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AIR FORCE HEALTH STUDY

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

SAIC Team
William D. Grubbs, Ph.D.
Michael B. Lustik, M.S.
Amy S. Brockman, M.S.
Scott C. Henderson, M.S.
Frank R. Burnett, M.S.
Rebecca G. Land, M.S.
Dawn J. Osborne, M.S.
Vanessa K. Rocconi, B.S.
Margaret E. Schrieber, B.A.
David E. Williams, M.D., SCRF

Air Force Team
Col William H. Wolfe, M.D., M.P.H.
Joel E. Michalek, Ph.D.
Col Judson C. Miner, D.V.M., M.P.H.
Col Gary L. Henriksen, M.D., M.P.H.
Lt Col James A. Swaby, Ph.D., B.C.E.

Project Manager: Manager E.B. Owens, Ph.D.
Statistical Task Manager: W.D. Grubbs
SAIC Editor: Jean M. Ault, B.A.

Program Manager: R.W. Ogershok

SCIENCE APPLICATIONS INTERNATIONAL
1710 Goodridge Drive
McLean, Virginia 22102

in conjunction with:

SCRIPPS CLINIC & RESEARCH FOUNDATION,
LA JOLLA , CALIFORNIA

NATIONAL OPINION RESEARCH CENTER,
CHICAGO, ILLINOIS

EPIDEMIOLOGIC RESEARCH DIVISION
ARMSTRONG LABORATORY
HUMAN SYSTEMS CENTER (AFMC)
BROOKS AIR FORCE BASE, TEXAS 78235

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6. AUTHOR(S)
W.D.Grubbs,SAIC;W.H.Wolfe,J.E.Michalek,USAF;D.E. Williams,SCRF;M.B.Lustik,A.S.Brockman,S.C.Henderson,F.R. Burnett,R.J.Land,D.j.Osborne,V.K.Rocconi,M.E.Schreiber, SAIC;J.C.Miner,G.L.Henriksen,J.A.Swaby,USAF

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Science Application International Corporation (SAIC)
1710 Goodridge Drive
McLean Virginia 22102

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Epidemiologic Research Division
Armstrong Laboratory
Human Systems Center
2510 Kennedy Circle
Brooks Air Force Base, Texas 78235-5119

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13. ABSTRACT *(Maximum 200 words)*

This report represents the results from an epidemiologic study to determine whether adverse health effects attributable to Herbicide Orange exist in Vietnam veterans who participated in Operation Ranch Hand. Data were analyzed for 12 clinical areas. The analysis focused on group differences between the exposed (Ranch Hand) and unexposed (Comparison) cohorts, as well as on the association of each health-related endpoint with extrapolated initial and current serum dioxin levels. Findings in this report reveal a consistent relationship between dioxin and body fat that was initially noted in the analysis of the 1987 examination results. Cholesterol and the cholesterol to HDL ratio were found to be associated with current serum dioxin levels. Evidence for a possible association between glucose intolerance, impaired insulin production, and dioxin exposure was revealed, but cause and effect remain to be established. Also revealed was a significant association between selected peripheral pulses and dioxin exposure, and a significant difference in self-perceived health status between Ranch Hands and Comparisons (although possible due to bias). Other health endpoints revealed no consistent patterns within or across clinical areas that were suggestive of health detriment due to dioxin exposure

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Epidemiologic Research Division
Armstrong Laboratory
Human Systems Center (AFMC)
Brooks Air Force Base, Texas 78235

NOTICE

This report presents the results of the 1992 followup of the Air Force Health Study, the fourth examination in a series of epidemiologic studies to investigate the health effects in Air Force personnel following exposure to herbicides. The results of the 1982 Baseline study, the 1985 followup study, and the 1987 followup study were presented in four reports: the Baseline Morbidity Study Results (24 February 1984), the Air Force Health Study First Followup Examination Results (15 July 1987), the Air Force Health Study 1987 Followup Examination Results (16 January 1990), and the Air Force Health Study Serum Dioxin Analysis of 1987 Examination Results (7 February 1991).

Given the relationship of the 1992 followup to the previous studies, portions of these documents have been reproduced or paraphrased in this report. In addition, portions of the Air Force Health Study Statistical Plan for the 1992 Followup (23 December 1993) have been used in the development of this report. The purpose of this notice is to acknowledge the authors of these previous study reports and documents.

EXECUTIVE SUMMARY

1992 FOLLOWUP EXAMINATION REPORT

The Air Force Health Study (AFHS) is an epidemiologic investigation to determine whether adverse health effects exist in Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971, and whether these adverse health effects can be attributed to occupational exposure to Herbicide Orange (and its dioxin contaminant). A comparison group was formed from Air Force veterans who flew or maintained C-130 aircraft in Southeast Asia (SEA) during the same time period as those who served in the Ranch Hand units. The Baseline study was conducted in 1982, and followup studies were performed in 1985, 1987, and 1992. Additional evaluations are planned for 1997 and 2002. This report presents the results from the statistical analyses of the data from the 1992 followup examination.

In the Baseline study, each living Ranch Hand was matched with a randomly selected Comparison based on age, race, and military occupation. At each followup study, noncompliant Comparisons were replaced from the set of living Comparisons, matched by age, race, military occupation, and self-perception of health. Participation throughout each examination cycle and at the 1992 followup examination remained high. Eighty-three percent (n=952) of the 1,148 eligible Ranch Hands and 77 percent (n=912) of the 1,191 eligible Original Comparisons participated in the 1992 followup examination and questionnaire process. Ninety-one percent of living Ranch Hands and 92 percent of living Comparisons who were fully compliant at the Baseline examination returned for the 1992 followup examination. In total, 2,233 study subjects (952 Ranch Hands and 1,281 Comparisons) participated in the 1992 followup examination.

This report presents conclusions drawn from the statistical analyses of more than 300 health-related endpoints in 12 clinical areas: general health, neoplasia, neurology, psychology, gastrointestinal, dermatology, cardiovascular, hematology, renal, endocrine, immunology, and pulmonary. Data were collected from medical records review, previous examination cycles, and the physical and laboratory examinations and questionnaire administered at the 1992 followup. The analyses focused on group differences between the exposed (Ranch Hands) and unexposed (Comparisons) cohorts, as well as on the association between serum dioxin levels and each health-related endpoint among the Ranch Hands.

Six statistical models were used to evaluate the relationship between the health status of study participants and their dioxin exposure. The first model (Model 1) examines contrasts between Ranch Hands and Comparisons using group as a proxy for exposure and does not incorporate serum dioxin measurements. However, it is assumed in this model that all Ranch Hands were exposed and all Comparisons were not. Each of the following five models incorporates estimates of serum dioxin in either initial or current form. Current serum dioxin is measured as of the 1987 examination. Initial serum dioxin is extrapolated from the current serum dioxin measurement to time of duty in SEA. The second model (Model 2) examines estimated initial serum dioxin levels, extrapolated from current serum dioxin measurements and assuming first-order kinetics and a constant dioxin decay rate. The

third model (Model 3) categorizes the Ranch Hand cohort according to serum dioxin levels and contrasts each Ranch Hand category with the Comparisons having background serum dioxin levels. The remaining three models (Models 4, 5, and 6) use three different measures of current serum dioxin: lipid-adjusted, whole-weight, and whole-weight adjusted for total lipids respectively. These three models assume nothing about serum dioxin elimination, but may not be good surrogates for exposure if elimination rates differ among individuals.

In the General Health Assessment, the Ranch Hand and Comparison cohorts seem comparable by all objective indices; however significant group differences, although possibly biased, were evident in self-perceived health status. Participants who knew they possessed an elevated dioxin level or whose occupation implied a greater risk for exposure may consciously or subconsciously have perceived their health to be poorer than their Comparisons. Percent body fat and sedimentation rate displayed significant associations with current serum dioxin levels, but the biological significance is uncertain.

In the Neoplasia Assessment, Ranch Hands had a slightly higher prevalence of benign and malignant skin neoplasms than Comparisons, as in previous examinations, but these group differences are not statistically significant for the 1992 study, although they were significant in previous examinations. Consistent with all previous examinations, none of the analyses revealed any significant group differences in the prevalence of systemic malignancies or an increased risk of any systemic malignancy in association with serum dioxin levels in Ranch Hands. At the end of a decade of surveillance, Ranch Hands and Comparisons appear to be at equal risk for the development of all forms of neoplastic disease, and there is no evidence to suggest a positive dose-response relationship between body burden of dioxin and neoplastic disease.

In the Neurological Assessment, the prevalence of historical neurological disorders was similar in the Ranch Hand and Comparison cohorts. In the analyses of the physical examination variables, Ranch Hand enlisted groundcrew, the occupational category with the highest levels of dioxin, had significantly more cranial nerve index abnormalities than Comparison enlisted groundcrew, but there was no evidence of a dose-response relationship in the serum dioxin analyses. Based upon indices aggregating dysfunction of various peripheral nerves, and upon the results of vibrotactile testing, a subclinical neuropathic effect may be developing in Ranch Hand veterans, although it has not manifested itself in any increase in clinical pathology and the results are not statistically significant. The analyses employing current serum dioxin yielded inconsistent results. A positive association was noted in relation to the cranial nerve motor variable smile and the peripheral nerve variables pin prick and patellar reflex, while inverse dose-response patterns were defined for smell and the Babinski reflex. In summary, the Neurological Assessment found the prevalence of neurological disease to be comparable between the Ranch Hand and Comparison cohorts, and showed no consistent evidence of a dose-response effect with serum dioxin levels.

In the Psychological Assessment, Ranch Hands exhibited higher psychological distress than Comparisons for the anxiety, obsessive-compulsive behavior, paranoid ideation, somatization, and global severity index scores in the Symptom Check List-90-Revised (SCL-90-R) inventory. A significant group contrast also was exhibited for the verified condition of other neuroses. However, when Ranch Hands were categorized according to

serum dioxin levels, significant group differences were found only in the contrasts of Ranch Hands having background serum dioxin levels versus Comparisons, and the serum dioxin analyses did not support a dose-response relationship. The differences in the Ranch Hand and Comparison cohorts together with the lack of an effect attributable to dioxin suggest that factors other than dioxin exposure continue to contribute to a relatively small, but notable, number of Ranch Hand SCL-90-R test score abnormalities. The possibility that a small subset of physically or psychologically vulnerable Ranch Hands may have suffered psychological injury in the context of their exposure to dioxin cannot be definitively ruled out at this time.

In the Gastrointestinal Assessment, the laboratory analyses revealed no biologically significant differences between the Ranch Hand and Comparison cohorts. The serum dioxin analyses indicated that estimated initial dioxin exposure was generally not associated with historical liver disorders or laboratory measurements. However, current dioxin levels were highly associated with lipid-related health indices, as well as some of the hepatic enzymes and proteins. Alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), serum triglycerides, and serum cholesterol revealed significant positive associations with current serum dioxin levels and a negative association was revealed between current serum dioxin and the cholesterol to high-density lipoprotein (HDL) cholesterol ratio. Analyses of the historical and clinical examination variables revealed no evidence of any overt hepatic disease related to the current body burden of dioxin. However, the elevated liver function tests in relation to current dioxin, though not clinically significant on an individual basis, are indicative of the presence of hepatocellular toxins as the result of dioxin exposure and may cause liver damage in conjunction with other toxins such as alcohol consumption. In summary, the gastrointestinal data reflect no apparent increase in organ-specific morbidity in Ranch Hands relative to Comparisons, nor do they reflect an association with serum dioxin levels. Although a subclinical dioxin effect on lipid metabolism cannot be excluded, some of the results may be related in part to body habitus and percent body fat.

