	22.1	20.0	21.9	21.5
3,000–3,499	49.0	48.6	53.1	52.1	42.1
3,500–3,999	25.0	24.9	21.7	24.7	30.8
4,000–5,100	4.5	4.5	5.1	1.4	5.6

* Weight (kg)/height $(m)^2$.
† Data were missing for 19 subjects (2%).
‡ DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane.
§ Data were missing for 53 subjects (7%).

rural residents, the median value was 4.4 μg/g if the home was sprayed and 3.6 μg/g if it was not; among urban residents, it was 2.4 μg/g if sprayed, 2.1 μg/g if not). The differences between hospitals essentially disappeared conditional on residence (among rural residents, the median value for both hospitals was 4.0 μg/g; among urban residents, medians were 2.2 μg/g for the Social Security hospital and 2.1 μg/g for the general hospital). DDE concentrations rose with age and declined with parity (details not shown). Because virtually all children in this population are breastfed, parity and lactation were confounded.

The variability of anogenital and penile measures is also shown in table 2. These outcome measures were all approximately normally distributed.

Mean anogenital distance was similar across categories of serum DDE, and adjustment for potentially confounding factors had essentially no effect on results (table 3). Modeling DDE as a continuous variable (table 3) and use of finer categories of DDE also indicated no association (figure 2). Similarly, for penis length and width, important variation in mean values across categories of DDE was not seen (table 3).

When similar analyses were performed for DDT instead of DDE, the findings were essentially the same as those shown. In analyses with DDE and the ratio of DDT to DDE included in the same model, neither showed any relation to the outcomes.

DISCUSSION

In this population with relatively high in utero exposure to DDE, we found no evidence that exposure was related to reduced androgen action as reflected by anogenital distance or penile dimensions at birth. If DDE has important antiandrogenic action in humans, it may be manifest only at higher levels of exposure or via effects on other outcomes.

Among African women who lived in homes regularly sprayed with DDT, the median serum DDE level was approximately 100 μg/liter (22). In our study population, 29 percent of mothers reported living in DDT-sprayed homes, and accordingly the median serum DDE level in our whole population was approximately 20 μg/liter ($n = 781$; see table 2). The half-life of DDE is approximately 5–10 years in adults, although lactation shortens this by several years (23, 24). Thus, even though use of DDT in the area we studied was stopped shortly before enrollment began, we had many subjects with relatively high exposure. Furthermore, in our population, the distribution of exposures was unusually wide, increasing the power to detect associations. Nonetheless, the possibility exists that in a population of women living in sprayed homes, with higher exposures, the power to detect an effect, if any, would be greater. It is also possible that in humans anogenital distance is not affected by minor changes in the androgen environment in utero. As noted above, however, recent data on in utero phthalate exposure in humans suggest otherwise (10).

On the other hand, imprecision in assessment of exposure or outcome was a less likely explanation for failure to detect an association. History of spraying homes with DDT, conditional on residence (urban vs. rural), may not have

TABLE 2. Distribution of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) compounds in maternal serum and of genital outcome measures in male infants ($n = 781$), Chiapas, México, 2002–2003

Measure	Minimum value	10th percentile	Median value	90th percentile	Maximum value
DDT measure					
DDT (μg/g lipid)	ND*	0.06	0.25	2.28	18.31
DDE* (μg/g lipid)	0.1	0.7	2.7	11.0	56.1
DDT:DDE	0	0.05	0.12	0.28	1.06
DDT (μg/liter)	ND	0.4	1.9	15.2	130.0
DDE (μg/liter)	0.8	5.1	19.5	78.0	398.0
Outcome measure					
Anogenital distance 1† (mm)	38.4	44.6	49.9	55.5	74.7
Anogenital distance 2‡ (mm)	19.8	39.1	45.4	51.8	70.4
Anoscrotal distance§ (mm)¶	8.7	13.4	19.1	23.4	35.8
Stretched penis length (mm)¶	15.5	21.6	27.1	33.2	42.9
Penis width (mm)¶	6.3	9.3	10.6	11.8	15.7

* ND, not detected (value below detection limit of assay); DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene.

† Distance from the anterior of the penis to the center of the anus.

‡ Distance from the posterior of the penis to the center of the anus.

§ Distance from the posterior of the scrotum to the center of the anus.

¶ Missing data: two measures of anoscrotal distance (unreliable), four measures of stretched penis length (one missing, three unreliable), and one measure of penis width (unreliable).

TABLE 3. Mean genital outcome measurements in male infants ($n = 781$) according to maternal serum 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) level and associated regression coefficients (β), Chiapas, México, 2002–2003

