Reproductive Effects of Occupational DDT Exposure among Male Malaria Control Workers

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To assess potential effects of human DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] exposure, we evaluated the reproductive history of 2,033 workers in the antimalaria campaign of Mexico. Data on occupational exposure to DDT and reproductive outcomes were gathered through a questionnaire, and workers provided information about 9,187 pregnancies. We estimated paternal exposure to DDT before each pregnancy using three approaches: *a*) a dichotomous indicator for pregnancies before and after exposure began, *b*) a qualitative index of four exposure categories, and *c*) an estimation of the DDT metabolite DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene] accumulated in fat. To assess associations, we used logistic regression models that accounted for correlated observations and adjusted for parents' age at each child's birth, exposure to other pesticides, exposure to chemical substances in other employment, smoking, and alcohol consumption. The odds ratio for birth defects comparing pregnancies after and before the first exposure was 3.77 [95% confidence interval (95% CI), 1.19–9.52]. Compared with the lowest quartile of estimated DDE in fat, the ORs were 2.48 (95% CI, 0.75–8.11), 4.15 (95% CI, 1.38–12.46), and 3.76 (95% CI, 1.23–11.44) for quartiles 2, 3, and 4, equivalent to *p,p′*-DDE in fat of 50, 82, and 298 μg/g fat, respectively. No significant association was found for spontaneous abortion or sex ratio. We found an increased risk of birth defects associated with high occupational exposure to DDT in this group of workers. The significance of this association at lower exposure levels found in the general population remains uncertain. *Key words:* birth defects, DDT, occupational exposure, sex ratio, spontaneous abortion. *Environ Health Perspect* 112:542–547 (2004). doi:10.1289/ehp.6759 available via *http://dx.doi.org/* [Online 6 January 2004]

DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane or dichlorodiphenyltrichloroethane was widely used to control malaria during the last half of the 20th century in many countries in the world. Most developed countries banned its use in the 1970s and 1980s because of its long persistence in the environment, unusual bioaccumulation, effects on wildlife, and the possibility of long-term adverse effects on human health [Turusov et al. 2002; U.S. Environmental Protection Agency (EPA) 1997; van Wendel de Joode et al. 2001]. In other countries, where malaria is a long-standing public health problem, however, DDT is still the main pesticide used for mosquito control. Mexico used DDT in malaria campaigns until 1999, not only because of its effectiveness but also because of its low cost and lack of acute toxicity to sprayers and exposed populations compared with alternative chemical pesticides.

Although the ban on DDT use provoked a serious debate (Schofield 2001; Walker 2000), the Mexican program has recently shown that malaria can be effectively controlled without the use of DDT. The operation of a comprehensive malaria control program has reduced the incidence of this disease substantially while gradually decreasing the reliance on DDT (Chanon et al. 2003). Although epidemiologic studies have yet to determine conclusively that DDT contributes to human disease, recent evidence emphasizes the need for further research aimed at assessing the risks of reproductive health impairment and cancer development related to DDT exposure (Cocco et al. 1997; Longnecker et al. 2001).

Mexican vector control workers were subjected to high levels of DDT exposure as detected in adipose tissue over the extended time period when they worked applying the pesticide during the antimalaria campaign (Rivero-Rodriguez et al. 1997). However, the overall impact on the health of exposed workers has not been quantified. This report is part of an extensive evaluation that Mexico is performing in support of the merits of banning DDT use.

Previous studies of potential reproductive effects of DDT in human populations have focused on maternal exposure (Cohn et al. 2003; Korrick et al. 2001; Longnecker et al. 2002), based on the antiandrogenic and estrogenic properties of the DDT metabolite *p,p′*-DDE (1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene) (Kelce et al. 1995). Studies of men have measured hormones and semen parameters (Hauser et al. 2003; Martin et al. 2002), but there are no reports on paternal exposure to DDT and reproductive outcomes such as congenital malformations, spontaneous abortion, and alteration of the sex ratio, which are indicators of teratogenicity, embryotoxicity, and endocrine disruption, respectively.

