Diabetes versus Dioxin Body Burden in Veterans of Operation Ranch Hand

Wolfe W.[A], Michalek J.[A], Miner J.[A], Needham. L.[B], Patterson, D., Jr.[B]
A Armstrong Laboratory, Brooks Air Force Base, Texas 78235, USA
B Centers for Disease Control, Atlanta, Georgia 30333, USA

The Air Force is conducting a 20-year prospective study[1] of veterans of Operation Ranch Hand, 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 glucose intolerance and diabetes versus dioxin levels in 930 Ranch Hands and 1,198 Comparisons who were compliant to the 1987 physical examination and who provided a serum specimen for the dioxin assay. These results are based on fasting glucose (mg/dl) and 2-hour postprandial glucose (mg/dl) collected during the examination. Additionally, a composite diabetes indicator was defined as positive if the subject had a verified history of diabetes or a 2-hour postprandial glucose greater than or equal to 200 mg/dl. Time to diabetes onset was determined through review of medical records to find the earliest verifiable diagnosis. Time to onset was defined as the time in years between departure from Vietnam and the date of first diagnosis. Subjects with a verified history of diabetes or an elevated 2-hour postprandial glucose were assigned to one of 4 severity categories based on medical record review: insulin requiring, oral medication, diet control, or no care. All others were categorized as nondiabetic.

Subjects whose blood contained HBsAg and subjects whose body temperature was greater than 100 degrees F were excluded from the analysis of fasting glucose. Subjects with a verified history of diabetes were excluded from the analysis of 2-hour postprandial glucose. Subjects with a verified pre-SEA history of diabetes were excluded from the analysis of the composite diabetes indicator.

The association between dioxin level and these diabetes indicators was assessed with three statistical models. Model 1 used an estimated initial dioxin level computed assuming first order elimination and a constant half-life of 7.1 years. Model 2 used current dioxin with adjustment for time since departure from SEA. Models 1 and 2 were applied to Ranch Hands having more than 5 parts per trillion (ppt) current dioxin (n=740) and then to Ranch Hands having more than 10 ppt current dioxin (n=518). Model 3 categorized Ranch Hands and Comparisons according to their dioxin level. The Background category (n=1027) contained Comparisons with less than or equal to 10 ppt dioxin. The Unknown category (n=346) contained Ranch Hands having dioxin less than or equal to 10 ppt. The Low category (n=194) contained Ranch Hands having more than 15 ppt but less than or equal to 33.3 ppt and the High category (n=187) contained Ranch Hands having more than 33.3 ppt.

Analyses of fasting glucose were adjusted for age, race, current alcohol use, alcohol history, industrial chemical exposure, and degreasing chemical exposure.

Analyses of 2-hour postprandial glucose were adjusted for age, race, personality type, and percent body fat (PBF). Analyses of the composite diabetes indicator were adjusted for age, race, personality type, and PBF.

Unadjusted Model 1 analyses revealed a statistically significant association ($p<0.001$) between fasting glucose and initial dioxin. The mean levels by stratum of initial dioxin (I) Low (25 ppt$<I\leq$56.9 ppt), Medium (56.9$<I\leq$218 ppt) and High ($I>218$ ppt) were 99.4, 101.6 and 104.6 mg/dl and this trend remained significant after adjustment for covariates ($p<0.001$). Although these means are well within normal limits and the difference of 5.2 mg/dl between the Low and High categories is not considered clinically significant, the data are consistent with a dose response effect. Unadjusted Model 2 analyses found that the trend is more pronounced in Ranch Hands furthest removed from Southeast Asia (>18.6 years), raising the possibility of a temporal effect. Adjusted Model 2 analyses found that this trend is significant in younger rather than in older Ranch Hands. Model 3 analyses found significant positive trends without ($p<0.001$) or with ($p<0.001$) adjustment for covariates. The analyses of 2-hour postprandial glucose found parallel trends but these were not significant after adjustment.

More important than the associations between serum dioxin and blood glucose levels is, perhaps, the significant association between dioxin and the prevalence of overt diabetes by verified history or by a 2-hour postprandial blood sugar of more than 200 mg/dl. The unadjusted Model 1 data are summarized in Table 1 for Ranch Hands having more than 10 ppt current dioxin.

