

Reproductive Outcome versus Paternal Dioxin Body Burden in Veterans of Operation Ranch Hand

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The Air Force is conducting a 20-year prospective study of veterans of Operation Ranch Hand¹, the unit responsible for aerial spraying of herbicides in Vietnam from 1962 to 1971. A comparison group of Air Force veterans who served in Southeast Asia (SEA) during the same period who were not occupationally exposed to herbicides was selected. The study, called the Air Force Health Study, now in its tenth year, is designed to determine whether exposure to the herbicides or their contaminant, 2,3,7,8 tetrachlorodibenzo-p-dioxin (dioxin), has adversely affected the health, survival or reproductive outcomes of Ranch Hands.

This report summarizes the findings of an investigation of reproductive outcomes of 872 Ranch Hands and 1,206 Comparisons for whom a dioxin level has been determined. When these analyses began in August 1991, these men had fathered 8,263 conceptions and 6,792 live births. All data in this report has been verified by review of birth certificates, newborn clinic records, health records and death certificates. The birth defect status of each child was verified through the age of 18.

This study is the first to combine an accurate measure of paternal dioxin exposure with documented and verified reproductive outcomes in a population of sufficient size to provide a reasonable opportunity to detect associations between paternal dioxin body burden and a range of common reproductive outcomes. This study evaluates semen abnormalities, inability to conceive, prematurity (birth weight below 2500 grams), neonatal death, birth defects, birth defect severity and developmental abnormalities.

The statistical significance of the association between the father's dioxin body burden and reproductive outcomes occurring after his service in Southeast Asia (post-SEA) were carried out with and without adjustment for reproductive outcomes occurring before his service in Southeast Asia (pre-SEA). Three statistical models were used. The first two of these were applied to Ranch Hands only and the third to Ranch Hands and Comparisons. Model 1 incorporates an estimate of the father's initial dioxin body burden based on a 7.1 year half-life. Model 2 uses the father's current dioxin level with adjustment for time since service in Southeast Asia. In Model 3, current dioxin is categorized to four levels, named Background, Unknown, Low and High. The Background category contains Comparisons with dioxin less than or equal to 10 parts per trillion (ppt), the Unknown category contains Ranch Hands with dioxin less than or equal to 10 ppt, the Low category contains Ranch Hands with dioxin greater than 15 and less than or equal to 33.3 ppt and the High category contains Ranch Hands with dioxin greater than 33.3 ppt. Each of these models was applied to data arising from all marriages and relationships of the father and again to data arising only from full siblings. The second series is termed "full sibship" analyses; these were carried

to reduce genetic variability. All analyses were conducted without adjustment for covariates. The covariates were the father's race (Black, White), mother's smoking during pregnancy (yes, no), the mother's drinking during pregnancy (yes, no), the mother's age at the time of the child's birth, the father's age at the time of the child's birth, the number of years between the father's return from SEA and the conception date of the child, and the father's military occupation (officer, enlisted flyer, enlisted nonflyer).

The association between the father's dioxin level and sperm count and the percentage of abnormal sperm was assessed based on serum dioxin levels measured in 1987 and semen specimens collected during the baseline physical examination in 1982. No significant associations between dioxin and sperm count or between dioxin and percentage of abnormal sperm were found.

The significance of associations between paternal dioxin level and miscarriage, total adverse outcome and total conceptions were assessed. Total adverse outcome was defined as miscarriage, tubal pregnancy, other abortive pregnancies or stillbirth. The results were generally negative. Significant associations were found in some analyses, but these were not plausibly related to dioxin. For example, significant results in the assessment of post-SEA miscarriage were caused by increasing miscarriage rates with dioxin in conceptions of Ranch Hands with late tours and decreasing miscarriage rates with dioxin in conceptions of Ranch Hands with early tours, a pattern not consistent with expected dose-response relationships. In a pattern similar to those of miscarriage rates, significant associations between total adverse outcome and dioxin were caused by increasing adverse outcome rates with dioxin in conceptions of Ranch Hands with late tours and decreasing trends in conceptions of Ranch Hands with early tours. The association between total conceptions and categorized dioxin was found significant because the average number of conceptions increased with dioxin level, opposite to the expected decreasing trend. In full context, these few findings are inconsistent and therefore appear artifactual.

No significant association was found between dioxin and birth weight or between dioxin and low birth weight.

