Air Force Health Study

An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides

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SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) This report presents the results of the serum dioxin analysis of the Air Force Health Study 1987 examination cycle. The purpose of the study is to determine whether long-term health effects are associated with serum dioxin levels for the participants in the study. For each health effect variable, analyses were performed to evaluate the relationships with initial serum dioxin (extrapolated from a first-order pharmacokinetics model); current serum dioxin and time since tour; and categorized current dioxin levels (providing contrasts of Ranch Hands with specified current dioxin levels versus Comparisons with background levels). Significant associations between serum dioxin and several lipid-related health indices were found in these analyses. Specifically, significant associations with dioxin were found for diabetes, percent body fat, cholesterol, HDL, and cholesterol-HDL ratio. Other variables, such as the spirometric indices in the pulmonary assessment and benign systemic neoplasms (over 70% were lipomas) in the malignancy assessment, showed significant associations that may be related to the body fat results. These findings and their possible relationship to dioxin elimination will be explored in future examination cycles. Other health variables revealed no patterns within or across clinical assessments that were indicative of a health detriment due to dioxin.

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An Epidemiologic Investigation of
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EPIDEMIOLOGY RESEARCH DIVISION
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NOTICE

This report presents the results of analyses comparing the serum dioxin assays with physical examination data collected in 1987. This serum dioxin report is an addendum to the Ranch Hand versus Comparison group contrasts contained in the 1987 examination report published in February 1990. That report was the third in a series of epidemiologic studies to investigate the health effects in Air Force personnel following exposure to herbicides. The results of preceding studies (the 1982 Baseline and 1985 examinations) were presented in the Baseline Morbidity Study Results (February 1984) and the Air Force Health Study First Followup Examination Results (October 1987). Given the relationship of the serum dioxin analyses to the previous studies, portions of these earlier documents have been reproduced or paraphrased in this report. The purpose of this notice is to acknowledge the authors of these documents and to refer the reader to the 1987 examination report for additional background details regarding this study. No further references are made.

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EXECUTIVE SUMMARY

SERUM DIOXIN ANALYSIS OF THE 1987 AIR FORCE HEALTH STUDY EXAMINATIONS

This publication is the fourth morbidity report resulting from the Air Force Health Study (AFHS), an epidemiologic investigation of the possible association between occupational exposure to Herbicide Orange (and its dioxin contaminant) and adverse health experienced by Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971. A Comparison group was formed from Air Force veterans who flew or maintained C-130 aircraft in Southeast Asia during the same time period. The 1982 Baseline examination, summarized in the first report, was followed by additional studies in 1985 and 1987. Additional evaluations are planned for 1992, 1997, and 2002.

The 19 chapters of this report present conclusions drawn from statistical analyses of approximately 300 health-related endpoints in 12 clinical areas: general health, malignancy, neurology, psychology, gastrointestinal, dermatology, cardiovascular, hematology, renal, endocrine, immunology, and pulmonary. The analyses focused on dioxin measurements in serum collected from 1,670 participants as part of the 1987 examination.

This report summarizes the first large-scale study of dose-response effects based on an accurate measurement of current dioxin levels. This investigation is an important enhancement of the AFHS and supplements previous AFHS reports, which focused on group contrasts between exposed (Ranch Hand) and unexposed (Comparison) cohorts.

Three statistical models were used to evaluate associations between the health of study participants and their serum dioxin levels:

- Model 1: Estimated initial dioxin levels, using Ranch Hand participants only
- Model 2: Current serum dioxin levels and time since military service in Vietnam, using Ranch Hand participants only
- Model 3: Categories of current dioxin levels, using both Ranch Hand and Comparison participants.

Analyses based on model 1 depend directly on first-order kinetics and a constant dioxin decay rate, while those based on model 2 assume nothing about dioxin elimination other than that Ranch Hands were exposed in Vietnam and that their body burdens have decreased in an unspecified manner over time. All health data were analyzed using both of these models to reduce the likelihood that an effect would be missed because of incorrect assumptions regarding dioxin elimination. Models 1 and 2 were implemented under two assumptions—minimal and maximal. The minimal assumption included only Ranch Hands with current dioxin levels above 10 parts per trillion (ppt) (n=521); the maximal assumption expanded the analysis to include all Ranch Hands with current dioxin levels above 5 ppt (n=742).

In addition, model 3, using both Ranch Hands and Comparisons, assessed the health consequences of current dioxin levels above background. This assessment required no assumptions about when or how increased dioxin body burdens were attained.

Statistical analyses were often applied to clinical endpoints in continuous (i.e., original measurement) and discrete (i.e., measurements grouped into categories based on abnormal levels) forms. Analyses were also performed to account for the effects that demographic and personal characteristics may have on the clinical measurements. Such analyses are termed "adjusted analyses."