DDE level (μg/g lipid)	No. of subjects	Anogenital distance 1* (mm)		Anogenital distance 2† (mm)		Anoscrotal distance‡ (mm)§		Stretched penis length (mm)§		Penis width (mm)§	
		Mean	95% CI¶	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Crude											
0.1–2.9	426	50.1	49.7, 50.5	45.5	45.0, 46.0	18.8	18.5, 19.2	27.4	27.0, 27.9	10.5	10.4, 10.6
3.0–5.9	175	49.9	49.3, 50.6	45.4	44.7, 46.1	19.4	18.8, 20.0	27.2	26.6, 27.8	10.6	10.5, 10.8
6.0–8.9	73	49.4	48.3, 50.5	44.8	43.6, 46.0	18.4	17.6, 19.3	26.3	25.2, 27.4	10.4	10.2, 10.7
9.0–56.1	107	50.6	49.6, 51.6	46.1	44.9, 47.3	19.2	18.3, 20.1	28.1	27.2, 29.1	10.7	10.5, 10.9
β (mm/μg/g)		0.032	−0.024, 0.088	−0.009	−0.075, 0.057	0.005	−0.047, 0.058	0.009	−0.048, 0.066	0.009	−0.005, 0.022
Adjusted#											
0.1–2.9	426	49.9	49.1, 50.7	45.2	44.2, 46.1	18.8	18.0, 19.5	27.2	25.8, 28.5	10.7	10.4, 10.9
3.0–5.9	175	49.8	48.9, 50.7	45.2	44.0, 46.3	19.3	18.4, 20.2	27.1	25.7, 28.6	10.8	10.5, 11.0
6.0–8.9	73	49.7	48.5, 50.8	45.1	43.7, 46.5	18.5	17.3, 19.6	26.3	24.7, 27.9	10.6	10.3, 10.9
9.0–56.1	107	50.3	49.3, 51.3	45.6	44.4, 46.9	19.5	18.5, 20.6	27.8	26.2, 29.3	10.9	10.6, 11.2
β (mm/μg/g)		0.029	−0.024, 0.082	−0.019	−0.082, 0.044	0.023	−0.028, 0.074	0.020	−0.034, 0.073	0.010	−0.003, 0.022

* Distance from the anterior of the penis to the center of the anus.

† Distance from the posterior of the penis to the center of the anus.

‡ Distance from the posterior of the scrotum to the center of the anus.

§ Missing data: two measures of anoscrotal distance (unreliable), four measures of stretched penis length (one missing, three unreliable), and one measure of penis width (unreliable).

¶ CI, confidence interval.

Anogenital distances were adjusted for birth weight (linear (g)), gestational age (36–37, 38, 39, 40, or ≥41 weeks), urban versus rural residence, hospital, and nurse (random). Penile measurements were adjusted for birth weight (linear (g)), maternal age (linear (years)), maternal height (linear (cm)), parity (1, 2–3, or ≥4), and nurse (random).

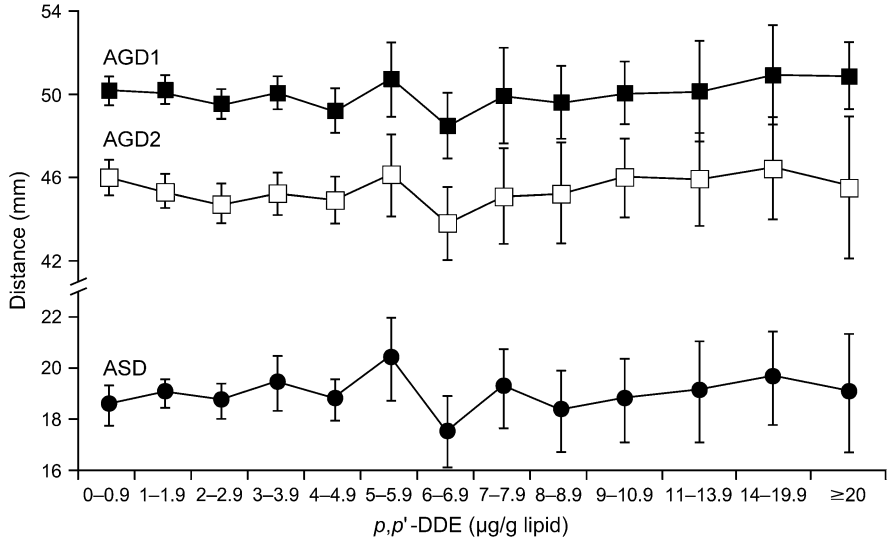

FIGURE 2. Adjusted mean anogenital distances according to maternal serum 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p′*-DDE) level among newly delivered male infants ($n = 781$), Chiapas, México, 2002–2003. Each category included at least 20 infants. AGD1, anogenital distance 1 (distance from the anterior of the penis to the center of the anus); AGD2, anogenital distance 2 (distance from the posterior of the penis to the center of the anus); ASD, anoscrotal distance (distance from the posterior of the scrotum to the center of the anus). Bars, 95% confidence interval.

predicted levels well because the subjects may not have detailed knowledge of what their homes were sprayed with. However, serum levels of DDE were measured with reasonable precision, a single measure of DDE at birth corresponds well with levels prevailing during pregnancy (25), and maternal serum levels of DDE are closely related to those in umbilical cord blood (26–28). Thus, a cross-sectional study design with exposure and outcome ascertained at birth should provide unbiased estimates of effect unless the subgroup of subjects susceptible to DDE effects was lost before birth (29, 30). Although the subjects in our study were not a random sample of those in the Tapachula area, we have no reason to suspect that the associations examined among our subjects would have been biased. Furthermore, our earlier study showed that the outcomes were measured with high reliability (11), which was slightly greater for the anogenital distance measures than for the penile dimensions.

In rodents as well as humans, the critical period for male sexual development is androgen-dependent and occurs before birth. Thus, even though rodents are less mature at birth than humans, the animal model is useful for understanding the potential effects of antiandrogenic exposures during the embryonic and fetal stages. Fetal rats are more sensitive than adults to the antiandrogenic effects of DDE (3, 31). In animal models, exposure to DDE in utero affects anogenital distance (3, 32) but does not cause cryptorchidism or hypospadias (7). Human data also indicate that exposure to DDE in utero is not associated with cryptorchidism or hypospadias (33–35). In adult humans, some data suggest that extremely high exposure to DDE has adverse effects on male reproductive hormone levels and semen quality, but these data come from small studies and are inconsistent (36–39).

In our data, antiandrogenic effects of DDE were not evident. However, other outcomes, such as fertility following in utero exposure, may be more sensitive to such effects. Furthermore, it is possible that outcomes mediated via other mechanisms could be a more important health consideration among persons living in homes sprayed with DDT.

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