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In utero exposure to organochlorines and age at menarche

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BACKGROUND: To examine the effect of *in utero* exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) on age at menarche in offspring, we conducted a cohort study over two generations. METHODS: Female participants (and their offspring) in a Michigan angler cohort in which organochlorine levels had been determined previously were studied. Of their 213 female offspring aged 20–50 years, 151 participated in the study (71%). We retrospectively determined age at first menstrual bleeding. Based on repeated maternal serum measurements between 1973 and 1991, we extrapolated PCB and DDE serum levels at the time of pregnancy. To estimate the association between *in utero* PCB and DDE exposure and age at menarche, we used linear regression analyses controlling for birth date period, maternal age at delivery, birth weight, breastfeeding, education status and maternal height. RESULTS: An increase in the *in utero* DDE exposure of 15 μg/l reduced age at menarche by 1 year ($P = 0.04$). There was no association with maternal PCB exposure. When controlling for estimated body size at menarche, the DDE association was no longer significant, based on a subsample of 102 women. CONCLUSION: The DDE effect on age at menarche encourages further research about *in utero* exposures. Prospective studies including the offspring's DDE level before menarche are of particular interest.

Key words: DDE/*in utero*/menarche/offspring/PCB

Introduction

The Great Lakes basin is home to more than one-tenth of the US population and one-quarter of the Canadian population. The five Great Lakes not only are major freshwater reservoirs, but also provide an excellent natural habitat for many species of wildlife. Many residents in the area around Lake Michigan practise fishing as a sport and consume three times as much fish as the average American (D'Itri and Kamrin, 1983). The Great Lakes have been polluted with industrial wastes from as early as the 1920s (Hicks, 1996). Two of the most important pollutants in Lake Michigan's waters are polychlorinated biphenyls (PCBs) and dichloro-diphenyl-trichloroethane (DDT). The latter was widely used as an insecticide after the Second World War (1945). It was banned in the USA in 1972, but is still used in other parts of the world (Turusov *et al.*, 2002). DDT has a biological half-life of ~7 years, but its metabolite dichlorodiphenyldichloroethylene (DDE) has a much longer half-life, accounting for its greater concentrations in humans (Longnecker *et al.*, 1997). PCBs are also lipophilic and have a half-life of ~7 years (Matthews and Dedrick, 1984; Kamrin, 1997). Because of their stability and low flammability, PCBs have been used as insulating materials in electrical equipment (transformers and capacitors), as plasticizers (softening materials) in plastic products, and for a variety of other industrial purposes. The production and use of PCBs have been discontinued in most countries, but large amounts remain in electrical equipment, plastic products, buildings and in the environment. Because PCBs and DDT from water and sediments tend to bioaccumulate in marine life, their concentration increases as they go through the food web (Kamrin, 1997). Humans are at the end of the food web, thus they have higher exposures to PCBs, DDE and DDT, especially those whose diets are based on sport-caught fish. Investigations in Michigan anglers and fish eaters have indicated that these populations possess higher serum levels of PCBs and DDE (Schwartz *et al.*, 1983; Humphrey and Budd, 1996; Kostyniak *et al.*, 1999).

Previous studies indicate that PCBs and DDE may exert endocrine-disruptive effects (McKinney and Waller, 1994; Kelce and Wilson, 1997; Sonnenschein and Soto, 1998; Yu *et al.*, 2000; Aoki, 2001; Bonefeld-Jorgensen *et al.*, 2001). A number of studies have investigated the potential impact of organochlorine compounds on sexual maturation (Gladen *et al.*, 2000; Krstevska-Konstantinova *et al.*, 2001; Staessen *et al.*, 2001), but to our knowledge only two reported age at menarche. In 120 girls from three Belgian villages with different PCB exposure levels, no regional differences were detected (13.1 ± 1.2 years) (Den Hond *et al.*. 2002). Blanck *et al.* (2000) reported that prenatal exposure to polybrominated biphenyls (PBBs) was associated with a lower age at menarche. PBBs have the same chemical structure as PCBs, but have a different halogen component (bromine instead of chlorine).