Table 1

Diabetes versus Initial Dioxin

Intitial Dioxin (I)	n	Percent Diabetic
52<I≤93	129	10.1
93<I≤292	257	12.5
292<I	131	14.5

The trend in Table 1 is significant without ($p=0.02$) or with ($p=0.001$) adjustment for covariates. Model 2 analyses found a significant positive association between current dioxin and diabetes in Ranch Hands furthest removed from SEA (>18.6 years) ($p=0.05$). Stratifying by current (C) dioxin (Low: $10<C\leq14.65$ ppt, Medium: $14.65<C\leq45.75$, High: $45.75<C$), the percent diabetic were 10.5%, 12.3% and 16.9%. This trend was also significant after adjustment for covariates ($p=0.002$). Model 3 analyses also found significant associations; these data are summarized in Table 2.

Table 2

Diabetes versus Current Dioxin Category

Category	Group	Current (C) Dioxin in ppt	n	Percent Diabetic
Background	Comparisons	0<C≤10	1027	8.3%
Unknown	Ranch Hands	0<C≤10	346	5.5%
Low	Ranch Hands	15<C≤33.3	194	8.3%
High	Ranch Hands	33.3<C	187	16.6%

Without ($p<0.001$) or with ($p=0.008$) adjustment for covariates, there is a significant overall association between categorized current dioxin and diabetes. The High versus Background contrast is significant without adjustment ($p<0.001$). Adjustment found a significant interaction with age. Analyses in subjects older than 43 years at baseline found additional interactions with age and PBF.

With regard to time of onset, an unadjusted Model 3 analysis found that Ranch Hands in the High category are experiencing diabetes significantly sooner than Comparisons in the Background category ($p=0.002$). The percent disease-free 15 years after service in SEA were: Background (96.2%), Unknown (98.0%), Low (95.4%), High (92.0%). Adjustment for covariates found significant interactions with age and PBF. Adjusted analyses within stratum of age at baseline (age ≤ 43, age >43) and PBF (PBF $\leq 25\%$, PBF $>25\%$) found additional interactions with PBF. Adjusted Model 1 analyses found a significant trend of earlier onset with increasing initial dioxin ($p=0.01$) in Ranch Hands with more than 10 ppt current dioxin. Adjusted Model 2 analyses also found a significant association ($p=0.002$).

Subjects are cross-classified by diabetic severity and category of current dioxin in Table 3.

Table 3

Diabetic Severity versus Current Dioxin Category

Dioxin Category	Diabetic Severity: Insulin Dependent	Oral Meds	Diet Control	No Care	Not Diabetic	Total
Background	5	14	24	42	942	1027
Unknown	4	1	6	8	327	346
Low	4	2	6	4	178	194
High	2	5	8	16	156	187
Total	15	22	44	70	1603	1754

There is a significant difference between the percent of diabetics with at least diet control across the four dioxin categories ($p=0.03$). Without adjustment, the proportion

of Ranch Hands in the High category with diabetes requiring at least diet control is significantly greater than that among Comparisons in the Background category ($p=0.02$). Adjustment found significant interactions with age and PBF. In old lean ($p=0.005$) and in old obese ($p=0.04$) subjects the proportion of Ranch Hands in the High category with diabetes requiring at least diet control was greater than that in Comparisons in the Background category. The relevant percentages were: old lean (17.1% versus 4.6%) and old obese (40% versus 14.3%). Similar results were found with severity restricted to at least oral medications.

These results must be interpreted with caution. Though the data clearly establish an association between glucose intolerance and dioxin exposure, it would be premature to draw conclusions regarding cause and effect. Clinically, obesity is well recognized as the most common cause of adult-onset diabetes mellitus. Dioxin has been shown to be strongly correlated with percent body fat. Pending further investigation into the pharmacokinetics of dioxin in lean versus obese individuals, a causal relationship between exposure to dioxin and diabetes remains to be proven.

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;264:1824-1831.