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]
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 years 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 mixes 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):

\[ \log [p,p'-\text{DDE}] = 3.68 + 0.0010 \times \text{INDEXPO} \]

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 groupa | Unexposed group |
| Dichotomous variable for exposure | Pregnanacies occurring after worker-initiated activities related to occupational DDT contact (application, mixing pesticide solutions, activities in the field or near DDT storage) (\( n = 6,666 \)) | Pregnanacies 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 | Pregnanacies occurring after occupational DDT exposure activities in the field or near DDT storage (\( n = 385 \)) | Pregnanacies occurring for workers who were never occupationally exposed to DDT (\( n = 2,536 \)) |
| Direct exposure | Pregnanacies occurring after occupational DDT exposure, applying or mixing pesticide solutions (\( n = 3,627 \)) | |
| Alternate direct and indirect exposure | Pregnanacies 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 (\( n = 2,619 \)) | The first quartile was the reference category |
| | 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 (\( n = 2,220 \)) | |

*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 (tiofentfen, 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 in the OR for DDT. Odds ratios were adjusted for maternal age, smoking, alcohol drinking, and other organochlorines pesticides at the time of pregnancy, and exposure to organophosphate pesticides (tiofentfen, malathion, and fenthion).

The most common congenital malformations reported were in the nervous system (13 cases, ICD codes Q00–Q07) and the osteoarticular 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), lopirion lip (6 cases, Q35–Q37), 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.
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 revealed 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 (Hausser et al. 2003). The report of

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

| 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 (0.77–7.85)                   | 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)                  | 0.63 (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) | 1.19 (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 fenothion vs. no application | 1.70 (0.39–7.49) | 0.50 (0.17–1.50) | 1.29 (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 (0.65–1.74)                  | 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. 1999).

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 Jockey 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 longago 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# 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 | 0.89 (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) |

*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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