Materials and Methods

To assess the potential health effects of occupational DDT exposure during the malaria control program, the Ministry of Health of Mexico assembled a historical cohort of malaria control workers who had been employed for at least 1 year between 1956 and 1990. An estimated 10,000 workers have been employed nationwide since 1956; however, at least half of them were only temporary employees during intensive campaigns for vector control and were not included in the study. Here we report cross-sectional data concerning the reproductive performance of the survivors up to the year 2000 of a subcohort corresponding to the Pacific area of Mexico.

Data were collected during the year 2000 after a roster of possible members of the cohort was constructed. The main sources for the roster were official labor registries at the regional level (85%), completed with information provided by local leaders of the vector control program and contemporary co-workers (15%). We were able to contact 2,328 of 3,580 listed workers in the Pacific area of Mexico. Main reasons for noncontact were unknown address, migration to the United States, and death before the time of the interview. Among those with information, 200 (8.6%) were eliminated because of incomplete occupational histories, and 25 (1%) were women.

After informed consent was obtained, a questionnaire was administered that included items on occupational history, environmental exposure to pesticides and other chemicals, tobacco and alcohol use, health conditions, and reproductive history. The questionnaire was administered in the state of residence by a group of 10 workers of the malaria control

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program who were trained to conduct the interviews. Because the objective of the principal study was the survival of the workers, neither the interviewers nor the workers had a special concern about reproductive effects.

Reproductive outcomes. Workers were asked to list all pregnancies they had fathered and then provide specific information for each pregnancy: year of pregnancy, spontaneous abortions and stillbirths, sex of newborn, and congenital malformations. The information was obtained by calendar year with no further detail. Congenital malformations were registered in a matrix as one of the outcomes of all pregnancies and later were grouped by organ systems in broad groups according to the *International Classification of Diseases*, Revision 10 (ICD codes Q00-Q99) [Organización Panamericana de la Salud (OPS) 1995]. In this article, we provide information for congenital malformations, spontaneous abortion, and sex ratio, the outcomes that provided large enough numbers for statistical analysis.

Exposure assessment. To assess exposure we obtained a detailed occupational history by applying a modified version of a previously designed questionnaire (Rivero-Rodriguez et al. 1997). The questionnaire contained a matrix with information on employment dates, job titles, activities on each job, specific questions for potential exposure to DDT and other pesticides, whether exposure was direct or indirect, and exposure timing for each pesticide during the 1956–1990 period.

In order to evaluate the sensitivity of different exposure-assessment methods, we assessed exposure using three approaches (Table 1), first, taking into account whether pregnancy occurred before or after the father was occupationally exposed for the first time; second, whether exposure was direct or indirect; and third, the accumulation of DDE in fat tissue. Thus, for the second approach, paternal exposure for each pregnancy was classified in the following four categories: *a*) never applied or prepared DDT mixtures before the pregnancy (unexposed to DDT); *b*) did not apply pesticides or prepare mixtures but worked in sprayed areas or near DDT storage facilities before the pregnancy (indirect exposure); *c*) applied DDT or prepared the mixture at some time before the pregnancy (direct exposure); *d*) and applied DDT and/or prepared DDT mixtures for some years, and during other years performed other activities where potential exposure occurred before the pregnancy (combined direct and indirect exposure). Most workers started as pesticide sprayers in the campaign and were later promoted to other activities; however, they occasionally sprayed pesticides again when the service was required for additional demands such as malaria outbreaks. The third approach was to estimate concentrations of *p,p′*-DDE (the most persistent metabolite of DDT) in fat for each pregnancy using a model developed by our group in a similar population of workers of the antimalaria campaign (Rivero-Rodriguez et al.1997) based on an index of occupational exposure (INDEXPO) constructed from the occupational history:

$$\text{INDEXPO} = \sum_{i=1}^{n} t_i p_i$$

where t_i = time spent working in i position (expressed in months), p_i = exposure intensity weighting for position i (0–10), and n = number of positions worked during the occupational history. Exposure intensity was estimated by a group of specialists of the malaria control program using a semiquantitative scale (0–10) based on job tasks and probable contact with the pesticide. Sprayers had the highest exposure intensity; multiple task and group leaders were rated 7; those involved in field evaluation and case detection, 6; supervisors, 2–4; and microscope operators, 0. The values of INDEXPO could vary for each worker at different periods of time as well as between workers. The range among workers was 100–4,000.

