ARE DIOXIN BODY BURDENS SURROGATES FOR OTHER RISK FACTORS IN ASSOCIATIONS BETWEEN DIOXIN AND DIABETES?

Haws LC[1], Scott PK[2], Unice KM[2], Gough M[3]; Harris MA[4]; Staskal DS[1], Paustenbach DJ[5], and Pavuk M[6]

[1]ChemRisk, Austin, TX, USA; [2]ChemRisk, Pittsburgh, PA, USA; [3]Consultant, Bethesda, MD, USA; [4]ChemRisk, Houston, TX, USA; [5]ChemRisk, San Francisco, CA, USA; [6]SpecPro Inc., San Antonio, TX, USA.

Introduction

In 1999, the National Academy of Science's Institute of Medicine (IOM) established a committee to examine the evidence regarding an association between Type II diabetes and exposure to dioxin and other chemicals in herbicides used in Vietnam. As a result of their review, the IOM committee concluded that there was "limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type II diabetes"[1]. In reaching this conclusion, the IOM committee stated, "No one paper or study was determinative in reaching this decision. Instead, the committee found that the information accumulated over years of research now meets the definition established for limited/suggestive evidence-that is, *evidence is suggestive of an association between herbicides and the outcome, but limited because chance, bias, and confounding could not be ruled out with confidence*" (emphasis in original)[1]. Examples of limitations cited by the IOM committee include the apparent lack of a dose-response in studies relating dioxin and diabetes, the inability to rule out potential confounders, and conflicting findings (e.g., negative [inverse] trend between diabetes mortality and cumulative TCDD exposure reported by Steenland and coworkers[2]).

The IOM Committee relied heavily upon data from the Air Force Health Study (AFHS), an ongoing prospective epidemiological study that compares the health of veterans of Operation Ranch Hand, the Air Force unit responsible for spraying millions of gallons of Agent Orange during the Vietnam War, with a Comparison population of Air Force veterans who served in Southeast Asia during the same time period (1962-1971) but were not involved in any spraying activities (hereafter referred to as "Comparisons")[3]. Comparisons were individually matched to Ranch Hands based on age, race, and military occupation. Physical examinations and interviews were conducted in 1982, 1985, 1987, 1992, 1997, and 2002.

In this paper, we describe our analyses of the relationships between known risk factors for diabetes, as well as between dioxin and diabetes. Henriksen and coworkers first reported an association between increasing blood lipid TCDD and diabetes prevalence in the Ranch Hands[4]. However, as the IOM noted, this apparent relationship "is difficult to understand, however, given that the diabetes rates in the comparison subjects were as high as in Ranch Hand Veterans despite the much lower dioxin levels in the comparison group"[1]. Longnecker and Michalek reported that diabetes increased with increasing dioxin serum levels in the Comparisons as well[5]. In a subsequent analysis, Michalek and Ketchum divided both populations into quintiles based on dioxin serum levels[6]. They found dose responses in both populations, but at different dioxin serum levels. Diabetes prevalence was 26% in the fifth (i.e., highest-exposed) quintile of Comparisons and 25% in the fifth quintile of Ranch Hands. However, the serum levels of dioxin differed significantly: the fifth quintile of Comparisons ranged from 6 to 55 ppt dioxin, whereas the fifth quintile of Ranch Hands from 36 to 618 ppt dioxin. We believe that these findings warrant further investigation of the association between Type II diabetes and dioxin.

Materials and Methods

Air Force researchers overseeing the AFHS provided us with study data regarding age, race, length of tour of duty, start and end dates for tour of duty, family history of diabetes, serum dioxin levels, changes in body weight, body mass index, percent body fat, severity of diabetes, and fasting glucose and insulin measurements in Comparisons

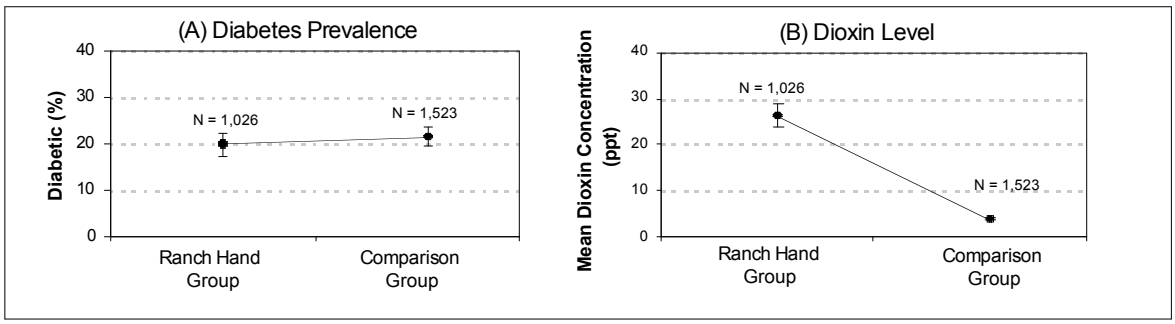
and Ranch Hands. The data set included information for 1026 Ranch Hands and 1523 Comparisons. All personal identifying information was excluded from the data set. Serum dioxin levels were determined in 1987 (or in 1992 or 1997 for veterans whose dioxin levels had not been measured previously or had not been previously quantifiable). Diagnosis of Type II diabetes was based on either 1) a self-report of physician-diagnosed diabetes at any interview with subsequent verification based on review of medical records, or 2) a postchallenge glucose of ≥200 mg/dL in 1992[5].