The Dermatologic Assessment showed no significant differences between Ranch Hands and Comparisons. The analyses of extrapolated initial and current serum dioxin did not provide evidence of a dose-response effect. However, Ranch Hands with current serum dioxin levels above background level demonstrated a lower occurrence of an abnormal dermatology index than Comparisons, and the dermatology index exhibited a significant negative association with current serum dioxin in Ranch Hands. In the four examination cycles to date (Baseline, 1985, 1987, and 1992), no cases of chloracne have been detected. Therefore, there is no consistent evidence to suggest an adverse dioxin effect on the dermatologic system at doses received by the Ranch Hand cohort in SEA.

In the Cardiovascular Assessment, the verified historical indices were similar in Ranch Hands and Comparisons. Several of the electrocardiograph (ECG) indices, including right bundle branch block (RBBB), non-specific ST- and T-wave changes, and arrhythmias, displayed significant positive associations with current serum dioxin levels, but none of these endpoints also displayed a group difference between Ranch Hands and Comparisons to confirm the dose-response relationship. In the longitudinal analyses of the pulses endpoints, Ranch Hands were slightly more likely than Comparisons to develop peripheral pulse deficits over time, although there was no consistent evidence of a dose-response relationship from the

analyses using calculated initial serum dioxin levels as a measure of exposure. Ranch Hands were found to be at slightly greater risk than Comparisons for the development of selected peripheral pulse deficits which, based on the analysis of hypertension, ST- and T-wave changes, and the increase in the number of deaths caused by diseases of the circulatory system among Ranch Hand nonflying enlisted personnel, suggests some effects from dioxin.

In the Hematologic Assessment, only platelet count exhibited significant associations with the herbicide exposure indices. Ranch Hands in the enlisted flyer and enlisted groundcrew categories possessed statistically significant higher mean platelet counts than Comparisons. Ranch Hands with high extrapolated initial dioxin levels also had significantly greater mean platelet count measurements than Comparisons. These results are consistent with those from the 1987 examination, but the biological significance is uncertain. Based on the analyses of white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR), and total platelet count, there is no longer evidence that a subclinical inflammatory reaction may exist in Ranch Hands, as was conjectured from previous examinations. There is no evidence from the current study to suggest an association between hematopoietic toxicity and prior dioxin exposure.

In the Renal Assessment, no significant group differences or association with serum dioxin were noted in the history of urinary tract disease. Although the prevalence of microhematuria (urinary red blood cell (RBC) counts) was similar in both groups, Ranch Hands with the highest levels of extrapolated initial serum dioxin had a significantly higher prevalence of microhematuria than Comparisons, and the analyses employing current serum dioxin yielded results consistent with a dose-response effect. However, the longitudinal analyses indicated that the prevalence of microhematuria has decreased in the Ranch Hand cohort at each of the last two cycles. The Ranch Hands most highly exposed to dioxin, the enlisted groundcrew, had twice the prevalence of pyuria as Comparisons, but the similar prevalence in Ranch Hands with low and high levels of serum dioxin does not support a dose-response effect. In general, no consistent evidence for any detriment to the renal system, with the possible exception of hematuria, was found to be related to the body burden of dioxin.

In the Endocrine Assessment, analyses of thyroid functions did not reveal significant differences between the Ranch Hand and Comparison cohorts, and the prevalence of diabetes mellitus in the two groups was not significantly different. Consistent with the 1987 examination, a significant inverse dose-response relationship between current serum dioxin and total serum testosterone in Ranch Hands was detected, but the clinical significance is uncertain. Significant results relating to the development of diabetes were limited to the current serum dioxin analyses. Fasting glucose in diabetics and 2-hour postprandial glucose in nondiabetics were positively associated with current serum dioxin levels and fasting glucose in nondiabetics was inversely associated with current serum dioxin. Similarly, though not statistically significant, serum insulin was inversely associated with current dioxin in diabetics and positively associated with current dioxin in nondiabetics. Although cause and effect remain to be established, these results imply a possible association between dioxin exposure and glucose metabolism and insulin production in diabetics.

The Immunologic Assessment did not reveal any relationship between dioxin exposure and physiologic abnormalities that could be considered clinically significant. The mouse stomach kidney (MSK) smooth muscle antibody, rheumatoid factor, and the lupus panel summary index displayed inverse associations with dioxin exposure, but did not support a dose-response relationship. A marginally significant positive association was found between serum IgA concentrations and extrapolated initial dioxin levels which, coupled with continuity over time, suggests a possible relationship that should be further evaluated because elevated IgA may indicate liver disease, chronic inflammation, or selective immune dysfunction.

The Pulmonary Assessment revealed no consistent evidence of an increased prevalence of pulmonary disease in the Ranch Hand cohort relative to the Comparison cohort or in relation to body burden of dioxin. Of interest, but of uncertain cause, Ranch Hand enlisted flyers appeared to be at an increased risk, relative to Comparisons, with respect to the history of bronchitis and thorax and lung abnormalities, but there was no evidence from the serum dioxin analyses to confirm a dose-response relationship. The ratio of observed FEV_1 to observed FVC in Ranch Hands revealed a significant relationship with initial dioxin that was consistent with a dose-response effect, but the changes in the ratio were slight and of doubtful physiologic significance.

Based on the statistical findings of the 1992 examination and subject to interpretive considerations and clinical evaluation, the following conclusions have been drawn.

1. Glucose Intolerance: The results indicate a statistically and potentially clinically significant association between serum dioxin and glucose intolerance. This association exhibits a dose-response relationship, and is present both for non-diabetic individuals (as manifested by elevated insulin levels) and diabetic individuals (as manifested by increased prevalence and severity of diabetes and decreased age of onset). This association was found with type II diabetes only. This association was also present longitudinally and occurs in other epidemiological studies in addition to the AFHS.

2. Cardiovascular Mortality: There is a statistically significant increase in cardiovascular mortality in the most heavily exposed subgroup, the enlisted groundcrew. This association persists longitudinally throughout the three examination cycles. Inclusion of this group with lesser exposed Ranch Hand subgroups results in a statistically nonsignificant overall relative risk. Less clinically severe criteria for altered cardiac functions including ECG findings of prior myocardial infarction, non-specific ST- and T-wave changes, and RBBB displayed significant positive associations with dioxin, although these associations did not cause significant group differences between all Ranch Hands and all Comparisons. Peripheral vascular function variables displayed significant subgroup differences for both the enlisted groundcrew and the high current dioxin category in relation to the Comparisons. Both groups had a greater prevalence of new pulse deficits arising since the 1985 followup examination than did their Comparisons.

3. Serum Lipid Abnormality: There is a highly significant positive statistical association between dioxin and cholesterol, dioxin and triglycerides, and dioxin and the cholesterol-HDL ratio in most models using either current dioxin levels or dioxin levels

extrapolated to the end of the tour of duty in SEA. In such models, the correlation between HDL cholesterol and dioxin was highly significant and negative. These lipid findings were consistent with the 1987 findings, but were not consistent with the 1982 examination when serum cholesterol in Ranch Hands was significantly lower than in Comparisons.

4. Liver Enzymes: Both lipid-adjusted and whole-weight current dioxin showed elevated mean aspartate aminotransferase (AST), ALT, and GGT associations. For ALT and GGT, this association was highly significant. This association had not been present in previous examinations. Although these elevations were statistically significant, mean enzyme levels remained well within normal limits and the prevalence of abnormally elevated liver enzymes was not statistically increased. Thus, although this laboratory finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

5. Increase in IgA: A marginally significant increase in IgA with increased serum dioxin was found. This paralleled similar findings of increased IgA, first noted in the 1987 followup. Although this elevation was marginally significant, mean IgA levels remained well within normal limits, and the prevalence of significant abnormally elevated IgA was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

6. Decrease in Serum Testosterone: A statistically significant inverse effect was seen between total serum testosterone and current dioxin in Ranch Hands. This paralleled similar findings first noted in the 1987 followup. Although this decrease was statistically significant, mean serum testosterone levels remained well within normal limits, and the prevalence of abnormally low serum testosterone was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

7. Decrease in MSK and Lupus Panel Positives: Significant and marginally significant decreases in the prevalence of positive reactions to MSK, lupus, and rheumatoid factor tests in relation to dioxin were seen in the 1992 followup. When present, these tests are indicative of potential autoimmune disorders. Their absence is therefore not normally considered pathologic, but the decreased prevalence could nonetheless indicate some degree of immune suppression. More specific tests of immune suppression were not significantly associated with dioxin.

8. No Significant Difference in Incidence or Prevalence of Neoplastic Disease: It has been theorized that dioxin can act as either an inducer or promoter of neoplastic disease. A detailed analysis of all forms of neoplastic disease over the course of a decade show no significant group differences in the incidence of benign or malignant neoplasms, including those neoplasms most often associated with herbicide exposure in the Ranch Hand population (e.g., Hodgkin's Disease, non-Hodgkin's lymphoma, soft tissue sarcoma). In the 1992 followup, there was again no significant group differences. The marginally significant differences in site-specific incidence that were found, more often favored a decrease in relative risk associated with dioxin exposure rather than an increased risk. As previously stated, because of its size, this study does lack power to ascertain modest increases in relative risk for uncommon neoplasms. As the population continues to age, the combination

of an increase in background rate of neoplastic disease, increased time for latent effects of past exposure, and increased time of total exposure may combine to increase the power of this study to determine neoplastic effects.

In summary, glucose intolerance, serum lipid abnormality, and cardiovascular abnormality and mortality are areas demonstrating associations that, if causality were established, would represent the most important dioxin-associated health problems seen in the AFHS to date. These three areas appear to have the greatest magnitude of effect in terms of absolute increase in risk, in common areas known to contribute to years of potential life lost and to overall healthcare costs. Clearly, there are biological interrelationships among all three of these variables that will make the task of establishing causality, as well as establishing primary versus secondary causality, challenging. From a public health perspective, these three areas demand the greatest attention.