To estimate the concentration of *p,p′*-DDE in fat tissue based on INDEXPO, we used the following regression model derived by Rivero-Rodriguez et al. (1997): log [*p,p′*-DDE] = 3.68 + 0.0010 (INDEXPO), where 3.68 is the minimum of the logarithm of the exposure, and 0.0010 is the increase in the DDE concentration per unit of the INDEXPO. For statistical analysis, the estimated fat concentrations were divided in quartiles equivalent to *p,p′*-DDE in fat of < 39.68, 39.68–61.12, 61.13–103.64, and > 103.64 µg/g fat, corresponding to average concentrations of 19.7, 50, 82, and 298 µg/g fat for quartiles 1, 2, 3, and 4, respectively.

Exposure to DDT and other pesticides was assessed separately for each pregnancy such that the same worker could have different levels or categories of exposure for each pregnancy. For example, if one man fathered a child before entering the program, that pregnancy was classified as unexposed for the first and second approach and in the lowest concentration group for DDE in fat. If he fathered other children after becoming a sprayer, those pregnancies were considered in the direct exposure category. However, the

Table 1. Paternal occupational DDT exposure groups during each pregnancy.

Exposure type	Exposed group[a]	Unexposed group
Dichotomous variable for exposure	Pregnancies occurring after worker-initiated activities related to occupational DDT contact (application, mixing pesticide solutions, activities in the field or near DDT storage) (n = 6,666)	Pregnancies occurring before worker-initiated activities related to occupational DDT contact (application, mixing pesticide solutions, activities in the field or near DDT storage) (n = 2,521)
Exposure level in three categories		
Indirect exposure	Pregnancies occurring after occupational DDT exposure activities in the field or near DDT storage (n = 385)	Pregnancies occurring for workers who were never occupationally exposed to DDT (n = 2,536)
Direct exposure	Pregnancies occurring after occupational DDT exposure, applying or mixing pesticide solutions (n = 3,627)	
Alternate direct and indirect exposure	Pregnancies occurring after occupational DDT exposure when worker had varied activities of application, mixing pesticide solutions, and carrying out activities in the field or near DDT storage (n = 2,639)	
Estimate of the concentration of *p,p′*-DDE in adipose tissue	Estimated concentration (µg/g) in fat according to Rivero-Rodriguez et al. (1997) The continuous variable was divided in four categories for analysis: Quartile 1: < 39 µg/g fat (n = 2,619) Quartile 2: 39–61 µg/g fat (n = 1,963) Quartile 3: 62–103 µg/g fat (n = 2,385) Quartile 4: > 103 µg/g fat (n = 2,220)	The first quartile was the reference category

[a]Exposure based on the offspring's date of birth and the date of initial paternal occupational exposure.

estimated cumulated concentration of DDE in fat tissue was different for each child because the seniority was different. For the second and third child, DDE levels could be 30 and 50 μg/g fat, respectively, depending on the activities and years exposed before each pregnancy.

Exposure to other organochlorine pesticides (lindane and dieldrin) was evaluated as a dichotomous variable if the pregnancy occurred before or after the exposure, because these substances also accumulate in the body. In the case of organophosphate pesticides (temephos, malathion, and fenthion), a dichotomous variable (yes or no) was used for exposures at the time of pregnancy.

Exposure to cigarette smoke for the pregnancy occurred if the father started smoking the year before the year in which the pregnancy occurred. Alcohol exposure was considered positive if the pregnancy occurred for a regularly drinking father (drank some alcoholic beverages > 3 days/week) who began drinking in the year before the year his child was conceived.