Table I. Equations for the backward extrapolation of maternal organochlorine serum oncentrations at delivery

Extrapolation period	Formula derived from linear regression analyses	ICC
1991–1979	$PCB = 10^{(-0.193 + \log10\ (PCB\ 1989/91\ survey) \times 0.781)} + (\text{years between measurement and birth} \times 0.049) + (\text{no. of preceding births} \times -0.145)$	0.77, lower 5% limit: 0.71
1982–1973	(PCB = PCB in the 1979/82 survey × 0.565) + (years between measurement and birth × –0.163) + (years of preceding fish consumption × 0.106)	0.89, lower 5% limit: 0.80

To the best of our knowledge, no study has investigated the association between prenatal DDE exposure and age at menarche in the offspring as a marker of an endocrine effect.

Contamination of fish in the Great Lakes led to three successive surveys conducted to assess the PCBs and DDE burden in Michigan anglers and fish eaters. The surveys took place between 1973 and 1991. To test the hypothesis that women exposed prenatally to PCBs and DDE have an early age at menarche, we contacted the female offspring of this cohort.

Materials and methods

Population

During three surveys conducted in Michigan between 1973 and 1991, anglers and their spouses were recruited by visits to sites of fishing or fishing-related activities (docks, bait shops, marinas) in 11 Lake Michigan shoreline counties. The first survey was conducted between 1973 and 1974 with 156 anglers. The second survey, performed between 1979 and 1982, had 115 participants from the previous survey and 1140 newly recruited subjects, yielding 1255 subjects. The third survey, conducted between 1989 and 1991, had a total of 728 participants, of which 717 were from the previous survey. PCB and DDE levels were determined for a total of 1177 subjects.

In 2000, we approached this cohort (first generation) again; the details are described elsewhere (Karmaus *et al.*, 2002a). The review boards on human subjects for Michigan State University and the Michigan Department of Community Health approved the study. A total of 391 women who were capable of having children between 1950 and 1980 and had recorded organochlorine measurements were included in these studies. Of these 391 potential participants, seven were deceased, 115 could not be contacted, and 10 did not give consent. The remaining 259 women (66.2%) provided information about 213 daughters 20–50 years of age (second generation). We focused on daughters in this age range for the purpose of studying reproductive health effects. The Michigan State University committee on research involving human subjects also approved the offspring study. The female offspring were then contacted and, after written consent was obtained, trained staff conducted telephone interviews on their reproductive history.

PCB and DDE determinations in the parent generation

Subjects of the three surveys, conducted between 1973 and 1991, provided non-fasting blood samples for serum determinations of PCBs, DDE and other organochlorine compounds. All serum samples were analysed at the Health Risk Assessment Laboratory of the Michigan Department of Community Health in Lansing. A modification to the Association of the Official Analytical Chemists-approved Webb-McCall packed column gas chromatography technique was used to determine PCB and DDE levels. The analytical methods used are described in detail elsewhere (Needham *et al.*, 1981; Price *et al.*, 1986). In brief, the procedure used methanol–ether/hexane extraction, microflorisil column clean-up and a silicon gel separation technique before injection into a programmed electron detection chromatograph. In the first two surveys (1973–1974 and 1979–1982), the laboratory PCB determinations were based on Aroclor 1254 and 1260 standards. The third survey (1989–1991) used Aroclor 1016 and 1260 standards. For purposes of comparison, we used the serum PCB measurements based on the Aroclor 1260 standard, which were available for all samples. The specimens with values less than the detection limit for Aroclor 1260 (3 μg/kg) were reported as 1.5 μg/kg. For PCBs, <5% of all samples were below the detection limit for all three surveys. DDE was not determined in the first survey (1973–1974). The technical detection limit for DDE in the following surveys was 1 μg/kg.

Backward extrapolation

Having repeated PCB measurements and additional survey information (1973–1974, 1979–1982 and 1989–1991) for mothers, we conducted linear regression analyses and used the results to backward-extrapolate serum organochlorine levels (Karmaus *et al.*, 2003). Each of the two regression models covers one period between two survey measurements. We estimated regression coefficients for the most parsimonious models (Table I), and tested how well the two equations predicted actual organochlorine measurement collected in the past. By means of intra-class correlation coefficients (ICCs), we compared estimated and measured past organochlorine exposures (Armstrong *et al.*, 1992). We identified two formulae that predicted past values with high reliability (ICC = 0.77 for the period 1991–1979, and ICC = 0.89 for the period 1982–1973, Table I). As we were able to derive our models from repeated measurements, our backward extrapolations more accurately estimated actual values than two other approaches regarding organochlorine contamination from fish consumption (Rylander *et al.*, 1998; Weisskopf *et al.*, 2003) that we additionally applied.

