

# **AIR FORCE HEALTH STUDY COMPREHENSIVE REPORT**

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

**February 1984 to March 2005**

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## 1    **PREFACE**

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2    The Air Force Health Study (AFHS) is an epidemiologic study to determine whether long-term health  
3    effects exist and can be attributed to occupational exposure to herbicides, with specific emphasis on  
4    Agent Orange. This report is a summary of the results of the six physical examinations conducted during  
5    the AFHS that began in 1982. Study results have been published in reports for each examination and also  
6    have been summarized in articles published in peer-reviewed scientific journals. This report is based on  
7    the journal articles and the seven reports published from these six examinations: the Baseline Morbidity  
8    Study Results (24 February 1984, referred to as the 1982 baseline examination in this report), the Air  
9    Force Health Study First Followup Examination Results (15 July 1987), the Air Force Health Study 1987  
10    Followup Examination Results (16 January 1990), the Air Force Health Study Serum Dioxin Analysis of  
11    1987 Examination Results (7 February 1991), the Air Force Health Study 1992 Followup Examination  
12    Results (2 May 1995), the Air Force Health Study 1997 Follow-up Examination Results (22 February  
13    2000), and the Air Force Health Study 2002 Follow-up Examination Results (31 March 2005).

14    The findings in the articles may differ from the physical examination reports because they may (a)  
15    combine data from two or more physical examinations, (b) use different methods of analysis, (c) focus on  
16    specific health endpoints, and (d) include different risk factors. The results in the journal articles are  
17    often consistent, but sometimes lead to conclusions that differ from the seven reports. For example,  
18    published articles on diabetes in Ranch Hand veterans revealed an association with dioxin exposure  
19    consistent with the examination report. Published articles on peripheral neuropathy, memory loss, and  
20    cancer, however, revealed associations not examined in the examination reports.

21    This report is written in a narrative format with the sparse use of statistical significance metrics. Where  
22    possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
23    demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized, with only a  
24    brief mention of nonsignificant results. Significant results that appeared consistently across examinations  
25    or have biological meaning are emphasized. Results that are significant, but sporadic, isolated, or  
26    inconsistent, are given less emphasis.

27    The lack of a particular finding does not prove that no association exists and should not lead the reader to  
28    conclude that there is no association between herbicide exposure and adverse health. Consistent with the  
29    protocol, study investigators continue to question the underlying assumptions of all analyses, explore new  
30    ways to analyze data, and collaborate with specialists to determine whether exposure to Agent Orange  
31    adversely affected the health of Ranch Hand veterans.

32    The AFHS is scheduled to end on September 30, 2006.

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# 1 INTRODUCTION

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2 This chapter describes the purpose and background of the Air Force Health Study (AFHS) and provides  
3 an overview of the study design and format of this report.

## 4 1.1 PURPOSE OF THE REPORT

5 The objective of the AFHS was to determine whether long-term health effects exist and can be attributed  
6 to occupational exposure to herbicides, with specific emphasis on Agent Orange, a one-to-one mixture of  
7 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), contaminated  
8 with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In this report, the use of the term “dioxin” refers to  
9 TCDD. The principal investigators and the AFHS reports used dioxin levels as a surrogate for exposure  
10 for most of the study, as derived from the early peer review groups, review of the literature, and the  
11 Ranch Hand Advisory Committee. Although there are approximately 75 different congeners of dioxin,  
12 TCDD is believed to be the most toxic and the only contaminant of 2,4,5-T.

13 This report is a discussion and a compilation of the findings from research related to the mortality,  
14 reproductive outcomes, and morbidity components of the AFHS. Subsequent to the protocol, which was  
15 published in 1982 (1), the baseline physical examination was conducted in 1982, and follow-up  
16 examinations were performed in 1985, 1987, 1992, 1997, and 2002. Reports and journal articles  
17 describing the findings of each of these examinations have been published (2-8).

## 18 1.2 BACKGROUND

19 In 1961, President Ngo Dinh Diem of South Vietnam asked the United States to conduct aerial spraying  
20 of herbicides in his country. In November 1961, President John F. Kennedy approved the use of  
21 herbicides, but only as a limited experiment (9). In January 1962, Operation Ranch Hand, the designation  
22 for the program, began for the purpose of defoliation and crop destruction in support of tactical military  
23 operations in the Republic of Vietnam (RVN). Gradually, limitations were relaxed and spraying became  
24 more frequent (9). Operation Ranch Hand dispersed approximately 19 million gallons of herbicides on an  
25 estimated 10 to 20 percent of the RVN from 1962 to 1971. The herbicides sprayed were code-named  
26 Herbicide Green, Herbicide Pink, Herbicide Purple, Herbicide Orange, Herbicide White, and Herbicide  
27 Blue. 2,4,5-T was an active ingredient in Herbicides Green, Pink, Purple, and Orange, and dioxin was  
28 produced as an inadvertent contaminant of 2,4,5-T during the manufacturing process. 2,4-D was an  
29 active ingredient in Herbicides Purple, Orange, and White. Picloram was an active ingredient in  
30 Herbicide White; cacodylic acid was the active ingredient in Herbicide Blue. Of the 19 million gallons of  
31 herbicide dispersed, approximately 11 million gallons were Herbicide Orange, also called “Agent  
32 Orange,” the primary defoliant of the six herbicides used in the program (9, 10).