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U.S. Air Force Coinvestigators:

Vincent V. Elequin, Medical Records Administrator
Alton J. Rahe, GTI, Mathematical Statistician

Support in Conducting the Statistical Analysis:

Lisette R. Bergeron, SAIC
David Moore, SAIC
Lewis Pfister, SAIC
Dung B. Phan, SAIC
George Wilkie, SAIC

Data Management:

Jay Bankhead, SAIC Consultant
Brian A. Berling, SAIC
Erin Hammond, SAIC Consultant
Shaila Kennedy, SAIC
Norma Ketchum, Mathematical Statistician, USAF
Melissa Palco, SAIC Consultant
Barbara G. (Bonnie) Palmer, SAIC Task Manager
Lydia Sanchez, GTI, Programmer
Jacqueline Teague, SAIC Consultant
Laura Thomas, SAIC Consultant
Jane Tsui-Wu, GTI, Systems Analyst
J. Kevin Whiteman, SAIC
John R. Whiteman, M.D., SAIC

Conduct of the Medical Records Coding:

Annette F. Compton, MRT, USAF
Gregorio Faragoza, SAIC, Records Manager
Calvin E. Hollowman, MRT, USAF
Maricela Luna, MRT, USAF
T. Sgt. Carla Y. Luster, USAF
Earl A. Metts, MRT, USAF
A1c. Egon R. Wright Jr., USAF
Edward E. Zimmerman, ART, USAF

Air Force Onsite Monitors:

Col. Judson C. Miner, D.V.M.
Lt. Col. Susan B. Mitchell, B.S.C.
Maj. Ronald W. Stout, M.D.
Col. Ronald D. Warner, D.V.M.
Col. William H. Wolfe, M.D.

Conduct of the Physical Examinations and Preparation of the Clinical Interpretations:

Administration
Adele Ball, R.N.
Mary Ann Crawford, R.N.
Devin Thomas, M.T. (ASCP)
Cindy Wiesner, M.T.

Neurology
Maung H. Aung, M.D.
Donald J. Dalessio, M.D.
Shirley M. Otis, M.D.
Steven Poceta, M.D.
John S. Romine, M.D.
Jack C. Sipe, M.D.

Dermatology
Roger C. Cornell, M.D.
Gene Izuno, M.D.
Peter W. Simoneaux, M.D.

Psychology
Sharon Cummins, Ph.D.
L. Dee Jacobsen, Ph.D.
Myrna Roberts, Ph.D.
Betty Waldheim, Ph.D.

Internal Medicine
Jane Boyd, M.D.
Merritt L. Hougen, M.D.
Donald E. Kaufmann, M.D.
Anthony P. Moore, M.D.
J. Mark Roberts, M.D.
Stephen K. Sargeant, M.D.
Tonia Vyenielo, M.D.
David E. Williams, M.D.

Cardiology
Richard Kahler

Allergy
Sandra Christiansen, M.D.
David A. Mathison, M.D.
Ronald A. Simon, M.D.
Donald D. Stevenson, M.D.
Bruce Zuraw, M.D.

Pulmonary
Arthur Dawson, M.D.
Darlene Elias, M.D.

Radiology
Paul Garver, M.D.
Joanne Guy, M.D.
Sheldon A. Kleiman, M.D.
Harry Knowles, M.D.
Mohsin Saud, M.D.
Stanley G. Seat, M.D.
David Sobell, M.D.
Dennis W. Thurston, M.D.
James A. Usselman, M.D.
Vincent C. Vint, M.D.
Murray Warmath, M.D.
Jack Zyroff, M.D.

Audiology
Erin Gee, M.A., CCCA
Elizabeth LeBaron, M.S., CCCA
Carol Reiker, M.A., CCCA
Janis Ryan, M.A., CCCA

Dermatology Specimen Interpretations
David J. Bylund, M.D.
Max L. Elliott, M.D.
David J. Francis, M.D.
James H. Graham, M.D.
Nick Petirs, M.D.
Bruce A. Robbins, M.D.
Amy C. Stoloff, M.D.

Clinical Pathology Interpretations
William R. Dito, M.D.
Richard A. McPherson, M.D.
Bruce A. Robbins, M.D.

Questionnaire Administration and Scheduling:

Leslie Athey, NORC Task Manager
Lucian Chuchro, NORC
Barbara Cope, NORC
Ron Dorsey, NORC
Susan Drury, NORC
Julie Feldman, NORC
Marilyn Feldman, NORC
Thea Filson, NORC
Betsy Gates, NORC
Charlene Harris, NORC
Nicholas Holt, NORC
Yin Kean, NORC
Richard Kulka, NORC
Sylvia Martin, NORC
Cynthia Peters, NORC
Irene Reiman, NORC
Karen Sundstrom, NORC
Ruth Tearson, NORC
Dolores Wray, NORC

Logistical Arrangements:

Jaqueline P. Kirk, SAIC Task Manager

Editorial Support and Report Production:

Rose Marie Alequin, SAIC
Jean M. Ault, SAIC
Diane Brown, SAIC
Jennifer Chessman, SAIC
John Melton, SAIC Consultant
Meghan Schreiber, SAIC
Katherine Trotter, SAIC
Suzanne Wolfe, SAIC

Management and Quality Review:

Donna L. Bareis, Ph.D., SAIC
Stephen J. Dalich, Ph.D., SAIC
Richard W. Ogershok, USAF
Maurice E.B. Owens, Ph.D., SAIC
Robert A. (Rosie) Rosenberg, SAIC
Meghan Schreiber, SAIC
Wanda Thomas, SAIC
Peter Wise, SAIC

Contractual and Administrative Support:

Hollie N. Cake, SAIC
Maurice Donnell, SAIC
Jane L. Gabriel, SAIC
Tricia A. Graves, SAIC
John Olszyk, SAIC
Virginia Passon, Sec. USAF
Jeannete Ybarbo, GTI

Scientific Review Committee:

Earl P. Benditt, M.D., University of Washington School of Medicine
Turner Camp, M.D., Veterans of Foreign Wars
Capt. Ronald F. Coene, U.S. Public Health Service
Elissa A. Favata, M.D., Robert Wood Johnson Medical School
Michael Gough, Ph.D., Office of Technology Assessment
Robert W. Harrison, M.D., University of Rochester
Leonard T. Kurland, M.D., Mayo Medical School
Peter C. O'Brien, Ph.D., Mayo Medical School
Dolores C. Shockley, M.D., Meharry Medical College
Paul D. Stolley, M.D., University of Maryland School of Medicine
Dr. John F. Young, National Center for Toxicology Research/Food and Drug Administration

Support and Encouragement:

Ranch Hand Association Members

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All Study Participants

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CHAPTER 1

INTRODUCTION

This chapter briefly describes the background of the Air Force Health Study (AFHS) and provides an overview of the study design, the morbidity component, and the purpose and format of this report. Additionally, this chapter provides considerations that should be made when interpreting the results provided in this report.

BACKGROUND

In January 1962, President John F. Kennedy approved a program of aerial herbicide dissemination for the purpose of defoliation and crop destruction, in support of tactical military operations in the Republic of Vietnam (RVN). This program, code-named Operation Ranch Hand, dispersed approximately 19 million gallons of herbicides on an estimated 10 to 20 percent of South Vietnam (1,2) from 1962 to 1971. Of the 19 million gallons dispersed, approximately 11 million gallons were "Agent Orange," the primary defoliant of the six herbicides used in the program.

From the start, Operation Ranch Hand was scrutinized intensely due to the controversial nature of the program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The concerns were initially based on military, political, and ecological issues, but shifted to issues of health in 1977. Numerous claims of exposure to herbicides, particularly Herbicide Orange and its dioxin contaminant, and subsequent perceived adverse health effects among U.S. military service personnel resulted in class action litigation and substantial controversy. Social concern for the Herbicide Orange issue continues to be manifest by continuing scientific research, media presentations, congressional hearings, and legal action.

The U.S. Air Force Medical Service's concern for the health of Air Force personnel exposed to herbicides was demonstrated in October 1978 when the Air Force Deputy Surgeon General made a commitment to Congress and the White House to conduct a health study on the Ranch Hand population, the aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The prevailing reasons behind the study commitment included the availability of a population with a definitive occupational exposure to herbicides, a sufficient sample size for survey and clinical research, the ability to ascertain the population at risk, and an opportunity for the Air Force Medical Corps to fulfill its pledge to care for the Air Force community.

The U.S. Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas, was tasked by the Surgeon General to develop the Study Protocol. In 1982, after extensive peer review, the epidemiologic study began, and the Study Protocol was published (3). When the School of Aerospace Medicine was reorganized in 1990, the Armstrong Laboratory assumed responsibility for the AFHS.

Since 1978, numerous human studies of dioxin effects have been planned or initiated by governmental agencies, universities, and industrial firms. The key scientific issue in these studies was the extent of exposure (e.g., who was exposed and to what extent each individual was exposed). Unfortunately, in many of the human studies, population identification and exposure estimation, which are critical for a valid study, have often been scientifically elusive.

Studies of serum dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD) levels have shown that of all the military personnel who served in the RVN, the Ranch Hand population was the most highly exposed to herbicides. In 1987, the Air Force initiated a collaborative study with the Centers for Disease Control (CDC) to measure the serum dioxin levels in the AFHS population. The results of that study clearly demonstrated that substantial elevated levels of dioxin could still be found in the serum of some Ranch Hands, as opposed to the absence of elevated levels of dioxin found in U.S. Army ground troops by the CDC (4,5). If dioxin should cause an adverse health effect, based on the principle of dose-response, the Ranch Hands should manifest more, or earlier evidence of adverse health.

STUDY DESIGN

The purpose of the study is to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study, consisting of mortality and morbidity components, is based on a matched cohort design in a nonconcurrent prospective setting with followup studies. The nonconcurrent aspect of the design results from Ranch Hand exposure over time between 1962 and 1971. The interwoven study elements of multiple mortality assessments, a Baseline morbidity study, and five followup morbidity studies over 20 years provide a comprehensive approach to the detection of attributable adverse health effects. Complete details on the design are provided in the Study Protocol.

For the Baseline study, the population ascertainment process identified 1,264 Ranch Hand personnel who served in the RVN between 1962 and 1971. At the outset of the study, a Comparison group was identified consisting of veterans assigned to Air Force units operating C-130 cargo aircraft in Southeast Asia (SEA). Using a computerized selection procedure to identify Comparisons with similar characteristics to each Ranch Hand, a maximum of 10 Comparisons for each Ranch Hand was selected, matching on age, race, and military occupation. After personnel record reviews, each Ranch Hand determined to be eligible and fully suitable for study had an average of 8.2 matched Comparison subjects.

In the 1992 followup study, 952 of the 1,148 eligible Ranch Hands (83%) participated. Of the 1,195 eligible Original Comparisons, 912 (76%) participated, while 369 of the 567 replacement Comparisons (65%) invited to the 1992 followup chose to take part. Four Ranch Hands, 20 Original Comparisons, and 37 Replacement Comparisons participated for the first time at the 1992 followup examination. Complete information on the selection and participation of study participants can be found in Chapter 5 of this report, Study Selection and Participation.

The mortality component addresses mortality from the time of the RVN assignment. A Baseline mortality study was conducted in 1982, and the mortality followup consists of annual mortality updates for 20 years. For the Baseline mortality study and the first four updates, five individuals were randomly selected from the matched Comparison set for each Ranch Hand for a 1:5 design. Subsequent to 1987, the design was expanded to include all 19,080 veterans in the Comparison population.

MORBIDITY COMPONENT

The Baseline morbidity component, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical records. A cross-sectional element, designed to assess the participant's current state of mental and physical health, was based on comprehensive questionnaires and physical examinations given to the participants. For this component of the study, each living Ranch Hand and the first living member of his Comparison set were selected to participate in the examination. The morbidity study followup comprises sequential questionnaires, medical record reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002.