Statistical analysis. Birth defects, spontaneous abortions, and sex were all treated as dichotomous outcomes, and odds ratios (ORs) were estimated by means of logistic regression using generalized estimating equation models to take into account the lack of independence of the observations for each worker (McCullagh and Nelder 1989). Separate assessments were made for association of malformations, spontaneous abortions, and sex ratio with the exposures of primary interest. Because DDT was the main exposure of interest, the inclusion of other variables as confounders in multivariate models was tested according to the change produced in the DDT OR, so the number of variables was kept at a minimum in final models. Variables tested for inclusion were paternal and maternal exposure to other organochlorine and/or organophosphate pesticides at the time of pregnancy, exposure to other chemical substances, exposure to agricultural pesticides, tobacco and alcohol consumption, paternal and maternal age, and socioeconomic status.

Because the amount of DDT sprayed in the antimalaria campaign declined during the period studied, we also evaluated the inclusion of a time variable representing the year of pregnancy using indicator variables for periods of 5 years. Additionally, to evaluate the effect of missing values in the date of the pregnancy, we conducted a sensitivity analysis testing the two extreme scenarios, one assuming that all pregnancies with missing values were exposed and the other assuming that all were unexposed.

Results

We were able to contact 2,033 workers; 1,186 were still active, 94 were retired, and 753 were working under temporary contract. Age at the interview varied between 28 and 82 years. The average age of entry in the malaria control program was 24 years, with a wide range. Average seniority was 18 years, with an average of 15 years of exposure to DDT and a range of 0–40 years. Retired workers had left the job after working 28 years on average. Workers with temporary contracts had shorter exposure duration but were more likely to have been directly exposed to DDT. Two hundred and ten workers from the central offices were never exposed to DDT and served as an unexposed referent group. The mean concentration of estimated DDE was 61 μg/g fat, with large variability (SD = 92).

Most of the workers were born in the area where they worked, and socioeconomic status was very similar among them. Ninety percent of the workers completed elementary school and possessed a home with basic amenities; 47% were smokers and 80% regular drinkers, and 43% both smoked cigarettes and drank alcohol; 15% neither smoked nor consumed alcohol. A total of 1,820 workers reported being employed in other occupations before entering the malaria program. Among these, 57% reported carrying out farming activities involving pesticide use, although these exposures were sporadic at 2–3 days of exposure per year.

Twenty-five workers had no children at the time of the interview. Eight of these were single with no children, and 17 were married or lived with a partner, had no children, and reported some infertility problem for themselves or their partner. Of the 2,008 workers who declared that they had fathered at least one child, 9,187 pregnancies were evaluated. The average number of offspring per worker was 4.6 (range, 1–18). More than 20% of the workers had children with more than one partner. Average worker age at the time of the child's birth was 31 years, with a range of 13–73 years, and the average mother's age at the time of pregnancy was 26 years, with a range of 14–56 years.

Table 2 summarizes the information on the pregnancies. Of the 9,187 pregnancies evaluated, 8,650 (94.2%) were live births and 118 were stillbirths. For 127 pregnancies, no data were available for paternal occupational DDT exposure because of inexact dates. Of the pregnancies, 72.5% occurred after the father was exposed to DDT through his occupational activities in the malaria control program; 55 children from these pregnancies were born with birth defects. The ratio of boys to girls was similar for pregnancies before and after the father's exposure to DDT. Four hundred twenty-five spontaneous abortions were reported, but for 26 of these, the date of the abortion was not known, and it was therefore impossible to determine whether the abortion occurred before or after the father's occupational exposure to DDT.

The most common congenital malformations reported were in the nervous system (13 cases, ICD codes Q00–Q07) and the osteomuscular system (12 cases, ICD codes Q65–Q79). The number of cases of other birth defects were as follows: eye and ear (7 cases, Q10–Q18), cardiovascular (6 cases, Q20–Q28), leporino lip (6 cases, Q35–Q37), chromosomal (9 cases, Q90–Q99), and other congenital malformations (9 cases, Q80–Q89). The greatest number of congenital malformations was observed in pregnancies occurring after the father's occupational exposure to DDT began.

Table 3 shows the crude estimated ORs for each type of reproductive event. The risk of birth defects increased after workers began employment in the program (OR = 3.37). The use of the second approach to classify pregnancies with direct and indirect exposures showed an increased risk for all three exposed categories compared with those never exposed. The OR for birth defects was 1.22 for indirectly exposed workers and 2.50 for directly exposed workers. The category for the combined direct and indirect exposure had the largest OR of 5.12, but this increase could be more related to increased years of exposure than to the simple classification of direct and indirect exposure. Because the risk did not increase linearly with the continuous estimate of DDE in fat, we used indicator variables for four categories

Table 2. Characteristics of the pregnancies with or without paternal occupational exposure to DDT in the malaria control program, 1956–1990.