The general health assessment found that higher levels of body fat and the erythrocyte sedimentation rate were significantly related to both the initial and current serum levels of dioxin. The findings for body fat are consistent with the association between dioxin and diabetes mellitus in the endocrine assessment and lipids in the gastrointestinal assessment. The sedimentation rate findings raise the possibility that a subtle, chronic inflammatory response may be related to higher levels of dioxin exposure.

The malignancy assessment determined that serum dioxin levels were not significantly associated with the incidence of skin neoplasms, except for an increase of basal cell carcinoma on sites other than the ear, face, head, or neck in Ranch Hand enlisted flyers. However, these results may be the result of a multiple-testing artifact, because they were not noted for the enlisted groundcrew who, as a group, had higher levels of serum dioxin than the enlisted flyers. Previous AFHS reports showed that the Ranch Hand group had a significantly increased risk of basal cell carcinoma relative to the Comparison group; however, the skin neoplasm findings in this report did not support a positive dose-response relationship. The serum dioxin analyses detected significantly increased risks of benign, but not malignant, systemic neoplasms (approximately 75% of the benign neoplasms in Ranch Hands and 70% in Comparisons were lipomas). There was one verified case of non-Hodgkin's lymphoma in a Ranch Hand at the 1987 examination.

The neurological analyses revealed no consistent evidence to indicate that dioxin was associated with neurological disease. The adjusted analyses for the verified neurological disorders were not significant. Dioxin was found to be significantly associated with coordination and a central nervous system index, but cranial nerve function and peripheral nerve status were not associated with dioxin.

Higher serum dioxin levels were unrelated to verified psychological and reported sleep disorders. Results of the two clinical psychological tests (the Symptom Check List-90-Revised [SCL-90-R] and the Millon Clinical Multiaxial Inventory [MCMI]) were inconsistent. Most of the adjusted results for the SCL-90-R variables were not significant. Many of the adjusted MCMI results were significant, but substantial overlap and correlation between test scales of the MCMI limit the clinical importance of these statistical differences.

The serum dioxin levels showed no association with verified liver diseases. However, the laboratory results showed a consistent pattern suggestive of a subclinical effect on lipid metabolism, possibly related to the positive association between dioxin and body fat observed in the general health assessment.

Dermatologic endpoints were not consistently associated with dioxin concentrations. For Ranch Hands with a later tour of duty in Vietnam (time since tour≤18.6 years), there were significant or marginally significant positive associations between current levels of dioxin and post-Southeast Asia acne and several of the other acne-related physical examination variables. However, the corresponding adjusted relative risks for Ranch Hands with an early tour (time since tour>18.6 years) were not significant or were significantly less than 1.

The cardiovascular findings offered no consistent evidence of an adverse dioxin effect among nondiabetics. There was a significantly increased risk of essential hypertension for Ranch Hands in the high current dioxin category (>33.3 ppt) relative to Comparisons in the background category (≤10 ppt) when the effect of body fat was not considered. By contrast, the analyses of verified heart disease (excluding essential hypertension) found that the adjusted relative risk was significantly less than 1 for Ranch Hands in the high current dioxin category. The analyses of systolic blood pressure and diastolic blood pressure in their continuous forms found that the adjusted mean level for both variables was significantly higher for Ranch Hands in the high current dioxin category relative to Comparisons in the background category when the effect of body fat was not considered. However, the corresponding analyses of the percentage of participants with abnormally high systolic or diastolic blood pressures did not show an association with dioxin. The assessment of peripheral vascular function found significant associations between dioxin and decreases in the peripheral pulses.

The hematologic results revealed no evidence that overt hematopoietic toxicity was related to dioxin exposure. The white blood cell count revealed statistically significant associations consistent with a positive dose-response effect in all three models; consistently significant results were not found for the other variables. A significant increased risk of an elevated platelet count was found for Ranch Hands in the high current dioxin category relative to the Comparisons in the background category. These findings suggest the presence of a low-level, chronic inflammatory response related to higher levels of dioxin exposure.

The analyses did not indicate any relationship between renal health and dioxin. Under the maximal assumption (but not the minimal), the initial dioxin analyses found a significantly increased risk of urinary occult blood cells, but results were not significant for the other models. Statistically significant results were not noted for the other variables.

The endocrine assessment established a strong positive association between glucose intolerance and dioxin, but concluding that dioxin directly causes diabetes would be premature. The initial and current levels of serum dioxin both were associated significantly with an increased incidence of diabetes. Significant positive associations also were noted for the analyses of fasting glucose and 2-hour postprandial glucose. These findings may be related to the association between dioxin and body fat observed in the general health assessment. The basis of these relationships will be investigated during subsequent phases of this study.

Assessment of testicular size as evaluated at the physical examination revealed significant positive associations in all three models between serum dioxin and decreased size. The serum dioxin analyses did not reveal a significant association with abnormally low

levels of serum testosterone, but the analyses found a significant negative correlation with testosterone when the effect of body fat was not considered. The clinical meaning of these findings is unclear. The results for thyroid stimulating hormone and T_3 % uptake treated as continuous variables were consistent with subclinical decreases in thyroid function related to dioxin exposure. However, the corresponding analyses on the percentage of participants with abnormally high levels for these variables did not show an association with dioxin.