The Baseline morbidity assessment, conducted in 1982, disclosed only minor differences between the Ranch Hands and Comparisons, and those differences were not traditional indicators of dioxin-related disease. The sustained commitment to pursue the Herbicide Orange question to its scientific conclusion was demonstrated by the conduct of the first two morbidity followups in 1985 and 1987. These followup examinations provided the opportunity to confirm or refute some of the Baseline findings and to explore subtle longitudinal changes. In the followup examinations, the mental and physical health status of the participants during the time interval since the Baseline study was assessed. The results of the followups showed a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the Baseline study in 1982. There was not sufficient evidence to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

For the Baseline and the 1985 and 1987 followup studies, the major focus of the analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the Comparisons (i.e., the unexposed cohort). During the 1987 physical examination, the Air Force initiated a collaborative study with CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (4,6,7). The measurement of serum dioxin levels led to a thorough statistical evaluation to assess dose-response relationships between dioxin and approximately 300 health-related endpoints in 12 clinical areas. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands, as well as contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels of serum dioxin (8). The analysis of dose-response relationships based on serum assays provided an important enhancement from the previous AFHS investigations. This was the first large-scale study of dose-response effects based on an accurate measurement of current dioxin.

In 1992, the third followup was initiated. During a 2½-year period, data were collected, automated, and analyzed. As in 1985 and 1987, this followup study was conducted by Science Applications International Corporation (SAIC) in conjunction with Scripps Clinic and Research Foundation (SCRF), and National Opinion Research Center (NORC), working as a team with the Air Force. The analysis of data collected at the 1992 followup is the basis for this report.

PURPOSE OF THE REPORT

The subject of this report is the 1992 morbidity followup to the AFHS. The objective of the morbidity followup is to continue the investigation of the possible long-term health effects following exposure to TCDD. This report describes the procedures and results of the third morbidity followup of the AFHS.

This report is written primarily for clinical epidemiologists, clinicians, and biostatisticians so that they may fully evaluate the data and analytic techniques. Familiarity with the Study Protocol and prior mortality and morbidity reports is essential to a full understanding of this 20-year study. The report format has been established to be complete, rigorous, and straightforward on all issues so that maximum scientific credibility will be maintained. The intent of the background sections of the clinical chapters is to provide a broad overview of the literature with respect to dioxin endpoints. It is important to note that all statistical analyses in this report were prescribed by the Air Force and none are ad hoc analyses.

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ORGANIZATION OF THE REPORT

This report is organized as follows:

- Chapter 1 (Introduction) provides summary background information on the AFHS and discusses specific technical items and issues that may affect the different clinical area assessments.

- Chapter 2 (Dioxin Assay) describes the procedure used to draw blood for the serum dioxin measurements, the analytical method used to determine the dioxin level from the serum, and the quality control (QC) procedures associated with the serum dioxin data.

- Chapter 3 (Questionnaire Methodology) gives an overview of the development and implementation of the participant questionnaires.

- Chapter 4 (Physical Examination Methodology) describes the conduct and content of the physical examinations.

- Chapter 5 (Study Selection and Participation) presents the methods by which participants were selected and scheduled and also presents a discussion of the participant replacement strategy and the factors known or suspected to influence study participation. Sources of potential bias also are discussed.

- Chapter 6 (Quality Control) provides an overview of the specific quality assurance (QA) and QC measures developed and used throughout the 1992 followup.

- Chapter 7 (Statistical Methods) documents the statistical methods used in the individual clinical area assessments, and the statistical procedures and results of the half-life analyses performed by the Air Force.

- Chapter 8 (Covariate Associations with Estimates of Dioxin Exposure) examines the associations between exposure (Ranch Hand, Comparison, and measures of dioxin exposure) and the individual covariates used in the different clinical assessments.

- Chapters 9 through 20 present the results and medical discussions of the statistical analyses of the dependent variables for each clinical area. Each chapter also contains a brief overview of pertinent scientific literature. The 12 clinical chapters are as follows:

  - Chapter 9: General Health Assessment
  - Chapter 10: Neoplasia Assessment
  - Chapter 11: Neurological Assessment
  - Chapter 12: Psychological Assessment
  - Chapter 13: Gastrointestinal Assessment
  - Chapter 14: Dermatologic Assessment
  - Chapter 15: Cardiovascular Assessment
  - Chapter 16: Hematologic Assessment
  - Chapter 17: Renal Assessment
  - Chapter 18: Endocrine Assessment
  - Chapter 19: Immunologic Assessment
  - Chapter 20: Pulmonary Assessment

- Chapter 21 (Conclusions) summarizes the findings and medical discussions of the 12 clinical areas.

- Chapter 22 (Future Directions) summarizes the anticipated future activities and discusses possible modifications to the existing instruments and methodologies used to investigate the association between health status and dioxin exposure.

INTERPRETIVE CONSIDERATIONS

In the interpretation of results from any epidemiologic study, no single result should be evaluated in isolation or at face value, but rather in the context of the overall study design, the data collection procedures, the data analysis methods, and the approach to evaluating results. This especially applies to the AFHS. This effort is a large-scale, prospective

observational study in which thousands of measurements are generated on each participant, and those measurements and diagnoses are subjected to extensive statistical analyses entailing the testing of thousands of individual hypotheses. Each positive result should be scrutinized relative to other findings in this and other studies and relative to the statistical methods used and the medical and scientific plausibility of the results. Conversely, the lack of a positive result only denotes that the hypothesis of no association was not rejected. This has a very different conclusion than the assertion that there is no effect.

In this section, critical considerations in the evaluation of results from this study are reviewed. These considerations include study design and modeling considerations, information bias, consistency of results, strength of association, biological plausibility, interpretation of nonsignificant results, interpretation of graphics, extrapolation to other populations, and summarizing results. Other interpretive considerations, such as adjustments to analyses for covariates and interactions, multiple testing, trends in results within a clinical area, and power limitations, are discussed in greater statistical detail in Chapter 7, Statistical Methods.

Study Design and Modeling Considerations

Biased results will be produced if the assumptions underlying any of the statistical models are violated. Six models are used in this report to analyze the health effects of herbicide exposure in Vietnam. The first model contrasts the exposed population (Ranch Hands) with an unexposed group (Comparisons). The second model evaluates the relationship between estimated serum dioxin levels from the time of exposure (i.e., initial dioxin) with each health endpoint. The group contrast model is extended in the third model so that the Ranch Hand group is divided into three categories depending on current and estimated initial levels of serum dioxin, and each category is contrasted with the Comparison group. The final three models evaluate the associations between current serum dioxin levels and each health endpoint. The following current dioxin measurements are used in models four through six: lipid-adjusted current dioxin, whole-weight current dioxin, and whole-weight current dioxin with adjustment in the model for total lipids respectively. The parameters of these six models are summarized in Table 1-1.

As in any epidemiologic study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis that both groups are equal, due to possible misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Current dioxin data indicate that 40 percent of the Ranch Hands have background serum dioxin levels (10 ppt or less). These Ranch Hands either were never exposed or their initially elevated serum dioxin levels may have decayed to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether or not Ranch Hands currently having background dioxin levels had elevated levels in the past.

The model analyzing the association of health endpoints with extrapolated initial dioxin levels also is vulnerable to bias, because it directly depends on two invalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life (7.1 years). If dioxin elimination is first-order, but some

Table 1-1.
Parameters of Exposure Assessment Models

Model	Cohort(s)	Subset of Cohort	Exposure Characterized By:	Covariates in Analysis (not including endpoint-specific covariates)
1	Ranch Hands and Comparisons	All participants	Group (Ranch Hands versus Comparisons and military occupation	--
2	Ranch Hands	Lipid-adjusted current dioxin measurement >10 ppt	Extrapolated initial dioxin	PBF at time of duty and PBF change
3	Ranch Hands and Comparisons	RH: Current dioxin measurement C: Lipid-adjusted current dioxin measurement ≤10 ppt	Group (Ranch Hands versus Comparisons); Ranch Hands categorized according to current and estimated initial dioxin levels	PBF at time of duty and PBF change
4	Ranch Hands	Current dioxin measurement	Lipid-adjusted current dioxin: (102.6*whole-weight current dioxin/total lipids)	--
5	Ranch Hands	Current dioxin measurement	Whole-weight current dioxin	--
6	Ranch Hands	Current dioxin measurement	Whole-weight current dioxin	Total lipids

Note: RH = Ranch Hands.
C = Comparisons.
"PBF at time of duty" = Percent body fat at the time of duty in SEA.
"PBF change" = Change in percent body fat from the time of duty in SEA to the date of dioxin draw.

Ranch Hands have a shorter half-life than others, then there would have been misclassification of initial dioxin exposure. If the clinical endpoint is not associated with a factor that affects the elimination rate (e.g., relative weight change), then estimates of the relative risk for common diseases associated with low and high levels of initial dioxin, in general, will be biased toward unity. However, if the clinical endpoint is associated with a factor that affects the elimination rate, then the relative risk will be biased away from unity.

The half-life of dioxin has been found to change significantly with percent body fat and age in the 337 Ranch Hands having paired dioxin measurements above 10 ppt; one derived from serum drawn in 1982 and the other from serum drawn in 1987 (9). Half-life increased significantly with higher levels of obesity and decreased significantly with weight gain and age. The constant 7.1 year half-life used in this report was derived from an earlier half-life study based on 36 subjects (6). The longer half-life estimate derived from 337 subjects was developed 3 years after the statistical plan for this report, too late for application to these data, because the statistical analyses summarized in this report had already begun. As a partial solution to the observed relationship of half-life to obesity and weight gain, analyses using estimated initial dioxin levels were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin (see Chapter 7, Statistical Methods).

The validity of the constant half-life assumption cannot be assessed until the half-life study is expanded to include dioxin measurements taken in 1992, giving three repeated dioxin measures for each of the Ranch Hands in the half-life study. These analyses are expected to be published in 1995. Dioxin measurements on multiple blood specimens taken from 20 males exposed during a factory explosion near Seveso, Italy (10), will be evaluated to further assess the first-order elimination assumption.

In order to account for the possible misclassification of exposure between groups, the third statistical model categorizes Ranch Hands into three levels of exposure: background levels of current dioxin, low levels of estimated initial dioxin, and high levels of estimated initial dioxin. Each Ranch Hand dioxin category is contrasted with Comparisons having background levels of current dioxin. Although this model is less dependent upon the accuracy of the initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the classification of the Ranch Hands is subject to bias if the half-life and first-order dioxin elimination assumptions are not valid. Also, the Ranch Hands with background levels of current serum dioxin (10 ppt or less) may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels have decayed to background levels. This will result in a bias towards the null hypothesis of no dioxin effect on the health endpoint.