The first formula used the PCB value determined in 1989/1991, the years that passed between the 1989/1991 and 1979/1982 determinations, and the number of births in that interval (Table I). It is worth noting that the predicted values were higher in the 1979/1982 measurements as indicated by the positive sign for the years that passed between 1989/1991 and 1979/1982. The second formula estimates the PCB values in 1973/1974 using the 1979/1982 determination, the years between 1973/1974 and 1979/1982, and the years of fish consumption. This formula has a negative sign for the years passed between the two organochlorine determinations, which indicates lower PCB values for 1979/1982 and before. Therefore, the estimations mirror the trends that were detected for PCB concentrations in fish which peaked around 1970 (Karmaus *et al.*, 2003). Using the last measurements, we applied these formulae to backward-estimate the maternal serum PCB and DDE concentrations at the time of each pregnancy.

Questionnaire

Information on potential confounders (date of birth, maternal age at birth, birth weight and breastfeeding) were acquired in the year 2000

Table II. Characteristics of the study population by age at menarche

	Age at menarche groups		
	9–11 years (n = 22)	12–14 years (n = 6)	14–17 (n = 43)
Backward-extrapolated maternal DDE serum concentration at birth (μg/l)[a]	7.0 (1.3–16.5)	4.2 (0.4–15.0)	3.8 (0–12.8)
Backward-extrapolated maternal PCB serum concentration at birth (μg/l)[a]	3.8 (0–16.1)	2.9 (0–13.3)	2.2 (0–12.8)
Mean age at interview[a]	41.4 (28–7-48.5)	34.7 (22.3–47.1)	37.5 (25.8–49.2)
Maternal height (cm)[a]	163.8 (149.9–170.2)	165.1 (157.5–172.7)	167.6 (152.4–177.8)
Mean maternal age at delivery (years)[a]	27 (21–35)	26 (21–34)	25 (20–43)
Birth weight (g)[a]	3147 (2027–4296)	3402 (2438–4082)	3445 (2807–4082)
Estimated body size group at menarche (1–9, 1 = most slender, 9 = most corpulent)[a]	3.0 (1–5)	2.5 (1–5)	2.0 (1–4)
Birth date group (%) 1950–1954	22.7	9.3	14.0
1955–1964	54.6	34.9	41.9
1965–1974	18.2	34.9	37.2
1974–1980	4.6	20.9	7.0
Breastfed (yes %)	31.8	47.7	41.9
Education level (%)			
High school or less	9.1	9.3	9.3
Some college	27.3	32.6	27.9
College graduate	40.9	29.1	34.9
Graduate school	22.7	32.6	27.9

[a]Mediane 5.95% values.

from the parents. Maternal height and weight were retrieved from the 1989–1991 survey. In 2001–2002, we conducted telephone interviews with the female offspring regarding their reproductive health, and asked them to recall their age at menarche and also to state their highest level of education. In a separate questionnaire, women estimated their body size at menarche using a standardized series of drawings to determine body size on a scale of 1–9, with 1 representing the most slender and 9 the most corpulent body size (Veron-Guidry and Williamson, 1996).

Data analysis

We linked each child with its backward-extrapolated maternal DDE and PCB serum concentrations at birth. After linearity between the backward-estimated maternal DDE and PCB concentrations and age at menarche was confirmed, the exposures were treated as continuous variables. We used maternal height as a categorical variable with three levels (<155 cm, 155–170 cm and >170 cm). The maternal body mass index (BMI) was calculated from height and weight (kg/m^2). The child's birth year was divided into four categories (1950–1954, 1955–1964, 1965–1974 and 1974–1980). Maternal age at birth and birth weight were used as continuous predictors, and breastfeeding was considered as a categorical variable (yes–no). Education of the offspring was classified as 'high school or less', 'some college', 'college graduate' or 'graduate school'.

In order to estimate the association between PCB and DDE levels and age at menarche for the female offspring, we conducted linear regression analysis controlling for birth year cohorts, maternal height and age, birth weight, breastfeeding, and educational status of the offspring. Additionally, we assessed a second model with estimated body size at menarche as an additional predictor for each exposure. The results of the linear regressions (GLM procedure) are presented as regression coefficient (estimate) and standard error. The data were analysed using SAS software version 8 (SAS Institute, 2002).