Pregnancy outcome	Pregnancy occurred before paternal exposure, or father was never exposed No. (%)	Pregnancy occurred after paternal exposure No. (%)	No information available on paternal exposure No.
Live births	2,308 (96.52)[a]	6,239 (93.55)[b]	97
Births defects	4 (0.167)	51 (0.766)	
Live births, female	1,127 (49.71)	3,031 (49.04)	
Live births, male	1,140 (50.29)	3,149 (50.96)	
Spontaneous abortion	59 (2.46)	340 (5.10)	26
Stillbirths	24 (1.00)	90 (1.35)	4
Total	2,391	6,669	127

[a]The sex was unknown for 41 live births. [b]The sex was unknown for 59 live births.

of exposure as divided in quartiles. Compared with the lowest quartile, the risk increased 2- and 4-fold at the second and third quartiles but showed a plateau at this level, with no further increase at the fourth quartile.

Exposures to other pesticides (lindane, temephos, and malathion) were also associated with increased risk of birth defects in this bivariate analysis. As expected, paternal and maternal age at the time of the child's birth was also associated with increased risk of birth defects. No noteworthy association was found for paternal exposure to chemical substances in other employment, agricultural pesticide use, smoking habits, or frequent alcohol consumption.

The evaluation of the association of DDT exposure with spontaneous abortion in the bivariate analysis showed an increased risk with the dichotomous approach to assess exposure and with the qualitative approach of direct and indirect exposure but no association with the estimated concentration of DDE in fat. Odds ratios were 1.52 [95% confidence interval (CI, 1.12–2.08] for the dichotomous classification of exposure, 2.05 (95% CI, 1.19–3.55) for indirect exposure, 1.57 (95% CI, 1.13–2.18) for direct exposure, and 1.36 (95% CI, 0.95–1.95) for combined indirect and direct exposure. Associations were also revealed between spontaneous abortion and tobacco smoking and alcohol consumption by the father and with maternal age at the time of the child's birth. There was no difference in the male-to-female sex ratio of children born after occupational exposure to DDT.

The sensitivity analysis to evaluate the potential bias caused by 7.62% of the exact dates of the pregnancies being missing showed that the OR for congenital malformations did not change substantially when all missing values were assigned as exposed (OR = 3.13; 95% CI, 1.20–8.86) or when all missing values were assigned as unexposed (OR = 4.42; 95% CI, 1.57–12.50). For spontaneous abortions, the risk increased only when missing values were substituted as exposed (OR = 1.95; 95% CI, 1.42–2.66). The sex ratio remained unchanged when missing values were substituted either as exposed or unexposed.

The inclusion of a time variable to assess whether changes in the amounts of DDT sprayed between 1956 and 1999 affected the association showed no change in the OR for the association of DDE and malformations. The ORs also did not change substantially after including exposure to chemical substances in other employment, smoking, and alcohol consumption in the multivariate model, so those variables were dropped from the final model. Because maternal and paternal age were highly correlated, we retained only maternal age in the final model. We also retained malathion exposure in the final model because dropping this variable did change the main estimators.

Table 4 shows results from multivariate models for the association of reproductive effects examined with the father's estimated DDE concentrations in fat tissue, adjusting for exposure to malathion and age of the mother at the time of pregnancy. The risk of birth defects increased for exposed men but without a clear trend. Compared with the least exposed, the ORs for the second, third, and fourth quartiles were 2.47 (95% CI, 0.75–8.1), 4.16 (95% CI, 1.38–12.46), and 3.76 (95% CI, 1.24–11.44), respectively. Exposure to malathion also increased the risk of birth defects after controlling for DDT exposure (OR = 2.06; 95% CI, 1.01–4.22).