We evaluated the relationship between diabetes prevalence and various potential predictor variables of diabetes including group membership (Ranch Hand or Comparison), TCDD serum levels, age in 2002, BMI at the end of a qualifying tour, length of a qualifying tour, year when the qualifying tour started, family history of diabetes, race, and occupation. Estimates of Pearson correlation coefficients of diabetes prevalence and predictor variables were used to identify significant correlations between diabetes prevalence and the variables and significant correlations among the variables. These correlation coefficients were estimated for the Ranch Hand and Comparison groups combined and variables that were significantly correlated with diabetes prevalence were then graphed to evaluate the relationship further. The continuous predictor variables (e.g.,age, BMI, serum dioxin levels) were categorized by their quintiles for the Ranch Hand and Comparison groups separately to evaluate their relationship with diabetes prevalence.

Results and Discussion

The results of comparing diabetes prevalence and serum dioxin levels in the Comparisons and Ranch Hands are presented in Figure 1. Diabetes prevalence in the two groups is similar, around 20 percent, despite the significantly higher mean TCDD serum in the Ranch Hands.

Figure 1: Comparison of diabetes prevalence (A) and dioxin level (B) by group

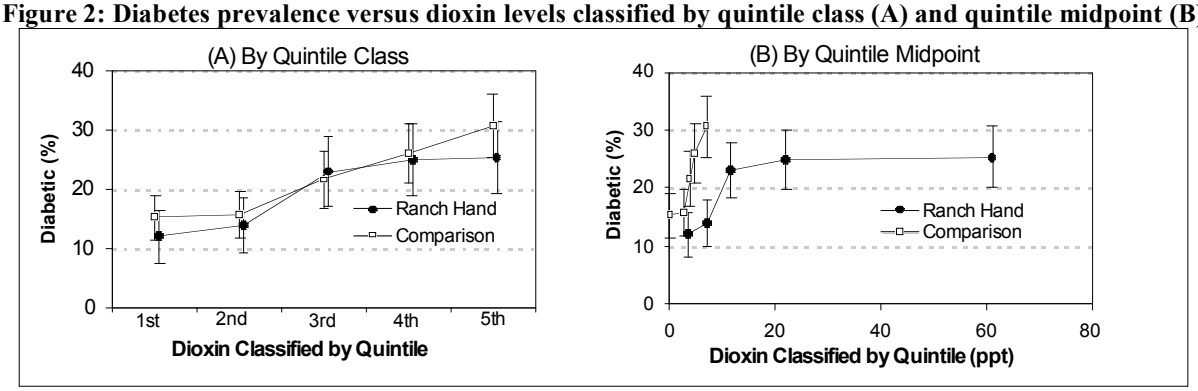


Based on the Pearson correlation coefficients, diabetes prevalence was significantly ($p<0.05$) correlated with family history of diabetes, dioxin serum levels, BMI at the end of qualifying tour, race, and age as of 2002 (data not shown). However, dioxin serum levels, BMI, and age were also significantly ($p<0.05$) correlated with each other as well. The intercorrelations among these predictor variables make it unclear whether diabetes prevalence is associated with dioxin serum levels or that the apparent association results from correlations of dioxin serum levels with BMI and age.

