

PATERNAL OCCUPATIONAL EXPOSURE TO 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN AND BIRTHWEIGHT OF OFFSPRING

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Introduction

Agent Orange, a phenoxy herbicide, is a 50/50 mixture of the herbicides 2,4-D [(2,4-dichlorophenoxy)acetic acid] and 2,4,5-T [(2,4,5-trichlorophenoxy)acetic acid], which was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). There have been few studies of paternal TCDD exposure and birthweight. The National Academy of Sciences (NAS) concluded there was insufficient or inadequate evidence to determine whether there is an association.¹

We studied the pregnancy outcomes among wives of male workers highly exposed to chemicals contaminated with TCDD and among wives of non-exposed neighborhood referents that participated in a cross-sectional medical study. In the current paper we evaluate the association between paternal exposure to TCDD at the time of conception and birthweight of offspring.

Materials and Methods

The reproductive health study was conducted as part of a cross-sectional medical study,² which was conducted in 1987-1988 and included 281 workers 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, 325 men with no self-reported occupational exposure to TCDD were selected as referents from the workers' neighborhoods, matched on age (± 5 years), race, and sex. Subjects were also asked to participate in a medical examination, which included drawing blood for determination of serum TCDD. The study was voluntary, and informed consent was obtained from all study subjects. Current and former wives/partners (hereafter referred to as "wives") of male participants were contacted and administered a telephone interview, which collected detailed information on reproductive history, medical history, lifestyle factors, and occupational factors.

Pregnancies conceived after the father's first date of exposure were considered exposed, while referent pregnancies and pregnancies conceived before the fathers' exposure (hereafter referred to as "pre-exposure" pregnancies) were considered unexposed. For exposed pregnancies, we estimated the worker's serum TCDD concentration at the time of conception using a pharmacokinetic model,^{3,4} based on the following factors: serum TCDD concentration at the time of examination, dates of employment in TCDD-related processes, body mass index (BMI) measured by NIOSH at the time of examination, and BMI measured by the employer during employment. This technique allows for changes in individual body burden over time.

TCDD serum measurements were obtained for a random sample of 79 referents at examination. Because the referent serum concentrations were assumed to be the accumulation of a lifetime of background environmental exposures, we assigned the TCDD serum values from the examination

to each referent pregnancy. For the remaining referent pregnancies, the median referent value of 6 picograms per gram of liquid (pg/g) was assigned.^{4,5} Pregnancies fathered by workers before exposure were also assigned the median referent value of 6 pg/g.

Only live, singleton full-term births were included in the birthweight analysis. Pregnancies not fathered by the study males were excluded. Birth certificates were requested for all births and were obtained for 82% of live births. Full term birth was defined as a live birth of 37 or more completed weeks from last menstrual period (LMP), or no more than three weeks before due date.

The primary dependent variable, birthweight, was modeled as a continuous variable. The primary independent variable, TCDD concentration, was modeled both as a continuous variable (using the log) and as a categorical variable (referents, <20 pg/g, 20 to <255 pg/g, ≥ 255 pg/g) using dummy variables. Repeated measures analyses of variance were performed using the SAS PROC MIXED procedure to account for the lack of independence among multiple pregnancies per mother. Univariate analyses were used to search for medical, lifestyle, and exposure factors that could potentially confound multivariate analyses.

Results and Discussion

Characteristics of the study participants have been reported previously.^{2,6} For the current report, 259 male workers who had supplied serum were included, along with 243 male referents. Of the wives interviewed, 211 of the worker wives and 217 of the referent wives had had at least one singleton live birth and were included in the birthweight analyses. Most of the study population was Caucasian race (89.4% referent wives and 90.0% worker wives), and a small percentage were of Hispanic ethnicity (1.8% of referent wives and 2.8% of worker wives). The educational status among both groups was similar; 38.2% of the referent wives and 33.6% of the worker wives had more than high school education.

Included in the analysis were a total of 1,155 live full-term births, 551 to worker wives and 604 to referent wives. Of the worker live births, 259 were conceived before the father was exposed to TCDD at the study company (pre-exposure births), and 292 births were conceived during or after exposure and are considered exposed births. The median paternal TCDD concentration for exposed births was 254 pg/g (range 3 to 16,340 pg/g). The median TCDD serum concentration for referent fathers who participated in the medical exam was 6 pg/g (range 2-19), which was the value assigned to all referent and pre-exposure births. The same percentage of referent and worker wives worked during their pregnancies (28%), and few reported pre-natal exposure to chemicals or radiation (0.3% to 3.0%).

Mean birthweight was similar in the three exposure groups. Figure 1 shows average birth weight by length of gestation for referent births and pre-exposure and exposed worker births. The graph is limited to gestational length of 37 to 43 weeks due to small numbers in the other weeks.

Table 1 shows results of the crude and adjusted analyses of birthweight and paternal TCDD concentration. The crude analysis shows a small but significant increase in birthweight with increasing TCDD concentration. However, there was no effect of continuous or categorical TCDD on birthweight when adjusting for the following confounding variables: sex of the infant, education of the mother, parity, cigarette smoking during pregnancy, and length of gestation.