33 The following chart lists the names, periods of use, and compositions of the major herbicide mixtures  
34 used in the RVN (9):

<b>Military Color Code or Trade Name*</b>	<b>Period of Use</b>	<b>Composition (Active Ingredient)</b>
Pink	1962-1964	60% n-butyl ester of 2,4,5-T, 40% isobutyl ester of 2,4,5-T
Green	1962-1964	100% n-butyl ester of 2,4,5-T
Pink-green mixture	1962-1964	80% n-butyl ester of 2,4,5-T, 20% isobutyl ester of 2,4,5-T
Dinoxol	1962-1964	50% butyloxyethanol ester of 2,4-D, 50% butyloxyethanol ester of 2,4,5-T
Trinoxol	1962-1964	100% butyloxyethanol ester of 2,4,5-T
Purple	1962-1964	50% n-butyl ester of 2,4-D, 30% n-butyl ester of 2,4,5-T, 20% isobutyl ester of 2,4,5-T
Blue	1962-1971	100% sodium salt of cacodylic acid
Orange	1965-1970	50% n-butyl ester of 2,4-D, 50% n-butyl ester of 2,4,5-T
Orange II	1965-1970	50% n-butyl ester of 2,4-D, 50% isooctyl ester of 2,4,5-T
White	1965-1971	80% triisopropanolamine salt of 2,4-D, 20% triisopropanolamine salt of picloram

35

36 \*Herbicide drums were identified by a circular band of paint colored in correspondence with these color codes.

37 From the start, Operation Ranch Hand was heavily scrutinized because of the controversial nature of the  
38 program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The  
39 concerns were initially based on military, political, and ecological issues, but shifted to the issue of health  
40 in 1970. The primary concern in the controversy over the human health effects of these herbicides was  
41 related to dioxin, a component in four of the six herbicides sprayed. The Air Force estimated that 368  
42 pounds of dioxin were released over 6 million acres in the RVN (10). Other researchers have estimated  
43 that the amount of dioxin released was nearly double the Air Force estimate (11). Claims of exposure to  
44 herbicides, particularly to Agent Orange, and perceived adverse health effects among U.S. military  
45 service personnel resulted in substantial controversy and, eventually, class-action litigation. Social  
46 concern for the Agent Orange issue continues to be reflected in scientific research, media presentations,  
47 congressional hearings, and legal action.

48 Since 1970, governmental agencies, universities, and industrial firms have funded numerous human and  
49 animal studies of dioxin effects. A key scientific issue in these studies was the degree of exposure (e.g.,  
50 who was exposed and to what extent each individual was exposed). Unfortunately, in many of the human  
51 studies, population identification and exposure estimation were scientifically elusive.

52 In October 1978, the Air Force Deputy Surgeon General made a commitment to Congress and the White  
53 House to conduct a health study on the Operation Ranch Hand population. This population comprised the  
54 aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The  
55 Surgeon General tasked the U.S. Air Force School of Aerospace Medicine at Brooks Air Force Base,  
56 Texas, to develop a study protocol. In 1982, after extensive peer review, the study protocol was  
57 published (1) and the epidemiological study began. The now Brooks City-Base organizations responsible  
58 for executing the protocol have been reorganized and renamed several times since 1982. Currently, the  
59 Air Force Research Laboratory, Human Effectiveness Directorate, is responsible for the technical aspects  
60 of the study, and the Human Systems Group, Agile Combat Support Systems Wing, is responsible for  
61 program management.

62 In 1987, when the serum dioxin assay became available, the Air Force entered into a collaborative effort  
63 with the Centers for Disease Control and Prevention (CDC) to measure the serum dioxin levels in the  
64 AFHS population. The results of that effort demonstrated that substantially elevated levels of dioxin

65 could still be found in the serum of some Ranch Hands (12, 13). Studies of serum dioxin levels have  
66 suggested that of all the military personnel who served in the RVN, the Ranch Hand cohort was one of  
67 the most highly exposed to herbicides containing dioxin (14). If herbicides caused an adverse health  
68 effect, then, based on the principle of dose-response, the Ranch Hands should have manifested more or  
69 earlier evidence of adverse health.