In the analyses of this model in this report and in the Serum Dioxin Analysis of the 1987 Followup, a "checkmark pattern" has become prevalent. The checkmark pattern is defined as the occurrence of a lower percentage of abnormalities in the Ranch Hands with background dioxin levels than in background Comparisons, but a greater percentage of abnormalities in Ranch Hands with high levels of serum dioxin than in the Comparisons. A checkmark pattern is expected when there is a positive association between disease and dioxin in Ranch Hands and the prevalence of disease in the two groups is nearly equal. This

circumstance could arise if there is a large degree of misclassification between the exposure groups (Ranch Hands and Comparisons) with regard to dioxin levels that conceal the difference between exposed and unexposed participants (11) (as may be the case with 40% of the Ranch Hands having background levels). As a corollary, the pattern is expected if body fat, but not dioxin, is associated with disease in Ranch Hands and the prevalence of disease in the two exposure groups is nearly equal. This circumstance could arise if there is a large degree of similarity between the two groups with regard to body fat (as is the case because the group means on body fat are nearly equal). A second corollary is that the checkmark pattern is expected when disease is associated with both dioxin and body fat in Ranch Hands and the prevalence of disease in the two groups is nearly equal. This last circumstance could arise if there is a large degree of similarity between the two groups with regard to body fat and dioxin (as is the case for the reasons described above).

The three models that analyze associations between current serum dioxin and health endpoints are less subject to bias than the previous models. However, current serum dioxin levels may not be good measures of exposure if serum dioxin elimination rates differ among individuals. Current serum dioxin levels also were extrapolated from 1992 measurements to 1987 for participants without current serum dioxin levels measured in 1987. Therefore, these current dioxin measurements are subject to the potential bias from the half-life and first-order elimination assumptions that also affect the initial dioxin estimates.

Information Bias

Information bias, represented by the over-reporting of disease symptoms, was minimized by verifying all diseases and conditions with medical records. It is possible that conditions in Ranch Hands may be more verifiable because they may have been seen by physicians more often than Comparisons; this would be revealed by group differences in the quantity and content of medical records. Because there is no way to quantify these aspects, this potential source of bias remains unexplored. This bias, however, if it exists, would affect only estimates of health effects used in the models contrasting Ranch Hands and Comparisons because Comparison data were not used in models assessing associations between health effects and dioxin. Information bias due to errors in the data introduced through data entry or machine error is negligible. All laboratory results were subject to strict QC procedures, historical data were verified completely by medical record review, and medical data were subjected to strict QC standards (Chapter 6, Quality Control).

Consistency of Results

Adverse health effects in Ranch Hands attributable to herbicide or dioxin should be confirmed by internally and externally consistent findings. An internally consistent finding does not contradict other findings in the report, and an externally consistent finding has been previously established by other research. All statistically significant findings in this report were subjected to clinical review and were compared to published results from other research to identify consistent findings.

Strength of Association

Ideally, an adverse effect, if it exists, would be revealed by a strong association between categorized dioxin and a disease condition; that is, by a statistically significant relative risk greater than 2.0 for Ranch Hands with high categorized dioxin levels relative to the Comparisons (12). Statistically significant relative risks less than 2.0 are generally considered to be less important than larger risks because relative risks less than 2.0 can easily arise due to unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The numbers 2.0 and 5.0 are epidemiologic guidelines regarding analyses of association between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as initial or current serum dioxin measurements).

Biological Plausibility

The assessment of biological plausibility requires consideration of the feasibility, in biological terms, of the exposure under study to produce the effect of interest. While a lack of biological credibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological explanation of results must be interpreted with caution. In the AFHS, statistically significant results are subjected to medical review and confirmation from previously published results in order to identify consistent and biologically plausible results.

Interpretation of Nonsignificant Results

In this study, a lack of significant results relating dioxin to a particular disease only means that the study is unable to detect a relationship between dioxin and health. This does not imply that a relationship may not exist, but that, if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relationship between dioxin and health. The AFHS was not designed to establish safety. Rather, this study was designed to determine whether a hazard existed for the exposed personnel. Determination of safety would require a study at least 10 times as large, as determined in a 1985 study presenting minimal sample-size criteria for proof of safety and hazard in studies of environmental and occupational exposures (13).

Graphics

Scatterplots of selected continuous health endpoints were included as aids to interpretation. The graphics alone are not sufficient to assess the relationship between dioxin and health. For example, a trend may be seen in a plot, but it could be statistically nonsignificant because the number of abnormalities is small. On the other hand, a statistically significant result can be clarified by the graphics, especially if the result depends on a few data points that appear far from the main cluster.

Extrapolation to Armed Forces Ground Troops

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 very different. Based on serum dioxin testing results done by CDC (7) and others (14), nearly all ground troops tested have current levels of dioxin similar to background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had current levels indistinguishable from levels in men who never left the United States (with mean dioxin levels of 4.2 ppt and 4.1 ppt respectively). The AFHS subgroup most like the ground troops in terms of current dioxin levels are Ranch Hands who currently have background levels of dioxin (10 ppt or less). Therefore, if the results of the AFHS are applied to the general population of Vietnam veterans, the focus should be on the "Background" Ranch Hand versus Comparison contrast. However, extrapolating the results of these analyses to Vietnam veterans still should be made cautiously. There may be demographic distinctions between the "Background" group of Ranch Hands and other Vietnam veterans that may be related to health. Also, if Ranch Hands with background levels of current serum dioxin showed a significant health detriment relative to Comparisons, but there was no significant detriment for Ranch Hands with high serum dioxin levels, the biological plausibility of such an effect would be questionable, because this would not indicate a dose-response effect. In general, the analyses in this report found that Ranch Hands with background levels of current serum dioxin did not show a significant health detriment relative to Comparisons. This was particularly true for the analyses that exhibited a statistically significant health detriment in Ranch Hands with high levels of current serum dioxin.

Summary of Results

A study of this scope with a multitude of endpoints demands, and at the same time defies, meaningful summary tabulation. Such summaries can be misleading because they ignore correlations between the endpoints, correlations between study-cycle results, and the nonquantifiable medical importance of each endpoint. In fact, many endpoints are redundant (e.g., psychological scales and indices developed from combining multiple variables). In addition, such tabulations combine endpoints that are not comparable. For example, diminished sense of smell is of less medical importance than the presence of a malignant neoplasm. Nevertheless, the AFHS presents a summary of all statistical results (see Appendix Q-1). However, these summaries can be misleading and must be interpreted carefully—an elementary tally of significant, or nonsignificant, results is not appropriate.

CHAPTER 1
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CHAPTER 21

CONCLUSIONS

INTRODUCTION

This section summarizes the conclusions drawn from the statistical analyses of data from the 1992 followup examination of the Air Force Health Study (AFHS). The 1992 followup was an extension of the Baseline, 1985, and 1987 followup examinations. Health endpoints measured at the 1992 examination were analyzed for associations with dioxin (TCDD) exposure and body burden of serum dioxin, and were examined longitudinally in relation to data from the previous examination cycles.

STUDY PERFORMANCE ASPECTS

Participation at the 1992 followup examination remained high. Of the 1,148 eligible Ranch Hands, 952 participated in the 1992 followup examination, while 912 of the 1,191 eligible Comparisons from the Baseline examination participated in the 1992 followup. Of the 571 Comparisons identified as replacements for Original Comparisons, 369 participated in the 1992 followup. Ninety-one percent of living Ranch Hands and 92 percent of living Comparisons who were fully compliant at the Baseline examination returned for the 1992 followup examination. Each of the 952 Ranch Hands and 1,281 Comparisons at the 1992 followup completed the physical examination, but two participants refused to complete the questionnaire. Despite requirements in the Study Protocol, 62 of 279 noncompliant Comparisons were not replaced as they should have been. However, the total number of fully compliant participants would have increased by less than 3 percent and any biasing effect is considered negligible.

POPULATION CHARACTERISTICS

Overall, Ranch Hands and Comparisons had similar personal characteristics and lifestyle habits. However, notable exceptions included duration of combat service, reported herbicide exposure, and high-density lipoprotein (HDL). Ranch Hands tended to serve in combat longer than Comparisons, because Ranch Hands were stationed in combat areas for their entire time of duty in Southeast Asia (SEA), whereas Comparisons returned to stations outside of combat areas between missions. A possible explanation for a greater percentage of Ranch Hands than Comparisons reporting herbicide exposure may have been the tendency of Ranch Hands to report their exposure during their time of duty in SEA, although the questionnaire was designed to capture post-SEA exposure only. The relationship between group and HDL is not clear—the group means are not significantly different, but the percentage of Ranch Hands considered abnormal (less than 35 mg/dl) is significantly greater than the percentage of Comparisons. In Ranch Hands, most of the significant associations between dioxin and the covariates can be attributed to, or partially explained by, the effects of occupation, age, or body fat.

STATISTICAL MODELS

The analysis of the 1992 followup examination results employed six statistical models to evaluate the relationship between the health status of study participants and their dioxin exposure and serum dioxin levels. The first model specifies contrasts between Ranch Hands and Comparisons using group as a proxy for exposure and does not incorporate serum dioxin measurements. The remaining five models all incorporate serum dioxin measurements in either current or initial form. The six models are summarized as follows:

- Model 1: Ranch Hands versus Comparisons
- Model 2: Estimated initial serum dioxin levels using Ranch Hand participants with greater than 10 ppt of current lipid-adjusted dioxin
- Model 3: Ranch Hands categorized according to serum dioxin levels versus Comparisons with 10 ppt of current lipid-adjusted dioxin or less
- Model 4: Current lipid-adjusted serum dioxin using Ranch Hands only
- Model 5: Current whole-weight serum dioxin using Ranch Hands only
- Model 6: Current whole-weight serum dioxin, adjusted for total lipids, using Ranch Hands only.

In Model 1, the use of group and occupation as a surrogate for exposure is not subject to the possible biases based on health conditions that can occur with serum dioxin estimates. However, an implicit underlying assumption is that Ranch Hands were exposed and Comparisons were not exposed. Model 2 is based on initial dioxin levels that were extrapolated from current lipid-adjusted dioxin measurements above background levels (10 ppt), assuming first-order kinetics and a constant dioxin decay rate. Model 3 is less dependent on the accuracy of the initial dioxin estimation algorithm, but all Ranch Hands with high serum dioxin levels are treated alike without emphasizing the unusually large dioxin doses received by some Ranch Hands. Models 4, 5, and 6 are based on current dioxin measurements from the 1987 examination and assume nothing about dioxin elimination other than that Ranch Hands were exposed in Vietnam and their body-burdens have decreased over time in an unspecified manner. However, current dioxin may not be a good surrogate for exposure if elimination rates differ among individuals.

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

CLINICAL RESULTS

This section provides the conclusions from the analyses of the twelve clinical areas—general health, neoplasia, neurology, psychology, gastrointestinal, dermatology, cardiovascular, hematology, renal, endocrine, immunology, and pulmonary. Appendix Tables Q-1-1 through Q-1-24 of Appendix Q-1 present the results for each of the six models for more than 300 health endpoints analyzed in the 12 clinical chapters. Appendix Q-2 presents graphical displays of 26 selected continuous health measurements versus the logarithm (base 2) of current lipid-adjusted serum dioxin. These graphics represent scatterplots, unadjusted for any covariates, of the data used in Model 4 analyses.