In Figure 2(A), diabetes prevalence is plotted against dioxin serum level based on the quintiles of the Ranch Hands and Comparisons separately. In both groups, diabetes prevalence increases with dioxin serum level. Remarkably, dioxin serum levels differ significantly between the groups. For example, the dioxin levels for the Ranch Hands in the 4th quintile (serum levels between the 60th to the 80th percentile) range from 16.5 to 35.8 ppt, while the TCDD levels for the Comparisons 4th quintile are lower, ranging from 4.4 to 5.7 ppt. In contrast, the diabetes prevalence for the 4th quintiles for the Ranch Hands and the Comparisons are similar, 25% and 26%, respectively. If diabetes

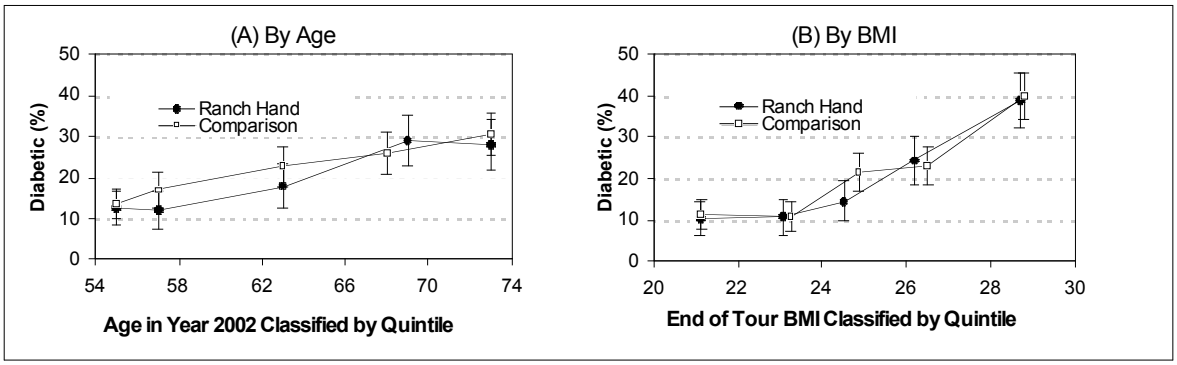
prevalence was related to dioxin serum levels, diabetes prevalence would be expected to increase with increasing dioxin levels regardless of the group being evaluated. However, as seen in Figure 2, this is not the case.
Figure 2(B) also shows the difference in relationships between dioxin serum levels and diabetes in the Comparisons and Ranch Hands. When plotted by quintile midpoint, the diabetes prevalence in the Comparisons occurs at a mean body burden of about 6 ppt dioxin (the fifth quintile of Comparison body burden). The prevalence of diabetes in the Comparisons was higher than the prevalence observed at the same serum level in the Ranch Hands. It is also higher than the prevalence seen at any quintile in the Ranch Hands, even though the mean serum dioxin levels are much higher.

Figure 2: Diabetes prevalence versus dioxin levels classified by quintile class (A) and quintile midpoint (B)



While the relationship between diabetes prevalence and dioxin serum levels is not consistent between the Ranch Hand and Comparison groups, the relationships between age as of 2002 and diabetes prevalence and between BMI measured at the end of a qualifying tour of duty and diabetes prevalence are consistent (Figures 3 (A) and (B)). Diabetes prevalence increases with increasing age and higher BMIs in both groups.

Figure 3: Diabetes prevalence versus age (A) and BMI (B) classified by quintile



These results indicate a complex relationship between dioxin levels and other risk factors for diabetes. In both the Comparisons and Ranch Hands, men with higher dioxin levels are more likely to be older and have higher BMIs, both risk factors for diabetes. Additional research is underway to better understand the co-linearity of age, BMI, and other possible predictors of diabetes risk with dioxin levels.

Acknowledgements
We would like to thank the Air Force for providing us with this data and are grateful for the peer-review provided by the AFHS researchers. Funding for the analyses described in this paper was provided in part by Southwire, Inc. Additional funding was provided by ChemRisk, Inc.

References

1. IOM (Institute of Medicine). 2000. *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*. Washington, D.C.: National Academy Press.
2. Steenland, K., Piacitelli, L., Deddens, J., Fingerhut, M., and Chang, LI. 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin . *J. Nat. Cancer Instit*, 91(9):779-786.
3. Wolfe, WH, Michalek, JE, Miner, JC, Rahe, A., Siklva, J, Thomas, WF, Grubbs, WD, Lustik, MB, Karrison, TG, Roegner, RH, and Williams, DE. 1990. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. *JAMA*. 264:1824-1831.
4. Henriksen, G.L., N.S. Ketchum, J.E. Michalek, and J.A. Swaby. 1997. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. *Epidemiology 8*:252-258.
5. Longnecker, M.P. and Michalek, JE. 2000. Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background levels of exposure. *Epidemiology 11*:44-48
6. Michalek, J.D. and N.S. Ketchum. 2002. Diabetes and dioxin in Air Force Health Study participants. Typescript of paper presented to the Department of Health and Human Services, Ranch Hand Advisory Committee, Rockville, MD., April 23, 2002.