Discussion

Retrospective information obtained on the reproductive history of the malaria control program workers in the Pacific region of Mexico reveals an increased risk of birth defects among those most exposed to DDT, without a clear dose response, and a small, nonstatistically significant difference in the risk of spontaneous abortion. No change in the sex ratio of newborns was associated with exposure.

Previous published studies have focused on maternal exposure (Leoni et al. 1989; Longnecker et al. 2001, 2002; Rogan et al. 1986). The mechanism of effects of DDT after paternal exposure is not so clear, but paternal occupational exposure could affect the unborn child via transport of toxic substances from work clothes into the home to expose the pregnant mother and, at the same time, the unborn child through placental transfer (Hodgson and Levi 1996; Saxena et al. 1981). Another hypothesis for damage to the offspring is that occupational exposure alters the sperm genetically before conception, affecting the susceptibility to development of harmful effects in the offspring (Colborn 1994).

Studies of males exposed to DDT have found decrements in serum bioavailable testosterone levels (Martin et al. 2002), semen volume of ejaculation, reduced sperm counts (Ayotte et al. 2001), and increased numbers of abnormal sperm (Bush et al. 1986) and sperm motility (Hauser et al. 2003). The report of

Table 3. Bivariate associations between occupational exposure to pesticides and reproductive effects in malaria control workers in Mexico.

	Reproductive event		
Exposures	Congenital malformation OR (95% CI)	Spontaneous abortion OR (95% CI)	Sex ratio (male:female) OR (95% CI)
Exposure to DDT			
Before vs after pregnancy	3.37 (1.19–9.52)	1.52 (1.12–2.08)	1.09 (0.87–1.38)
Indirect exposure vs. no exposure	1.22 (0.13–11.29)	2.05 (1.19–3.55)	1.02 (0.91–1.14)
Direct exposure vs. no exposure	2.50 (0.83–7.41)	1.57 (1.13–2.18)	1.06 (0.93–1.20)
Direct and indirect exposure vs. no exposure	5.12 (1.76–14.90)	1.36 (0.95–1.95)	1.09 (0.87–1.38)
DDE concentration quartile 2	2.50 (0.77–8.75)	1.06 (0.77–1.48)	1.03 (0.97–1.10)
DDE concentration quartile 3	4.47 (1.48–14.16)	1.14 (0.84–1.56)	1.02 (0.96–1.08)
DDE concentration quartile 4	4.41 (1.41–13.84)	1.29 (0.94–1.70)	1.01 (0.94–1.07)
Exposure to other organochlorine pesticides			
Lindane: before vs. after	6.20 (1.40–27.38)	1.22 (0.68–2.20)	0.69 (0.39–1.04)
Dieldrin: before vs. after	0.96 (0.22–4.25)	1.22 (0.68–2.20)	1.09 (0.88–1.01)
Application of organophosphate pesticides			
During the application period of temephos vs. no application	2.62 (1.28–5.34)	1.13 (0.76–1.68)	1.18 (0.98–1.39)
During the application period of malathion vs. no application	2.71 (1.23–5.96)	0.99 (0.62–1.59)	0.95 (0.79–1.15)
During the application period of fentothion vs. no application	1.70 (0.39–7.49)	0.50 (0.17–1.50)	1.28 (0.95–1.73)
Nonoccupational exposure: personal and environment			
Exposure to chemical substances in other employment	1.15 (0.45–2.94)	0.92 (0.58–1.45)	0.89 (0.76–1.05)
Exposure to agricultural pesticides prior to the pregnancy	1.12 (0.50–2.53)	1.33 (0.95–1.86)	1.08 (0.95–1.24)
Paternal smoker vs. no smoker	0.67 (0.37–1.21)	1.36 (1.05–1.74)	1.01 (0.93–1.11)
Paternal alcohol consumption vs. alcohol abstention	0.80 (0.43–1.50)	1.44 (1.05–1.98)	1.00 (0.90–1.11)
Father's age at time of child's birth (years)	1.05 (1.02–1.09)	1.01 (0.99–1.03)	1.00 (0.99–1.01)
Mother's age at time of child's birth (years)	1.06 (1.02–1.10)	1.03 (1.01–1.05)	1.00 (0.99–1.01)

decreased fertility and increased frequency of stillbirths and birth defects in workers exposed to pesticides in cotton fields supports the hypothesis of a possible role of DDT exposure (Rupa et al. 1991).