General Health Assessment

General health was assessed by five measures, selected for sensitivity to the overall state of health rather than specific to any organ system; the five measures were: self-perception of health, appearance of illness or distress as assessed by a physician, relative age as assessed by a physician, percent body fat, and sedimentation rate.

At the 1992 examination, Ranch Hands perceived themselves as less healthy than Comparisons, just as they had at the 1982 and 1985 examinations (though not at the 1987 examination). Enlisted groundcrew, who experienced the highest levels of dioxin exposure, were particularly inclined to view their health negatively. A highly significant association between the current level of serum dioxin and a negative self-perception of health also was found in Ranch Hands. Because participants were aware of their serum dioxin levels, the possibility of bias in these results should be considered. Participants who knew they possessed an elevated dioxin level, or whose occupation implied a greater risk for exposure (i.e., enlisted groundcrew), may have consciously or subconsciously perceived their health as poorer than that of their Comparisons. Indeed, apart from the self-perceived health status, the examining physicians, in their objective observations, recorded no significant group differences as to the appearance of illness or distress and appearance in terms of relative age.

The prevalence of obesity was similar in the Ranch Hand and Comparison cohorts. However, in Ranch Hands, a highly significant positive association between percent body fat and current serum dioxin was found in all of the occupational categories. These results imply a difference in the dioxin pharmacokinetics in obese versus lean participants; but clinically, it is difficult to explain the higher levels of serum dioxin in obese participants relative to any health detriment. It is not clear whether a causal relationship exists between dioxin exposure and increased body fat.

In previous AFHS examinations, sedimentation rate, a sensitive, but nonspecific index of general health usually associated with serious underlying disease, was significantly higher in Ranch Hands than in Comparisons. However, the 1992 examination revealed only a slight clinically insignificant difference in the Ranch Hand enlisted groundcrew and their Comparisons. Analyses showed a statistically significant dose-response effect in the association between sedimentation rate and current serum dioxin in Ranch Hands, but the biological significance is uncertain.

The longitudinal analyses revealed that results from the 1992 examination contrasted with those of previous examinations. Between 1982 and 1987, the percentage of Ranch Hands and Comparisons reporting fair or poor self-perceptions of health was greatly reduced and the difference between the groups had narrowed. However, in the 1992 examination, the change in self-perception of health between 1982 and 1992 was significantly associated with calculated initial serum dioxin levels (of which participants had become aware). The potentially negative effect of known exposure status and serum dioxin level may have affected the more recent results.

In conclusion, the general health of the Ranch Hands and Comparisons appeared comparable by all objective indices; however significant, although possibly biased, group differences were evident in self-perceived health status. Percent body fat and sedimentation rate displayed significant associations with current serum dioxin levels, but the biological significance is uncertain.

Neoplasia Assessment

In the neoplasia assessment, skin and systemic neoplasms were evaluated by behavior, cell type, and location or site. As the anatomic point of contact with industrial toxins and as the only organ system with a clearly defined clinical endpoint (i.e., chloracne) for TCDD exposure, the skin deserves the special emphasis it has received in this study. Although there is no evidence that TCDD exposure causes—or that chloracne is associated with—basal cell carcinomas, the Ranch Hand cohort was found to be at increased risk for the occurrence of these skin cancers in each of the three prior examination cycles.

In the analyses of the 1992 examination, Ranch Hands continued to have a slightly higher prevalence of benign and malignant skin neoplasms than did Comparisons, including basal cell skin cancers at all sites. However, these group differences are no longer statistically significant. Consistent with results from the 1987 examinations, many analyses revealed a significant inverse dose-response with current serum dioxin levels.

Consistent with all previous examinations, none of the analyses revealed any significant group differences in the prevalence of systemic malignancies in the Ranch Hand and Comparison cohorts; neither did the analyses disclose an increased risk of any systemic malignancy in association with either the current or extrapolated initial levels of serum dioxin in Ranch Hands. Longitudinal analyses discovered no significant group differences in the incidence of benign or malignant neoplasms including those thought by some to be related to herbicide exposure (i.e., Hodgkin's disease, non-Hodgkin's lymphoma, and soft tissue sarcoma [STS]).

In summary, at the end of a decade of surveillance, Ranch Hands and Comparisons appear to be at equal risk for the development of all forms of neoplastic disease and there is no evidence to suggest a positive dose-response relationship between body burden of dioxin and neoplastic disease.

Neurological Assessment

The neurological assessment examined historical neurological disorders in addition to central nervous system (CNS), cranial, and peripheral nerve indices, all of which can provide specific clues to the anatomical site of neurological lesions and clarify the need for additional diagnostic studies. The neurological examination is highly sensitive in detecting the presence of peripheral neuropathy, a suspect clinical condition related to TCDD exposure.

The prevalence of historical neurological disorders was similar in the Ranch Hand and Comparison cohorts. In contrast, but of doubtful clinical significance, an inverse dose-response was noted in the analyses relating current serum dioxin to the history of hereditary and degenerative disorders.

In the analyses of the physical examination variables, Ranch Hand enlisted groundcrew, the occupation category with the highest current levels of dioxin, had significantly more cranial nerve index abnormalities than Comparison enlisted groundcrew, but there was no evidence of a dose-response relationship in the serum dioxin analyses. In relation to the extrapolated initial level of serum dioxin, no significant associations were noted for any of the directly measured physical examination variables. The analyses employing current serum dioxin yielded inconsistent results. A positive association was noted in relation to the cranial nerve motor variable smile and the peripheral nerve variables pin prick and patellar reflex, while inverse dose-response patterns were defined for smell and the Babinski reflex.

In summary, the neurological assessment found the prevalence of neurological disease comparable between the Ranch Hand and Comparison groups, and showed no consistent evidence of a dose-response effect with either estimated initial dioxin exposure or current TCDD levels.

Psychological Assessment

Verified psychological conditions and the Symptom Check List-90-Revised (SCL-90-R) inventory of nine primary symptom dimensions and three global indices of distress were examined in the psychological assessment. The SCL-90-R was retained in the 1992 examination because of its effectiveness as a co-measure of variables included in the verified questionnaire as well as to maintain psychometric continuity across the four phases of the AFHS completed to date (Baseline, 1985, 1987, and 1992).

Among the SCL-90-R inventory variables, Ranch Hands exhibited higher psychological distress than Comparisons on the index scores measuring anxiety, obsessive-compulsive behavior, paranoid ideation, somatization, and global severity. A significant group contrast also was exhibited for the verified condition of other neuroses. However, when Ranch Hands were categorized according to serum dioxin levels, significant group differences were revealed only in the contrasts of Ranch Hands with background serum dioxin levels versus Comparisons. The serum dioxin analyses also did not support a dose-response relationship, because there were no significant findings in any of the analyses relating extrapolated initial dioxin and current serum dioxin levels with psychological distress

indicators. Each of the analyses produced a smaller number of significant results from the adjusted analyses than from the unadjusted analyses due to the adjustment for important confounding effects such as education and occupation.

In conclusion, the differences revealed between the Ranch Hand and Comparison cohorts, together with a lack of any effects attributable to dioxin, suggest that factors other than dioxin exposure continue to influence a relatively small but notable number of abnormalities in Ranch Hand test scores. Previous studies in clinical medicine continue to indicate the need for caution when interpreting the outcome of large statistical studies. The possibility that a small subset of physically or psychologically vulnerable Ranch Hands may have suffered psychological injury in the context of their exposure to dioxin cannot be definitively ruled out at this time.

Gastrointestinal Assessment

The historical, physical examination, and laboratory parameters included in the gastrointestinal assessment are well established in clinical practice as screening tools for investigating digestive disorders in outpatients. There are limitations of reliance solely on data from the patient history and physical examination when diagnosing digestive disorders because digestive symptoms are frequently nonspecific and intermittent. However, data collected in the laboratory can provide early insight into the presence of occult liver disease.

Few of the laboratory analyses revealed any significant differences between the Ranch Hand and Comparison cohorts. Ranch Hands had a slightly higher mean alkaline phosphatase than Comparisons, but the difference in the means cannot be considered biologically significant. Analyzed in the discrete form, which is clinically more relevant, the group difference was not significant.

The serum dioxin analyses indicated that estimated initial dioxin exposure was generally not associated with historical liver disorders or current laboratory measurements. However, the analyses revealed that current dioxin levels were often highly associated with lipid-related health indices. In continuous (but not in discrete) form, two of the four liver enzymes studied, ALT and GGT, revealed highly significant positive associations with current serum dioxin levels. Similar results were noted with serum triglycerides and serum cholesterol, which contributed to a negative association between current serum dioxin and the cholesterol-HDL ratio. These results may be explained in part because the analyses of extrapolated initial serum dioxin were adjusted for differential half-life elimination related to percent body fat, whereas no adjustment was made in the analyses of current serum dioxin.

Analyses of the historical and clinical examination variables revealed no evidence of any overt hepatic disease related to the current body burden of dioxin. Most of the statistically significant associations that occurred in relation to the extrapolated initial level of serum dioxin were limited to laboratory indices. These associations more often were found in the continuous, rather than the more clinically relevant discrete, analyses. While the observed dose-response findings are not accompanied by clinical disease, they may still represent subclinical effects.

Over a decade of observation, the longitudinal analyses yielded significant results in several of the laboratory indices. In particular, ALT, serum triglyceride, and cholesterol levels tended to increase over time in Ranch Hands more than in Comparisons. Although these results are consistent with a subtle effect of herbicide exposure on lipid metabolism, the difference was more pronounced in the enlisted flyer category than it was in the more exposed enlisted groundcrew category.

In summary, the gastrointestinal data confirm observations that would be anticipated in a clinical practice and reflect no apparent increase in organ-specific morbidity in Ranch Hands relative to Comparisons nor do they represent an association with serum dioxin levels. Although a subclinical dioxin effect on lipid metabolism cannot be excluded, some of the results may be related in part to body habitus and percent body fat.

Dermatology Assessment

The dermatologic assessment was based on occurrence of acne, location of acne, other dermatologic abnormalities, and a dermatology index based on the presence of comedones, acneiform lesions, acneiform scars, and inclusion cysts, depigmentation, and hyperpigmentation.

In the study of biological effects of herbicides in humans, the dermatologic examination assumes special importance. Of the organ systems analyzed in this report, only the skin has a clinical endpoint (chloracne) that has been related conclusively to dioxin exposure. Experimental dose-response studies in animals and humans have confirmed that the topical concentrations of dioxin required to produce overt lesions are far greater than the concentrations to which participants in the current study were likely to have been exposed during their times of duty in SEA. It is therefore not surprising that, in the four examination cycles to date, no cases of chloracne have been detected.

In general, the dermatology variables showed no significant differences between Ranch Hands and Comparisons. Although the lifetime occurrence of acne, as self-reported by the questionnaire, was similar in both groups, Ranch Hand enlisted groundcrew, those most heavily exposed to dioxin, appeared to be at increased risk for the development of acne subsequent to time of duty in SEA. There is a possibility of bias associated with self-reporting, however, because no group differences were found in the physical examination indices.