Results

From parental records, we identified 213 eligible women (offspring), of whom 71% (n = 151) agreed to participate. Twenty-two declined to participate stating that they were not interested in the study, while we could not contact the other 40 women since they have moved or changed their phone numbers.

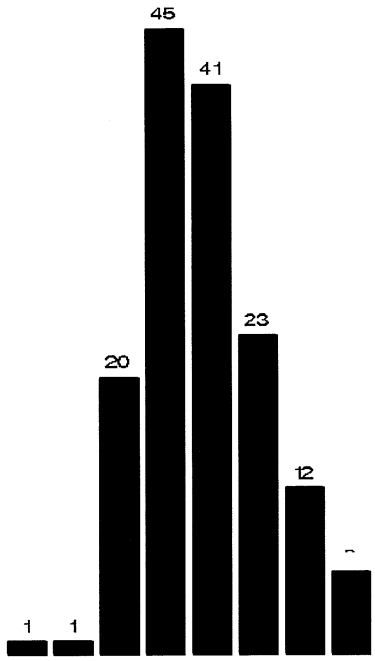

Figure 1. Distribution of age at menarche (absolute numbers, n = 151).

The study population consisted predominantly of non-Hispanic Caucasian women (99%). Age at menarche in the offspring ranged between 9 and 17 years (Figure 1). Both the extrapolated maternal PCB and DDE at birth were higher in women with a younger age at menarche. More women with age at menarche between 9 and 11 years belong to earlier birth cohorts (Table II).

Using linear regression models, age at menarche was multivariate, normally distributed. The analysis indicates that DDE (P = 0.038) but not PCB (P = 0.76) lowered age at

Table III. Regression coefficients and statistical significance for the estimated maternal DDE and PCB serum concentrations at birth, controlling for confounders

	Estimate (years)[a]	SE	*P* (*F*-test)
Backward-extrapolated maternal DDE serum concentration at birth (μg/l)	–0.07	0.03	0.038
Backward-extrapolated maternal PCB serum concentration at birth (μg/l)	–0.01	0.04	0.76
Maternal height group			
<155 cm	–0.52	0.48	0.0002
155–170 cm	–1.21	0.29	
>170cm	Reference		
Mean maternal age at delivery (years)	0.033	0.03	0.23
Birth weight (g)	0.0002	0.0003	0.55
Birth date group (%)			
1950–1954	0.87	0.48	0.76
1955–1964	0.73	0.36	
1965–1974	0.99	0.37	
1974–1980	Reference		
Breastfed (%)	–0.027	0.25	0.91
Education level (%)			
High school or less	0.37	0.52	0.41
Some college	Reference		
College graduate	–0.34	0.29	
Graduate school	–0.26	0.31	

[a]Adjusted for all variables above and for birth weight.

menarche with statistical significance (Table III and Figure 2). The estimate for DDE is –0.07 years per μg/l serum concentration. Hence, an increase of 15 μg/l reduced the age at menarche by 1 year. Additionally, maternal height shows a curvilinear association with age at menarche in offspring. Large maternal size is related to a later age at menarche in daughters. There was no significant association between age at menarche and birth weight, breastfeeding or offspring's education.

A higher BMI in adolescence is considered to be related to a lower age at menarche (dos Santos Silva *et al.*, 2002). Hence, we additionally collected retrospective data on body size at menarche. When controlling for body size at menarche (provided by 102 women), the association between the DDE levels and adjusted mean age at menarche was reduced and no longer significant (–0.04 years per μg/l serum DDE concentration). However, the estimate still indicates a decline with increasing DDE concentrations.

Discussion

Our results suggest that higher DDE, but not PCB exposure, *in utero* is associated with younger age at menarche. To the best of our knowledge, this is the first study to report an association between DDE and age at menarche.

The study subjects were identified from parents who were recruited in Michigan in three surveys between 1973 and 1991. Of the offspring identified, who had maternal DDE and/or PCB determinations (n = 213), 71% participated in our study. We assume that our findings did not result from selection biases.