Analyses of neonatal mortality were generally negative. In the only significant finding, children of Ranch Hands in the high dioxin category had a higher neonatal death rate (22 per 1000) than children of Comparisons in the background category (4.1 per 1000) and this contrast was also significant after restriction to full siblings. However, the first of these two analyses is based on only 13 deaths, 4 among children of Comparisons in the Background category, 3 among children of Ranch Hands in the Unknown category, 1 among children of Ranch Hands in the Low category and 5 among children of Ranch Hands in the High category. In the second analysis, there were 12 deaths, with one fewer in Ranch Hand children in the High category. Analyses of initial dioxin versus neonatal death in Ranch Hand children found no significant associations. These findings are inconsistent and therefore are considered unrelated to dioxin. There were too few infant deaths (3 in Ranch Hands having more than 10 ppt) to allow statistical analysis of the data.

The significance of the association between dioxin and post-SEA birth defects was assessed within each of 13 categories of anomalies: total congenital, nervous system, eye, ear face and neck, circulatory system and heart, respiratory system, digestive system, genital, urinary, musculoskeletal, skin, chromosomal and other unspecified anomalies. Without consideration of dioxin levels, Ranch Hand versus Comparison contrasts on total post-SEA congenital anomalies adjusted for pre-SEA anomalies found a significant reversal in anomaly rates with time of birth of the child relative to the

father's tour of duty in SEA; the Ranch Hand rate was less than the Comparison rate among pre-SEA children and greater than the Comparison rate among post-SEA children. However, we found no evidence that this effect was confined to a specific birth defect category. Additional analyses with adjustment for the father's dioxin level found no significant association between this change in risk and dioxin.

In the assessments of dioxin versus post-SEA birth defects, few significant associations were found. Those that were found did not appear consistently across analyses and most were not suggestive of a plausible dioxin effect. For example, a significant association was found between initial dioxin and circulatory system and heart anomalies, but the rate (6.4 per 1000) among children of Ranch Hands having highest initial dioxin levels was less than that among children of Ranch Hands at the lowest initial dioxin levels (28.3 per 1000). In a Model 3 analysis restricted to full siblings, a significant association was found between categorized dioxin and circulatory system and heart anomalies, but this was caused by a high rate (47.3 per 1000) among children of Ranch Hands in the Low category relative to children of Comparisons in the Background category (17.2 per 1000) and a low rate among children of Ranch Hands in the High category (0 per 1000). In a Model 2 analysis, a significant association was found between current dioxin and anomalies of the ear, face and neck, but this was caused by an increase in anomalies with dioxin among children of Ranch Hands having early tours and a decrease in anomalies among children of Ranch Hands having late tours, a pattern not consistent with the expected dose-response. A significant association was found in a Model 3 analysis of genital anomalies, but the pattern was not consistent with the expected dose-response. The rate among children of Ranch Hands in the Low dioxin category (51.7 per 1000) was greater than that among children of Ranch Hands in the High category (13.2 per 1000).

All live births were assigned to one of three birth defect severity categories (none, minor, major) and the significance of the association between dioxin and birth defect severity was assessed with Models 1, 2 and 3 under various combinations of constraints on severity, sibship, and statistical adjustment. Few significant associations were found. Those that were found were weak and inconsistent with expected dose-response relationships. For example, in an unadjusted Model 3 analysis, a significant association was found between categorized dioxin and birth defect severity, but this was caused by a high rate of major anomalies (126.4 per 1000) in children of Ranch Hands in the Low dioxin category relative to children of Comparisons in the Background category (57.1 per 1000) and a low rate in children of Ranch Hands in the High dioxin category (57.3 per 1000). After restriction to full siblings, the same finding was observed; however, the lowest rate (46.2 per 1000) occurred in children of Ranch Hands in the High dioxin category. The adjusted analyses were complicated by significant interactions with maternal smoking history and the military occupation of the father. The finding was caused by an increased rate in children of Ranch Hands in the Low dioxin category whose mother smoked during pregnancy and whose father was an enlisted nonflyer in Vietnam. This finding is not considered to be caused by dioxin because the rate of major anomalies in children of Ranch Hands in the High dioxin category was not significantly elevated.

Sixteen specific birth defects (anencephaly, spina bifida, hydrocephalus, cleft palate, cleft lip/palate, esophageal atresia, anorectal atresia, polydactyly, limb reduction defects, hypospadias, congenital hip dislocation and Down's syndrome) and three categories of developmental anomalies (disturbance of emotion specific to childhood and adolescence, hyperkinetic syndrome of childhood, specific delays in development and mental retardation) were investigated. No significant associations with dioxin were

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found and no trends suggestive of a dioxin effect were apparent.

In conclusion, the few significant associations found between dioxin and reproductive outcome were generally weak, inconsistent or biologically implausible. There is no evidence in these data to support a hypothesis of adverse effects of paternal dioxin on reproductive outcome.

Reference

1. Wolfe W, Michalek J, Miner J, Rahe A, Silva J, Thomas W, Grubbs W, Lustik M, Karrison T, Roegner R, Williams D. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. *J Amer Med Assoc* 1990;14:1824-1831.