Paternal Serum Dioxin, Preterm Birth, Intrauterine Growth Retardation, and Infant Death

Joel E. Michalek* and Coleen A. Boyle**

*Directed Energy Bioeffects Division, Air Force Research Laboratory, 2606 Doolittle Road, Brooks Air Force Base, Texas 78235-5250
**National Center for Environmental Health, Centers for Disease Control, 4770 Buford Highway, Mail Stop F-15, Atlanta, Georgia 30341-3724

Introduction

The Air Force is conducting a 20-year prospective study of veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam from 1961 to 1971. This report summarizes the findings of an investigation of dioxin body burden and preterm birth, intrauterine growth retardation (IUGR) and infant death in offspring of Ranch Hand veterans[1].

Methods

In 1982, 1985, 1987 and 1992, participants, their wives and other partners were asked about the health of their children. Participation was voluntary and consent forms were signed at the examination site. Participants were asked to provide access to medical records documenting each pregnancy and the health of each child through the age of 18. In 1987 and 1992, blood from each willing participant was collected and assayed for dioxin[5]. Of the 995 Ranch Hands and 1,299 Comparison subjects who participated in the 1987 physical examination, 932 Ranch Hands (93.7%) and 1,202 Comparison subjects (92.5%) volunteered for the dioxin assay. Subjects who refused in 1987 or received a nonquantifiable dioxin result in 1987 were asked to give blood for the dioxin assay at the 1992 physical examination. We refer to dioxin levels obtained in 1987 or 1992 as current dioxin levels.

All reported pregnancies, regardless of the biological relationship of the fetus or live born infant to the study participant or the time of conception relative to the father's service in Southeast Asia (SEA), were subjected to medical record verification. We attempted to verify all pregnancies reported by study participants, their wives or partners through the retrieval of medical documents, birth certificates, death certificates and autopsy reports. We also attempted to verify the existence, lineage, birth weight, gestation and vital status of all live births. We classified underlying causes of death in accordance with the rules and conventions of the 9th revision of the International Classification of Diseases (ICD). We restricted reproductive outcomes to verified singleton live births fathered by a study participant with a quantifiable dioxin result and conceived during or after the father's service in SEA. We refer to live births as children. Since our first report, some study

subjects fathered additional children and additional dioxin results were obtained. A summary of the sample reduction, starting with the published total, is given in Table 1.

Table 1 Numbers of Children by Group

Source	Ranch Hand	Comparison	Total
Total from last report (January 1995)	3,482	4,618	8,100
Additional children since last report	19	104	123
Conceived before the father's service in Southeast Asia	(2,269)	(2,858)	(5,127)
Existence not verified	(3)	(1)	(4)
Not fathered by a participant	(165)	(189)	(354)
Father missing dioxin	(161)	(394)	(555)
Comparison father, dioxin >10 ppt		(26)	(26)
Missing birth weight	(27)	(23)	(50)
Product of a multiple birth	(17)	(8)	(25)
Available for analysis	859	1,223	2,082

Among Ranch Hand children whose father's current dioxin level was above 10 ppt, we computed the extrapolated initial dioxin level (I) at the time of conception of the child using a first order decay rate model with a fixed 8.7 year half-life. We stratified children to four categories determined by study group and dioxin level. Children of Comparison veterans having current dioxin levels less than or equal to 10 ppt (N=1,223) serve as referents for Ranch Hand children. We assigned children of Ranch Hands with current dioxin less than or equal to 10 ppt to a category called "Background" (N=323). We assigned children of Ranch Hand veterans with dioxin levels greater than 10 ppt to "Low" or "High" categories determined by the extrapolated initial dioxin level (I); we assigned children with I≤79 ppt to the Low category (N=267) and those with I>79 ppt to the High category (N=269). The cut point of 79 ppt is the median initial dioxin value for Ranch Hand children having an initial dioxin level.