We did not identify an effect of birth weight on age at menarche as suggested by Adair (2001). However, age at menarche was significantly associated with maternal height,

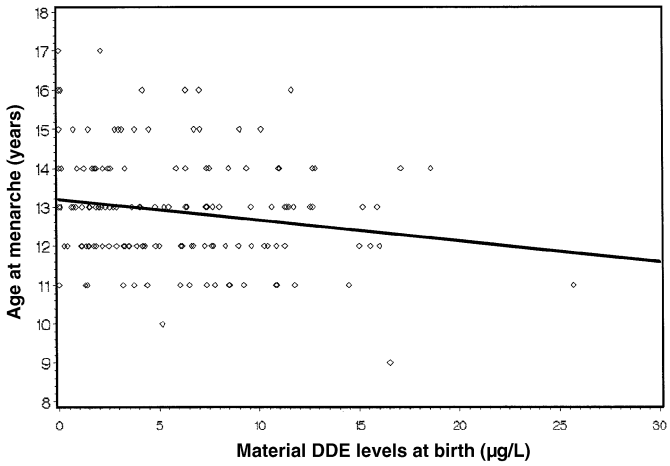

Figure 2. Plot of age at menarche over the extrapolated maternal DDE concentration at birth (n = 151). The linear regression line is the estimate of age at menarche (13.185 – 0.0525 × extrapolated maternal DDE concentration, non-adjusted regression). See Table III for the adjusted regression coefficient.

which in turn may predict birth weight and length (Adair, 2001). Since a higher maternal DDE level may be associated with a higher percentage of body fat, in a prior model, we also investigated maternal BMI (kg/m^2). We detected a weak association between maternal BMI and DDE serum level (Spearman's r = 0.15, P = 0.07); however, maternal BMI was not a significant predictor of offspring age at menarche. The rank correlation coefficient between maternal BMI and age at menarche was Spearman's r = –0.10 (P = 0.21).

One strength of this study was the availability of repeated maternal serum DDE and PCB measurements conducted during three investigations. Of the mothers, 7.5% had three organochlorine determinations, 63.8% had two, and 28.9% had one. The individual serum DDE and PCB concentrations at each investigation were incorporated into the extrapolation models in order to provide the backward-estimated exposure of the offspring *in utero*. We additionally investigated whether results changed when we used DDE and PCB measurements that were closest to the date of delivery. This approach also showed a significantly lower age of menarche in offspring with higher maternal DDE levels. The reason is that the backward extrapolation did change the DDE concentrations but did not change their order significantly.

DDT was widely used after 1945, and maternal DDE levels are positively correlated with earlier year of birth (Spearman's r = 0.39). If it were the case that the association between DDE and early age at menarche may only be due to a presumed higher exposure between 1950 and 1964, we would assume that offspring born in this period would have a younger age at menarche. However, in this group of women, age at menarche did not vary significantly with calendar time: born 1950–1954, 12.7 years (n = 19); born 1955–1964, 12.8 years (n = 60); and born 1965 and later, 12.9 years (n = 72). Thus, higher historic exposure and calendar time cannot explain the DDE effect.

Frisch and colleagues have suggested that a critical percentage of body fat may be necessary for the onset of menses (Frisch, 1980, 1990; Rich-Edwards *et al.*, 1994)

Furthermore, it has been suggested that body size during childhood and adolescence is associated with various pubertal stages (Duran-Tauleria *et al.*, 1995; Bini *et al.*, 2000; Luo *et al.* 2003). For this reason, we additionally asked participants to rate their body size at menarche using drawings developed by Veron-Guidry and Williamson (1996). Body size was significantly associated with age at menarche, and adjusting for body size reduced the effect and statistical significance of maternal DDE on age at menarche. However, since only 102 women provided these ratings, the statistical power to detect significant DDE differences in age at menarche was reduced when controlling for body size at menarche. In addition, a basic conceptual problem emerges when controlling for body size, since both age at menarche and body size are considered as responses to changes in the activity and metabolism of sex steroid hormones (Apter, 1980; Danilovich *et al.*, 2000; Legro *et al.*, 2000; Meseguer *et al.*, 2002) Hence, endocrine disruption during the intrauterine development may simultaneously increase the risk for higher body mass and early menarche. In this case, we should not control for body size at menarche, since body size is not a cause, but just a different phenomenon potentially resulting from endocrine disruption. This view is supported by further analyses of our offspring cohort. We demonstrated that a higher intrauterine DDE exposure was also associated with increased adult weight (Karmaus and Eneli, manuscript submitted).