In the analyses of extrapolated initial and current serum dioxin, Ranch Hands with current serum dioxin levels above the background level demonstrated lower occurrence of an abnormal dermatology index than did Comparisons. The dermatology index also exhibited a significant negative association with current serum dioxin in Ranch Hands. Although nonsignificant, all other dermatologic indices displayed negative associations with current dioxin. These results provide evidence against a dose-response effect.

In summary, there is no consistent evidence to suggest an adverse dioxin effect on the dermatologic system at levels received by the Ranch Hand cohort in SEA.

Cardiovascular Assessment

The cardiovascular assessment examined historical, physical examination, and questionnaire indices, divided into central and peripheral cardiovascular functions used to alert clinicians to the presence of underlying cardiovascular disease.

The verified historical indices (history of heart disease, hypertension, and myocardial infarction) were similar in Ranch Hands and Comparisons, but the analyses employing serum dioxin measurements revealed inconsistent results. In Ranch Hands, an increase in current dioxin levels was associated with a decrease in the prevalence of verified heart disease and an increase in the history of essential hypertension. Although a plausible biologic explanation for this phenomena is lacking, these results are consistent with findings from the 1987 examination.

In general, the analyses of the central cardiac function variables were not positively associated with serum dioxin. Although Ranch Hand enlisted flyers displayed a significantly higher prevalence of bradycardia than did Comparison enlisted flyers, bradycardia exhibited a significant inverse dose-response with initial and current dioxin. Several other electrocardiograph (ECG) indices, including right bundle branch block (RBBB), non-specific ST- and T-wave changes, and arrhythmias, displayed significant positive associations with current serum dioxin levels, but none of these endpoints also displayed a group difference between Ranch Hands and Comparisons to confirm the dose-response relationship.

The analyses of the peripheral vascular function variables displayed significant group differences for a few of the pulse endpoints among enlisted groundcrew personnel (the occupational category with the highest exposure) and between Ranch Hands with the highest current level of serum dioxin and their Comparisons. However, none of these relationships were reinforced by a significant association with initial or current serum dioxin. In the longitudinal analyses of the pulses endpoints, Ranch Hands were slightly more likely than Comparisons to develop peripheral pulse deficits over time. Again, the analyses using extrapolated initial serum dioxin levels as a measure of exposure did not show consistent evidence of a dose-response relationship.

Dorsalis pedis pulse abnormalities were far more prevalent in both Ranch Hands and Comparisons in the 1985 examination than they were in the 1992 examination. The change in results between the two examinations may relate to the use of different and more accurate Doppler instrumentation in the 1992 examinations. During the 10 years of observation, both Ranch Hands and Comparisons have demonstrated a similar reduction in systolic blood pressure and incidence of hypertension. This trend may reflect the beneficial effects of risk factor identification and life-style modification consequent to participation in this study.

In summary, consistent with the results of prior examinations, Ranch Hands were found to be at slightly greater risk than Comparisons to develop selected peripheral pulse deficits, suggesting some effects from dioxin. These findings are based on the 1992 analysis of hypertension and ST- and T-wave changes, taken in conjunction with the 1994 AFHS mortality update showing an increased number of deaths caused by diseases of the circulatory system among Ranch Hand nonflying enlisted personnel. By all other objective and

subjective indices, the development of cardiovascular disease does not appear to be associated with dioxin exposure or current serum dioxin levels.

Hematologic Assessment

The 13 laboratory endpoints analyzed in the hematology assessment provided a comprehensive evaluation of the three peripheral blood lines (erythrocytes, leukocytes, and platelets). These variables are relied upon heavily to reflect disease of the hematopoietic system and also to alert the clinician to the presence of disease in other organ systems.

Of the laboratory variables examined, only platelet count exhibited significant associations with the dioxin exposure indices. Ranch Hands in the enlisted flyer and enlisted groundcrew categories possessed statistically significant higher mean platelet counts than Comparisons, although the differences cannot be considered clinically significant. Ranch Hands with high extrapolated initial dioxin levels also had significantly greater mean platelet count measurements than Comparisons. These results are consistent with those from the 1987 examination, but the biological significance is uncertain.

In the 1987 examination, the mean white blood cell (WBC) counts, platelet counts, and erythrocyte sedimentation rates (ESR) were each higher in Ranch Hands than in Comparisons, raising the possibility of a subclinical inflammatory response associated with prior dioxin exposure. In the current study, no group differences were noted in either the WBC or, as reported in the General Health Assessment (Chapter 9), the ESR. Furthermore, in the current study, current serum dioxin was inversely related to the prevalence of abnormally elevated WBC counts.

In the longitudinal analyses, a gradual reduction was documented in the total platelet count in each group and across all occupations. Ranch Hands continue to have a greater reduction in the total platelet count over time than do Comparisons, but the means from the current examination are nearly equal.

In summary, there is no evidence from the current study to suggest an association between hematopoietic toxicity and prior dioxin exposure. Based on the analyses of WBC, ESR, and total platelet count, there is no longer any evidence that a subclinical inflammatory reaction may be present in Ranch Hands as was thought possible in the 1987 examination.

Renal Assessment

The renal assessment was based on the medical history of kidney disease, physical examination for kidney stones, and five laboratory indices. Pertinent to the interpretation of these analyses is the frequent finding in ambulatory medicine of isolated abnormalities in the routine urinalysis of healthy individuals who, in fact, have no disease of the genitourinary system. No significant group difference or association with serum dioxin was noted in the history of urinary tract disease, as measured by a verified history of kidney disease and the presence of renal calculi detected by plain films of the abdomen.

Although the prevalence of microhematuria (urinary red blood cell counts) was similar in both groups, Ranch Hands with the highest levels of extrapolated initial serum dioxin had a significantly higher prevalence of microhematuria than did Comparisons. These results are similar to those from the 1987 examination. Although not statistically significant, the analyses employing current serum dioxin yielded results consistent with a dose-response effect; however, the longitudinal analyses indicated that the prevalence of microhematuria has decreased in the Ranch Hand cohort since 1985. Clinically, the finding of hematuria can signal the presence of "silent" renal calculi or neoplastic disease; however, the analyses of kidney stones do not support the presence of silent renal calculi.

In the analysis of urinary WBC counts (pyuria), the enlisted groundcrew Ranch Hands—those most highly exposed to dioxin—had twice the prevalence of pyuria than did Comparisons. Longitudinal analyses also showed that the enlisted groundcrew Ranch Hands are twice as likely as the enlisted groundcrew Comparisons to develop pyuria over time, but the similar prevalence of pyuria in Ranch Hands with low and high levels of serum dioxin does not support a dose-response effect.

The analysis of urine specific gravity documented a statistically significant positive association with current serum dioxin, but the magnitude of the association was not clinically significant. Analyses of serum creatinine and proteinuria revealed no differences between the cohorts.

In summary, the renal assessment displayed no consistent evidence for any detriment, with the possible exception of hematuria, related to current body burden of dioxin or to the estimated severity of prior exposure.

Endocrine Assessment

In the endocrine assessment, analyses were performed on 36 historical medical records, physical examination, and laboratory variables—five of which were analyzed separately for diabetics, nondiabetics, and all participants. These indices provide a comprehensive assessment of thyroid, gonadal, and endocrine pancreatic function in the population under study.

Analyses of thyroid functions did not reveal significant differences between the Ranch Hand and Comparison cohorts. Similarly, the prevalence of diabetes mellitus in the two groups was not significantly different, although significant positive associations were found between current serum dioxin levels and the onset of diabetes, specifically in the early stages requiring only dietary intervention or oral hypoglycemic therapy.

In assessing glucose metabolism, along with examining the possibility that dioxin may be a risk factor for the development of diabetes, significant results were limited to the current serum dioxin analyses. Diabetic Ranch Hands with high levels of current serum dioxin had significantly higher fasting glucose levels than those with lower levels of dioxin. Nondiabetics, on the other hand, exhibited an inverse association between fasting glucose and current serum dioxin and a positive association between 2-hour postprandial glucose and current serum dioxin. Although not statistically significant, serum insulin levels in diabetics,

in contrast to nondiabetics, were inversely related to dioxin levels, indicating that serum insulin decreases as dioxin levels increase in diabetics. These results are consistent with a fundamental impairment of islet cell responsiveness to hyperglycemia with compromised insulin production and point to a potential mechanism for an effect of dioxin on glucose metabolism. However, the analyses of serum C peptide and serum proinsulin yielded no significant results and did not reveal the biochemical mechanisms by which dioxin might have an effect on insulin production and glucose metabolism.

Analyses of gonadal function detected a significant inverse dose-response relationship between current serum dioxin and total serum testosterone in Ranch Hands. These results are consistent with those from the 1987 examination, but the clinical significance is uncertain.

The longitudinal analyses yielded results that would be anticipated over time with no significant differences between Ranch Hands and Comparisons. Age-related increases were documented in fasting glucose, 2-hour postprandial glucose, and the incidence of diabetes, while serum testosterone decreased with age.

In summary, after 10 years of observation, the prevalence of endocrine disease remains similar in Ranch Hands and Comparisons. Although cause and effect remain to be established, the current endocrine assessment provides further evidence for an association between glucose intolerance and dioxin exposure. The possibility is raised that, in a subset of individuals predisposed to diabetes, dioxin may impair insulin production.

Immunologic Assessment

Immunologic competence was assessed by analyzing physical examination and laboratory data from skin tests for delayed hypersensitivity response, cell surface marker studies on a randomized subset of the study population, immunoglobulin quantitation, and autoantibody detection. This evaluation went far beyond typical medical examinations employed for general health assessments, and included elements of measurement used frequently to define specific diseases.

Overall, the immunologic assessment did not reveal any relationships that could be considered clinically significant between dioxin exposure and physiologic abnormalities. The MSK smooth muscle antibody, rheumatoid factor, and lupus panel summary index displayed inverse associations with dioxin exposure, but did not support a dose-response relationship; additionally, the magnitude of these associations was small and could not be interpreted as conveying a health risk.

A marginally significant positive association was found between serum IgA concentrations and extrapolated initial dioxin levels. Although the magnitude of this effect was small, its statistical significance coupled with continuity over time suggests a possible relationship that should be evaluated further because elevated IgA may indicate liver disease, chronic inflammation, or selective immune dysfunction.

The longitudinal analyses of the CD4-CD8 ratio did not consistently show significant differences between the 1985 and 1992 measurements in relation to dioxin exposure.

In summary, these findings do not provide evidence of a clinically significant dose-response effect for body burden of dioxin on parameters of immunologic assessment. The minor, statistically significant relationships that do have a small magnitude bear potential for long-term evaluation to identify trends, but currently cannot be interpreted to indicate specific health impairment caused by immune system dysfunction.

Pulmonary Assessment

The pulmonary assessment consisted of three historical variables, physical examination of thorax and lung abnormalities, and six laboratory measurements. Because the lung is often involved secondarily in numerous infectious, inflammatory, and neoplastic disorders, the assessment of lung disease includes a comprehensive multisystem review conducted during the examinations and reported in other chapters. All episodes of pulmonary disease were verified by medical records review.