The immunologic assessment did not find any clinically significant alterations related to the current or initial levels of serum dioxin. An evaluation of immunoglobulins found a significant association between initial dioxin level and increased IgA levels, consistent with a subtle inflammatory response. The analyses of the other immunoglobulins (IgG and IgM) did not indicate the presence of any dioxin-related effects. Analyses for the other laboratory variables revealed several statistically significant findings, but they either were internally inconsistent or were not in a direction expected in an impaired immune system. Serum dioxin was not significantly associated with delayed hypersensitivity skin-test response. The previous report of the 1987 examination data had showed that significantly more Ranch Hands had possibly abnormal skin-test reactions than Comparisons. These new analyses suggest that the previously noted group difference may not be related to dioxin.

Analyses of the pulmonary disease history found no evidence of a dioxin relationship for the five respiratory illnesses studied. However, based on physical examination results, the risk of thorax and lung abnormalities for Ranch Hands in the high current dioxin category was significantly increased relative to Comparisons in the background category. Abnormal spirometric measurements were often significantly associated with dioxin levels, but the differences in the mean levels between high- and low-exposed participants were not clinically important. These findings may be related to the association between dioxin and body fat noted in the general health assessment because obesity is known to cause a reduction in vital capacity. These relationships will be investigated during subsequent phases of the study.

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is difficult because Ranch Hand and ground troop exposure situations were quite different. Based on serum dioxin testing results done by others, nearly all ground troops tested currently have levels of dioxin similar to background levels. Even the ground troops who served in herbicide-sprayed areas of Vietnam had current levels indistinguishable from those of men who never left the United States. The AFHS subgroup most like the ground troops in terms of current dioxin levels is those Ranch Hands who currently have background levels of dioxin (designated as the "unknown" category in the model 3 analyses). Therefore, if the results of the AFHS are applied to the general population of Vietnam veterans, the focus should be on the unknown Ranch Hand versus background Comparison contrasts. However, extrapolating the results of these analyses to Vietnam veterans should still be made cautiously. In general, the adjusted model 3 analyses found that Ranch Hands in the unknown category did not show a significant health detriment relative to Comparisons in the background category.

Small but significant mean differences in a continuously measured health variable when there are no corresponding differences in the percentage of abnormal tests are difficult to assess in any study. For example, in the discrete analysis of serum testosterone, abnormally

low levels were not significantly associated with dioxin. However, the adjusted continuous analysis found a significant negative association between dioxin and testosterone when the effect of body fat was not considered. The continuous and discrete analyses of systolic and diastolic blood pressure also exhibited conflicting results. Observations such as these could represent an early subclinical effect, or they could be the result of a multiple testing artifact. Significant trends in the mean with increasing levels of dioxin are interpreted as a dioxin-related effect if a corresponding trend is seen in the proportion above or below the normal range. These observations emphasize the importance of continued evaluation of a broad spectrum of health endpoints in the subsequent physical examination phases of the AFHS.

The serum dioxin analyses in this report detected significant associations with lipid-related health indices. In particular, diabetes and body fat were associated positively with dioxin. Cholesterol, high-density lipoprotein (HDL), cholesterol-HDL ratio, and 2-hour postprandial glucose also were associated significantly with dioxin. Erythrocyte sedimentation rate, white blood cell count, platelet count, and IgA were positively associated with dioxin, suggesting the presence of a chronic dose-related inflammatory response. Other variables, such as the spirometric indices in the pulmonary assessment and benign systemic neoplasms in the malignancy assessment showed significant associations with dioxin that may be related to body fat (approximately 75% of the benign neoplasms in Ranch Hands and 70% in Comparisons were lipomas). These findings and their possible relationship to dioxin elimination will be explored in future examination cycles. The serum dioxin analyses also revealed a significant positive association between dioxin and decreased testicular size, but the importance of this finding is unclear (fertility and other reproductive outcomes will be assessed in a separate report). Results for other variables revealed no consistent pattern, within or across clinical areas, indicative of a health detriment due to dioxin exposure.

In summary, many of the findings in this report reveal a consistent relationship between dioxin and body fat. Two hypotheses may explain the observed relationships. In one, dioxin could cause an increase in body fat, or the level of body fat could influence the dioxin decay rate, which in turn alters physiologic outcomes, such as blood pressure, serum lipid alterations, and blood sugar levels. An alternative hypothesis involves dioxin as a direct cause of two or more of the observed endpoints, including body fat. Whether dioxin causes these observed effects directly or is a step in an extended causal pathway cannot be determined from these data. Additional analyses following the physical examination scheduled for 1992 may help resolve this question.

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