We defined gestation as the length of pregnancy (measured in weeks). We obtained this information from the mother's clinical record of labor and delivery. We defined preterm birth as a birth with gestation less than 37 weeks; we refer to children born preterm as preterm children and children not born preterm as term children. Using gestation-specific norms derived from a population study, we defined IUGR as a birth weight less than the tenth percentile of birth weight for each week of gestation. We obtained the dates of death from death certificates and defined infant death as any death occurring on or before the first birthday. We obtained histories of smoking and alcoholic beverage consumption while pregnant during in-person interviews with wives and partners. A pediatrician blinded to the fathers dioxin exposure classified the underlying cause of death by reviewing diagnoses coded from death certificates and autopsy reports. When the underlying cause of death could not be determined with certainty from these records, the pediatrician also reviewed the child's hospital medical record.

We adjusted all analyses via stratification for the father's race (black, nonblack), the mother's smoking during pregnancy (yes, no), the mother's alcohol drinking during pregnancy (yes, no), the mother's age at the time of the child's birth (<25 years, ≥25 and <30 years, ≥30 years), the father's age at the time of the child's birth (<28 years, ≥28 and <33 years, ≥33 years), and the father's military occupation in SEA (officer, enlisted flyer, enlisted ground personnel).

Results

Demographic characteristics of the cohorts are summarized in Table 2.

Table 2 Distribution of Demographic Conditions of Children and Fathers by Dioxin Category

			Ranch Hand	
Characteristic	**Comparison**	**Background**	**Low**	**High**
Sex of the child (% female)	49.6	49.8	51.3	46.5
Father's race (% nonblack)	92.3	93.5	88.0	93.7
Father's military occupation (%)				
Officer	29.8	47.1	22.1	1.5
Enlisted flyer	10.3	9.9	12.7	10.0
Enlisted Ground Personnel	59.9	43.0	65.2	88.5
Median birth year of children (range)	1974 (1959-1992)	1973 (1963-1991)	1975 (1967-1992)	1973 (1963-1986)
Median paternal dioxin (range) (ppt*)	3.7 (0-10)	5.6 (0-10)	39.0 (11.1-78.8)	153.4 (79.2-1424.8)

*Parts per trillion.

Children in the High category (Table 3) were at increased risk of preterm birth (relative risk=1.3) as were those in the Background category (relative risk=1.4). The risk of IUGR was not increased in any Ranch Hand exposure category. The risk of infant death was increased in all Ranch Hand children; the greater increases occurred in the Background (relative risk=3.2) and High (relative risk=4.5) categories.

Table 3 Preterm Birth, Intrauterine Growth Retardation and Infant Death

		Ranch Hand		
Outcome	**Comparison**	**Background**	**Low**	**High**
Preterm Birth				
N (%)	54 (4.4)	20 (6.2)	6 (2.2)	16 (5.9)
RR	1.0	1.4	0.5	1.3
95% CL	Referent	(0.9, 2.3)	(0.2, 1.2)	(0.8, 2.3)
Intrauterine Growth Retardation				
N (%)	116 (9.5)	29 (9.0)	22 (8.2)	22 (8.2)
RR	1.0	0.9	0.9	0.9
95% CL	Referent	(0.6, 1.4)	(0.6, 1.3)	(0.6, 1.3)
Infant Death				
N (%)	6 (0.5)	5 (1.6)	2 (0.8)	6 (2.2)
RR	1.0	3.2	1.5	4.5
95% CL	Referent	(1.0, 10.3)	(0.3, 7.5)	(1.5, 14.0)

We classified infant deaths by underlying cause. Five of the 6 deaths in the High category and all 5 deaths in the Background category were caused by disorders related to short gestation and unspecified low birth weight and one death in the High category was caused by injury, poisoning, starvation or neglect. We did not analyze these counts owing to small numbers.

Discussion

There was a modest increase in risk of preterm birth among children in the High and Background exposure categories and a decreased risk in the Low category. The increased risk in the Background category implies that these fluctuations in risk may not due to dioxin exposure. We found no increase in the risk of IUGR in any dioxin exposure category. The risk of infant death was increased among Ranch Hand children whose fathers had the highest and among children whose fathers had background dioxin levels. These patterns imply that these outcomes may not be related to paternal dioxin level.

Reference

1. Michalek JE, Rahe AJ and Boyle CA. Paternal dioxin, preterm birth, intrauterine growth retardation, and infant death. *Epidemiology* **1998**,9,161-167.