Animal studies have reported that DDT exposure could be implicated in increased congenital malformations, specifically sexual dimorphism (Fry and Toone 1981), endocrine disruption (Guillette et al. 1995), decreased testicular weight and number of implanted fetuses (Krause et al. 1975), and decreased fertility and low sperm counts (de Solla et al. 1998).

The male-to-female ratio has been proposed as an indicator of environmental endocrine disruption to explain the reduction of the proportion of men over the last five decades (Lyster 1977; Moller 1996). However, the use of this indicator is still under discussion because other factors could be implicated in this phenomenon (Bromen and Jockel 1997; Davis et al. 1998). No specific studies have been reported in relation to DDT exposure. In our study, the sex ratio did not change with exposure level. However, we agree with other authors who recommend looking for more specific time windows of exposure, such as exposure during puberty in men, to evaluate the sex ratios of their descendents (Kline et al. 1989).

Some inherent limitations in the study design must be considered when interpreting these findings. Possible misclassification of outcomes and exposures could occur. Because workers typically began as sprayers and advanced to jobs involving indirect exposure, they might have overreported indirect exposure if their recall of the jobs they performed most recently was better than their recall of long-ago jobs.

Birth defects have different pathogenesis and should ideally be studied separately (Kline et al. 1989); however, the small numbers of specific malformations prevent the assessment of individual outcomes. An additional limitation is that we were not able to medically confirm the cases of birth defects based on the information provided by the father, but it is likely that errors of recall are equally distributed by exposure level because the same effect was found using three different approaches to assess exposure. Mothers are usually considered better informants than fathers of the reproductive history of the couple. Another potential bias is faulty recall among older workers, whose memory of past pregnancies may not be as precise as that of younger workers describing children born recently. However, a sensitivity analysis to assess this possible bias by controlling for the time the event occurred (year of pregnancy) showed no change in the estimated OR.

The study of spontaneous abortions, especially those that occurred recently, could provide a good indicator of embryo toxicity (Stein et al. 1975). Unfortunately, the dates of spontaneous abortions were not well recalled by workers and hence prevented assigning exposure. Although a sensitivity analysis of missing values showed generally consistent associations, the limitations of the data prevent further interpretation of the results.

In addition, 23.3% of the workers had children by more than one woman. Reproductive information could be different for each of the respective partners. Information on the pregnancies with the legal wife is possibly the most reliable because there may be a tighter family bond between husband and wife, compared with the other partners. To account for this, we adjusted our model with a dichotomous variable for those workers having children with more than one woman, with no significant change in the results.

Our results provide some evidence that occupational exposure to DDT affects the reproductive health of male workers. The dose–response relations were not consistent, however, and the significance of these effects at lower exposures remains uncertain because the estimated doses are far above the exposure of the general population where DDT has been used for malaria control.

Table 4. Adjusted ORs[a] for reproductive effects in malaria control workers.

Reproductive effect	OR (95% CI)
Congenital malformations	
DDE concentration quartile 2	2.47 (0.75–8.11)
DDE concentration quartile 3	4.15 (1.38–12.46)
DDE concentration quartile 4	3.76 (1.24–11.44)
Application of malathion	2.43 (1.17–5.07)
Spontaneous abortion	
DDE concentration quartile 2	1.05 (0.76–1.46)
DDE concentration quartile 3	1.13 (0.83–1.53)
DDE concentration quartile 4	1.24 (0.91–1.70)
Application of malathion	0.88 (0.56–1.39)
Sex ratio (male:female)	
DDE concentration quartile 2	1.03 (0.97–1.10)
DDE concentration quartile 3	1.02 (0.96–1.09)
DDE concentration quartile 4	1.01 (0.94–1.07)
Application of malathion	0.98 (0.90–1.08)

[a]Obtained from a multivariate model including variables shown in table, and age of the mother to the pregnancy.

Correction

Values in Table 2 and in the paragraph describing the table (p. 544) were incorrect in the manuscript published online; the values have been corrected here.

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