

Paternal Occupational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Birth Outcomes of Offspring: Birth Weight, Preterm Delivery, and Birth Defects

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Agent Orange is a phenoxy herbicide that was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). We studied pregnancy outcomes among wives of male chemical workers who were highly exposed to chemicals contaminated with TCDD and among wives of nonexposed neighborhood referents. For exposed pregnancies, we estimated serum TCDD concentration at the time of conception using a pharmacokinetic model. The mean TCDD concentration for workers' births was 254 pg/g lipid (range, 3–16,340 pg/g). The mean referent concentration of 6 pg/g was assigned to pregnancies fathered by workers before exposure. A total of 1,117 live singleton births of 217 referent wives and 176 worker wives were included. Only full-term births were included in the birth weight analysis (≥ 37 weeks of gestation). Mean birth weight among full-term babies was similar among referents' babies ($n = 604$), preexposure workers' babies ($n = 221$), and exposed workers' babies ($n = 292$) (3,420, 3,347, and 3,442 g, respectively). Neither continuous nor categorical TCDD concentration had an effect on birth weight for term infants after adjustment for infant sex, mother's education, parity, prenatal cigarette smoking, and gestation length. An analysis to estimate potential direct exposure of the wives during periods of workers' exposure yielded a nonstatistically significant increase in infant birth weight of 130 g in the highest exposure group (TCDD concentration > 254 pg/g) compared with referents ($p = 0.09$). Mothers' reports of preterm delivery showed a somewhat protective association with paternal TCDD (log) concentration (odds ratio = 0.8; 95% confidence interval, 0.6–1.1). We also include descriptive information on reported birth defects. Because the estimated TCDD concentrations in this population were much higher than in other studies, the results indicate that TCDD is unlikely to increase the risk of low birth weight or preterm delivery through a paternal mechanism.

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Agent Orange is a phenoxy herbicide that was widely used as a defoliant in Vietnam. A mixture of the herbicides 2,4-D [(2,4-dichlorophenoxy)acetic acid] and 2,4,5-T [(2,4,5-trichlorophenoxy)acetic acid], Agent Orange was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Most of the general population is exposed to low levels of TCDD, primarily through dietary intake of animal fats. Occupational exposure to TCDD occurred in the United States during the manufacture of Agent Orange, as well as among U.S. Vietnam veterans who were exposed to Agent Orange during Operation Ranch Hand. Because most of these workers and veterans were men, there has been heightened interest in male reproductive health outcomes associated with exposure to TCDD.

Extensive data on laboratory animals suggest that developing tissues are highly sensitive to TCDD, so associations between TCDD exposure and adverse reproductive outcomes are biologically plausible [Eskanazi and Kimmel 1995; National Academy of Sciences (NAS) 2003]. A recent review of TCDD by the NAS concluded that TCDD is one of the most toxic chemicals known to affect animals, although there is an extreme range of effects among species, and that the most sensitive

time of exposure to TCDD is during fetal development (NAS 2003). There have been few studies of paternal TCDD exposure and birth weight or preterm delivery in humans, however. In the fourth biennial update of the health effects of Vietnam veterans of exposure to herbicides, therefore, the NAS concluded there was insufficient or inadequate evidence to determine whether there is an association between paternal herbicide exposure and low infant birth weight or preterm delivery (NAS 2003). The NAS further concluded that there was limited suggestive evidence of an association between paternal exposure to herbicides and spina bifida (NAS 1997), but the evidence was inadequate regarding other birth defects (NAS 2003).

Low birth weight has been associated with infant mortality as well as outcomes later in life such as asthma, lower IQ, and hypertension (Wilcox 2001). Low-birth-weight babies either are born preterm (< 37 weeks of gestation) or are full-term but small (Wilcox 2001). Historically, etiologic research on pregnancy outcomes, such as birth weight or birth defects, has focused on maternal and fetal exposures. However, paternal exposures could be related to adverse reproductive outcomes through genetic damage to the male

germ cell, transfer of chemicals via seminal fluid, or exposure from chemicals that the father brings home from the workplace or hobbies (referred to as take-home exposure).

We studied the pregnancy outcomes among wives of male chemical workers who were highly exposed to chemicals contaminated with TCDD and among nonexposed neighborhood referents who participated in a cross-sectional medical study. Previous reproductive health analyses of this cohort reported subtle alterations in reproductive gonadotrophin and testosterone levels in male workers (Egeland et al. 1994) but no association between paternal TCDD exposure and spontaneous abortion or sex ratio (Schnorr et al. 2001). In the present study we evaluated the association between paternal exposure to TCDD at the time of conception and birth weight and preterm delivery of offspring. We also describe birth defects as reported in maternal interviews.

Materials and Methods

Study population. The reproductive health study was conducted as part of a cross-sectional medical study, described previously in detail (Sweeney et al. 1989, 1993). Briefly, the study was conducted in 1987–1988 by the National Institute for Occupational Safety and Health (NIOSH) and examined workers from plants in New Jersey and Missouri. Workers were exposed to TCDD during the production of sodium trichlorophenol or one of its derivatives, such as hexachlorophene [2,2'-methylene-bis-(3,4,6-trichlorophenol)] or 2,4,5-T, which was used to formulate Agent Orange.

For comparison, referents with no self-reported occupational exposure to TCDD were selected from the workers' neighborhoods, matched on age (± 5 years), race, and sex. Selection of worker-matched referents was based on a procedure requiring neighborhood

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