A limitation is the lack of information about individual PCB congeners. We had to use the total PCB concentration based on the Aroclor 1260 standard. This may be a problem because various PCB congeners may have different, sometimes antagonistic effects (Connor *et al.*, 1997; Kodavanti *et al.*, 2001), which may have attenuated the observed association between total PCB and age at menarche. However, a strength is that the technique of organochlorine determination did not change over the three surveys in the parent generation (1973–1991), which facilitated the backward extrapolations. Our backward estimates were based on reliable predictions for the period of pregnancy (ICCs between 0.77 and 0.89). Nevertheless, we do not have information on DDE levels during childhood.

Since fish consumption is a relatively stable habit, an alternative possible explanation is that offspring with higher maternal DDE levels (higher fish consumption) (He *et al.*, 2001) were also exposed to a higher fish consumption and higher DDE intake early in life. In this case, exposure during childhood rather than an interuterine exposure would be more critical. However, evidence provided through animal and human studies supports a fetal origin of altered adult reproductive function (Rabinovici and Jaffe 1990; Jongbloet *et al.*, 1994, 2002), in particular estrogen suppression and changes in the expression of estrogen receptor genes (Pepe *et al.*, 2002; Zachos *et al.*, 2002, 2003). Changes in the expression of genes, regulating sex steroid activity and their metabolism, is also known to occur after exposure to endocrine disruptors (Chen *et al.*, 1997; Klotz *et al.*, 1997; Kaya *et al.*, 2002).

Age at menarche was reported in years as it was recalled, which is likely to introduce a non-differential misclassification. Additionally, women had to recall over a median period of 24 years (range 7.7–40 years). However, other studies showed a good agreement between actual age at menarche and recalled menarcheal age, for both short- and long-term recollections (Damon *et al.*, 1969; Bergsten-Brucefors, 1976; Damon and Bajema, 1974; Casey *et al.*, 1991; Koprowski *et al.*, 2001; Must *et al.*, 2002).

It is of importance that different markers of sexual development may be dissociated. For instance, Den Hond *et al.* (2002) reported that age at menarche was significantly associated with breast development but not with pubic hair growth. Hence, studies on pubertal development are not directly comparable with investigations of age at menarche. For instance, Gladen *et al.* (2000) reported no association between DDE exposure and pubertal stages, but did not report the association with age at menarche. Staessen *et al.* (2001) reported for girls that a delay in adult breast development was associated with the estimated concentrations of dioxin-like compounds in serum samples of participants. Krstevska-Konstantinova *et al.* (2001) suggested that precocious puberty and DDT/DDE exposure may be related. To our knowledge, there are only two reports on age at menarche: one identified an earlier age associated with PBB exposure; one found no difference with regard to PCB exposure (Blanck *et al.*, 2000; Den Hond *et al.*, 2002). However, a different endocrine activity may be ascribed to different halogenated compounds.

Menarche is linked to elevated estrogen production (Apter, 1980; Apter and Vihko, 1985; Legro *et al.*, 2000). Our findings suggest that DDE may exert such an estrogenic effect. In rats, DDE exposure significantly increased circulating levels of 17β-estradiol (O'Connor *et al.*, 1999). Proposed mechanisms of DDE include androgen blocking, binding to estrogen receptors, a weakly estrogen-mimicking effect (Kelce *et al.*, 1995a,b; Sonnenschein and Soto, 1998) or aromatase induction (You *et al.*, 2001). Aromatase is an enzyme that catalyses the conversion of C19 steroids (e.g. testosterone, androstenedione) to estrogens. Krstevska-Konstantinova *et al.* (2001) discussed the pros and cons of central mechanisms (e.g. involvement of the hypothalamus) versus peripheral activities and leaned toward the former. Thus, more research is necessary to identify possible mechanisms.

Our results support an intrauterine programming of age at menarche as suggested by Adair (2001). The assumption of *in utero* programming is supported further by findings showing that girls who had been exposed to male co-twins had a significantly higher age at menarche than like-sex dizygotic female twins (Kaprio *et al.*, 1995). Thus, we hypothesize that *in utero* exposure to the estrogenic effect of DDE may result in earlier age at menarche.

Further research is necessary to understand the mosaic of possible endocrine effects of DDE that includes reduced growth in females (Karmaus *et al.*, 2002b), younger age at menarche in the present report, reduction of breastfeeding (Gladen and Rogan, 1995) and earlier age at menopause (Cooper *et al.*, 2002).

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