The current study does not support a causal relationship between low birthweight and high paternal TCDD exposure. These results are consistent with two of three previous studies of low birthweight and paternal dioxin exposure.^{7,8,9} Michalek, et al⁷ studied Vietnam veterans who were

exposed to Agent Orange and TCDD during Operation Ranch Hand. The median estimated dioxin concentration at LMP among Ranch Hand veterans was 79 ppt with a range of 0 to 1,425 ppt. The risk of intrauterine growth retardation was not increased in any Ranch Hand exposure category. In a study of sawmill industry workers, no increase was found in risk for lower birthweight among offspring of men occupationally exposed to dioxin-contaminated chlorophenols, as measured by expert raters' estimations of hours of exposure.⁸ Though the chlorophenols in that study were not contaminated with TCDD, the workers were exposed to other polychlorinated dioxins. A study of Australian veterans showed a significantly increased risk ratio of 1.6 for low birthweight, though insufficient detail is given for a meaningful interpretation of the results.⁹

The men in our occupational study group were exposed to TCDD at substantially higher concentrations than other cohorts, with estimated concentrations at the time of conception ranging from 3 to 16,340 pg/g. The strengths of the current study include biological measurements of internal dose and a pharmacokinetic modeling technique that allowed for changes in individual body burden over time. Another strength is that we were able to adjust for confounding variables that were collected with a telephone interview. In addition, the majority of our birthweight data was verified by birth certificate.

Our study's limitations included a lengthy recall period and the reliance of maternal report of birthweight when birth certificates were not available. However, previous literature shows that mothers' recall of birthweight is generally found to be accurate (Troy 1996, Sanderson 1998, Tomeo 1999). When we conducted a sub-analysis which excluded those individuals (18%) for whom birthweight was not confirmed by certificate, the results were similar.

In conclusion, these results do not support a causal relationship between paternal TCDD exposure and lowered birthweight. 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 birthweight at levels above those observed in the general population.

Figure 1: Average Birth Weight v. Weeks of Gestation

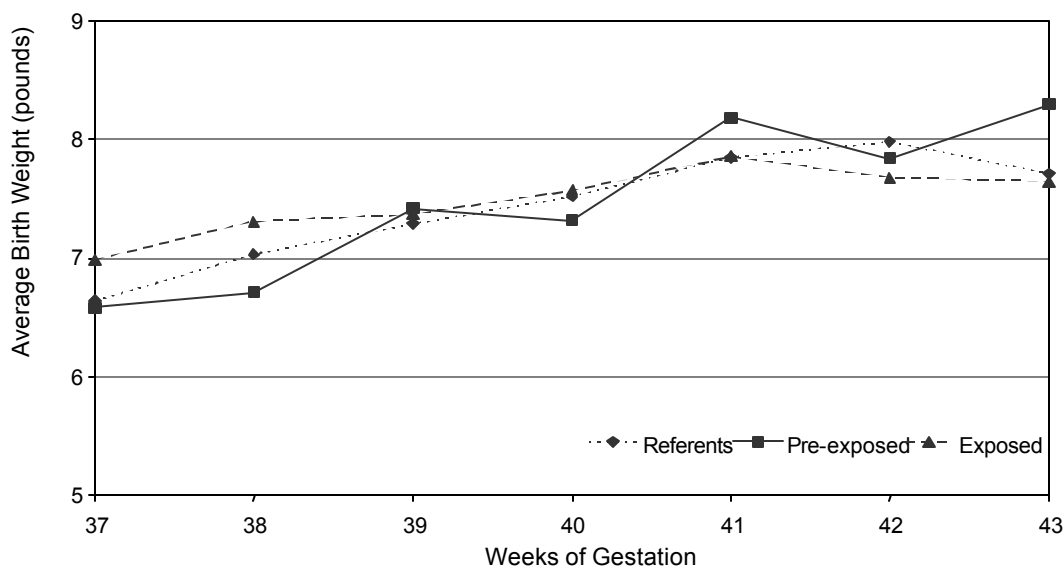


Table 1: Paternal TCDD Exposure and Birthweight among Term* Infants

Variable	Crude			Adjusted**		
	N=	Estimate (S.E.)	P-Value	N=	Estimate (S.E.)	P-Value
TCDD Estimated Concentration at LMP (log)	1,139	0.055 (0.020)	0.005	1,131	0.030 (0.020)	0.12
TCDD category:						
Referents	596	--		592	--	
< 20 pg/g	301	-0.14 (0.10)	0.15	299	-0.03 (0.09)	0.74
20 to <255 pg/g	98	-0.13 (0.14)	0.32	98	-0.09 (0.13)	0.46
≥255 pg/g	144	0.26 (0.12)	0.03	142	0.18 (0.11)	0.12

* Gestational Age \geq 37 Weeks

** Adjusted for infant sex, mother's education, parity, cigarette smoking, and length of gestation.

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