In the group analyses, Ranch Hands had a significantly higher prevalence of bronchitis and thorax and lung abnormalities. Conversely, pneumonia was less common in Ranch Hands than in Comparisons, though not statistically significant. Of interest, but of uncertain cause, Ranch Hand enlisted flyers appeared to be more at risk than Comparisons, respecting history of bronchitis and thorax and lung abnormalities; however, there was no evidence from the analyses of extrapolated initial and current serum dioxin measurements to confirm a dose-response relationship.

For the laboratory variables, a statistically significant inverse relationship was revealed between percent of predicted forced vital capacity (FVC) and initial and current serum dioxin in Ranch Hands. However, when Ranch Hands were contrasted with Comparisons, no significant differences were detected. The ratio of observed forced expiratory volume in 1 second (FEV_1) to observed FVC in Ranch Hands also revealed a significant relationship with initial dioxin, indicating that the ratio increased (became closer to 1) for increasing levels of extrapolated initial dioxin; this effect may be due to the diminishing magnitude of FVC in the denominator of the ratio. Although consistent with a dose-response effect, the changes in the ratio were slight and of doubtful physiologic significance.

In the longitudinal analysis of the ratio of observed FEV_1 to observed FVC, a significant group difference was shown for the enlisted flyers. The Ranch Hand enlisted flyers had a larger decrease in the ratio between 1982 and 1992 than did the Comparison enlisted flyers, but the difference is not physiologically significant, and there was no evidence for any trend in relation to the extrapolated initial or current serum dioxin levels.

In summary, the historical, physical examination, and laboratory data analyzed for the pulmonary assessment revealed no consistent evidence of an increased prevalence of pulmonary disease in the Ranch Hand cohort relative to the Comparison cohort or in relation to body burden of dioxin.

INTERPRETIVE CONSIDERATIONS

There are certain facts that need to be understood in drawing conclusions from the statistical analysis of the 1992 followup examination results. For example, there are often difficulties associated with multiple testing. With multiple models applied against hundreds of variables, the likelihood of a statistical test indicating some artifactual association is high. But longitudinal comparisons of previous examinations may show a consistent association, supporting a non-artifactual relationship. However, longitudinal tests of the same population are clearly not independent tests. If a chance association was present at the first physical examination, it would tend to persist in subsequent examinations.

Conversely, depending on putative site and mode of action, the association would be expected to increase with time (if latency or other chronic effects predominate) or decrease with time (if current dioxin level predominates in the mechanism). It is also important to note that some conditions do not appear with reasonable frequency until middle age or later, and, in the early years of the study, an eventual significant increase in relative risk in a population easily might be masked by data too sparse for meaningful analysis.

The putative site and mode of action in the body could itself either cause or obscure a relationship. Receptors might be activated only after a certain dioxin threshold value had been exceeded—that is, a value exceeding the body's capability to safely store dioxin. If, on the other hand, dioxin caused a competitive inhibition of receptor actions normally stimulated by other substances, there might be a "no-threshold" effect. Depending on the nature (lipid or non-lipid) and type of function of the hypothetical receptor site, an increase in body fat over time might either cause an increase in dioxin effect because of a greater volume of distribution or a decrease in dioxin effect because of a lesser concentration at the receptor site.

Strength of association is also an issue in a study of a population this size. A study with a population of 2,233 lacks power to determine increases in relative risks for rare events, because rare events are unlikely to occur in a group this small. While certain occupational toxins have truly pathognomonic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually non-existent in the absence of the toxin, other toxins merely increase the risk of non-pathognomonic pathology. For example, in the absence of a dioxin-pathognomonic lesion, this study would likely not discern an increase in the relative risk for a rare tumor. By assessing the pathology observed in association with other known environmental risk factors (e.g., tobacco use, alcohol use) it is sometimes possible to provide an upper bound for the magnitude of effect missed. However, this study has inherent limits in detecting modest increases in relative risk for infrequent pathology.

A final difficulty is the presence of a true association that is non-causal. An example might be a condition not caused by dioxin, but resulting in or from an altered biological dioxin half-life. In this case, a correlation might be high in the total absence of causality.

Clearly, there are many issues to be considered in interpreting data for this study. With these issues in mind, certain assessments were made by looking at a number of factors. Among these factors are longitudinal trends, biological plausibility, consistency with animal

toxicology, the presence of a plausible dose-response relationship, and strength of association. But, meeting all of these criteria would not guarantee causality, nor would failing these criteria guarantee the lack of a dioxin effect. It can be argued, however, that the good faith application of these particular filters should be the starting point for generating hypotheses for experimental examination through in vitro and in vivo testing, as well as through further epidemiological analysis of these and other dioxin exposed groups.

SUMMARY

Based on the statistical findings of the 1992 examination, and subject to the qualifications considered above, the principal investigators have drawn the following conclusions.

Glucose Intolerance

The results indicate a statistically and potentially clinically significant association between serum dioxin and glucose intolerance. This association exhibits a dose response relationship, and is present both for non-diabetic individuals (as manifested by elevated insulin levels) and diabetic individuals (as manifested by increased prevalence and severity of diabetes, and decreased age of onset). This association was found with type II diabetes only. This association was also present longitudinally and occurs in other epidemiological studies in addition to the AFHS.

Cardiovascular Mortality

There is a statistically significant increase in cardiovascular mortality in the most heavily exposed subgroup, the enlisted groundcrew. This association persists longitudinally throughout the three examination cycles. Inclusion of this group with lesser exposed Ranch Hand subgroups results in a statistically nonsignificant overall relative risk. Less clinically severe criteria for altered cardiac functions including ECG findings of prior myocardial infarction, non-specific ST- and T-wave changes, and RBBB displayed significant positive associations with dioxin, although these associations did not cause significant group differences between all Ranch Hands and all Comparisons. Peripheral vascular function variables displayed significant subgroup differences for both the enlisted groundcrew and the high current dioxin category in relation to the Comparisons. Both groups had a greater prevalence of new pulse deficits arising since the 1985 followup examination than did their Comparisons.

Serum Lipid Abnormality

There is a highly significant positive statistical association between dioxin and cholesterol, dioxin and triglycerides, and dioxin and the cholesterol-HDL ratio in most models using either current dioxin levels or dioxin levels extrapolated to the end of the tour of duty in SEA. In such models, the correlation between HDL cholesterol and dioxin was highly significant and negative. These lipid findings were consistent with the 1987 findings, but were not consistent with the 1982 examination when serum cholesterol in Ranch Hands was significantly lower than in Comparisons.

Liver Enzymes

Both lipid-adjusted and whole-weight current dioxin showed elevated mean aspartate aminotransferase (AST), ALT, and GGT associations. For ALT and GGT this association was highly significant. This association had not been present in previous examinations. Although these elevations were statistically significant, mean enzyme levels remained well within normal limits and the prevalence of abnormally elevated liver enzymes was not statistically increased. Thus, although this laboratory finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Increase in IgA

A marginally significant increase in IgA with increased serum dioxin was found. This paralleled similar findings of increased IgA, first noted in the 1987 followup. Although this elevation was marginally significant, mean IgA levels remained well within normal limits, and the prevalence of significant abnormally elevated IgA was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Decrease in Serum Testosterone

A statistically significant inverse effect was seen between total serum testosterone and current dioxin in Ranch Hands. This paralleled similar findings first noted in the 1987 followup. Although this decrease was statistically significant, mean serum testosterone levels remained well within normal limits, and the prevalence of abnormally low serum testosterone was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Decrease in MSK and Lupus Panel Positives

Significant and marginally significant decreases in the prevalence of positive reactions to MSK, lupus, and rheumatoid factor tests in relation to dioxin were seen in the 1992 followup. When present, these tests are indicative of potential autoimmune disorders. Their absence is therefore not normally considered pathologic, but a decreased prevalence could nonetheless indicate some degree of immune suppression. More specific tests of immune suppression were not significantly associated with dioxin.

No Significant Difference in Incidence or Prevalence of Neoplastic Disease

It has been theorized that dioxin can act as either an inducer or promoter of neoplastic disease. A detailed analysis of all forms of neoplastic disease over the course of a decade show no significant group differences in the incidence of benign or malignant neoplasms, including those neoplasms most often associated with herbicide exposure in the Ranch Hand population (e.g., Hodgkin's Disease, non-Hodgkin's lymphoma, soft tissue sarcoma). In the 1992 followup, there was again no significant group differences. The marginally significant differences in site-specific incidence that were found more often favored a decrease in relative risk associated with dioxin exposure rather than an increased risk. As previously

stated, because of its size, this study does lack power to ascertain modest increases in relative risk for uncommon neoplasms. As the population continues to age, the combination of an increase in background rate of neoplastic disease, increased time for latent effects of past exposure, and increased time of total exposure may combine to increase the power of this study to determine neoplastic effects.

In summary, glucose intolerance, serum lipid abnormality, and cardiovascular abnormality and mortality, are areas demonstrating associations that, if causality were established, would represent the most important dioxin-associated health problems seen in the AFHS to date. These three areas appear to have the greatest magnitude of effect in terms of absolute increase in risk, in common areas known to contribute to years of potential life lost and to overall healthcare costs. Clearly, there are biological interrelationships among all three of these variables that will make the task of establishing causality, as well as establishing primary versus secondary causality, challenging. From a public health perspective, these three areas demand the greatest attention.

CHAPTER 22

FUTURE DIRECTIONS

A careful review of the results of the past four physical examinations provides an opportunity to refine and focus the remaining two examinations of the Air Force Health Study. The current and prior examination outcomes have identified several medical tests requiring more intense evaluation and other analyses that can be reduced or eliminated in the 1997 and 2002 studies without sacrificing scientific value.

Immunological testing of skin test reactivity, T-cell type, and T-cell function were important parts of all four examinations, and high-quality data in this area were gathered in the 1985, 1987, and 1992 studies. After exhaustive evaluation, there appear to be some effects that may be dioxin-related. Therefore, many of these measurements will remain in the 1997 study. However, the skin test reactivity measurement is medically redundant with the battery of cell function tests, and thus will be eliminated from the next examination. Additionally, many of the highly nonspecific tests in the protein profile and lupus panel will be eliminated. Many of these tests are poorly understood by clinical pathologists and immunologists and should be removed from consideration.

The Doppler evaluation of the large artery pulses (radial and femoral) also will be eliminated, reducing examination time and stress on the participants. Our data does not indicate any dioxin-mediated effect on these arteries. However, the relationship between dioxin and diabetes makes it imperative that the smaller arteries of the legs and feet remain a key part of the examination.

Because no association was found between testicular abnormality detected during ultrasound and dioxin, the ultrasound evaluation of the testicles will be eliminated.

Additional dioxin assays will be performed on willing Ranch Hands who have participated in our studies of dioxin half-life. A fourth measurement, taken from blood collected in 1997, will further refine our estimate of half-life, allow study of the fit of the first order elimination model, and permit better estimates of the initial dose in Ranch Hands with elevated current dioxin levels.

The 1997 examination will be expanded to include additional measurements of the cellular metabolism of glucose. The possible development of a laboratory measurement of specific enzymes involved in glucose transport into the cell would be an important addition to the current evaluation of diabetes.