### 70 **1.3 AIR FORCE HEALTH STUDY DESIGN**

71 For the baseline examination, the population ascertainment process identified 1,264 Ranch Hand  
72 personnel who served in Southeast Asia (SEA) between 1962 and 1971. At the beginning of the AFHS, a  
73 Comparison group was identified. Comparison veterans flew primarily transport missions in SEA during  
74 the same time period that the Ranch Hand unit was active. Their units used C-130 transport planes flown  
75 and serviced by crews with similar training and background as those of Ranch Hand veterans. While  
76 Ranch Hand veterans spent most of their SEA service in the RVN, Comparison veterans spent on average  
77 less than 30 percent of their SEA service in the RVN and were stationed mostly in Taiwan, the  
78 Philippines, Guam, Japan, and Thailand. These Comparison veterans may have been stationed in one, but  
79 usually in at least two countries; many had repeated tours of duty in the region. A computerized selection  
80 procedure was used to identify Comparisons with similar characteristics to each Ranch Hand veteran.

81 Comparisons were matched to a Ranch Hand, based on age, race, and military occupation (officer-pilot,  
82 officer-navigator, officer-other, enlisted flyer, enlisted groundcrew). As many as 10 Comparisons were  
83 identified for each Ranch Hand. The purpose of identifying multiple Comparisons was an attempt to  
84 maintain the size of the Comparison group when a previously chosen Comparison declined to participate  
85 in a subsequent follow-up examination. Ranch Hands could not be replaced because the entire population  
86 was asked to participate. Comparisons, however, could be replaced. A protocol was established to  
87 describe the circumstances under which a Comparison was replaced and the method for replacement of  
88 Comparisons. After a personnel records review, an average of eight Comparison subjects were matched  
89 to each Ranch Hand.

### 90 **1.4 MORTALITY AND MORBIDITY COMPONENTS**

91 The mortality component addressed noncombat mortality from the time of the SEA assignment. A  
92 baseline mortality review was conducted in 1982, and the mortality follow-up reports included periodic  
93 mortality updates over the course of the AFHS. For the baseline mortality review and the first four  
94 updates, five individuals were randomly selected from the matched Comparison set for each Ranch Hand  
95 for a 1:5 design. In 1987, the design was expanded to include all 19,078 veterans in the Comparison  
96 population.

97 The baseline morbidity component, begun in 1982, reconstructed the medical history of each participant  
98 by reviewing and coding past medical records. A cross-sectional element, designed to assess the  
99 participant's current state of physical and mental health, was based on comprehensive physical  
100 examinations and questionnaires. Information on reproductive outcomes also was collected. For the  
101 morbidity component of the study, each living Ranch Hand and a random living member of his  
102 Comparison set were selected to participate in the examination. The morbidity follow-up examinations  
103 comprised sequential questionnaires, medical records reviews, and physical examinations in 1985, 1987,  
104 1992, 1997, and 2002. Participation was voluntary and each participant signed an informed consent form  
105 at the examination site.

106 For the baseline examination and the 1985 and 1987 follow-up examinations, the major focus of the  
107 analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the  
108 Comparisons (i.e., the unexposed cohort). Methodology to measure dioxin body burden in blood was not  
109 made available until February 1987. During the 1987 physical examination, the Air Force began a  
110 collaborative study with the CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons  
111 (12, 13, 15). The measurement of serum dioxin levels led to a statistical evaluation to assess dose-  
112 response relations between dioxin and health endpoints in 12 clinical areas. This was the first large-scale  
113 study of dose-response effects based on a direct measurement of dioxin. The statistical analyses  
114 associated with the serum data evaluated the association between a specified health endpoint and dioxin  
115 among the Ranch Hands. The analyses also contrasted the health of various categories of Ranch Hands  
116 having differing serum dioxin levels with the health of Comparisons having background levels (10 parts  
117 per trillion or less) of serum dioxin (5). The analysis of dose-response relations based on serum assays  
118 provided an important enhancement to the previous AFHS investigations.

119 In 1992, the fourth examination was initiated. The analysis focused on group differences between the  
120 Ranch Hand and Comparison cohorts and on the association of each health endpoint with serum dioxin  
121 levels. The fifth examination began in 1997, and the sixth and final examination began in 2002. As in  
122 1992, the analyses in 1997 and 2002 focused on group differences between the Ranch Hand and  
123 Comparison cohorts and on the association of each health endpoint with extrapolated initial and 1987  
124 serum dioxin levels (described in Chapter 2).

## 125 **1.5 TYPES OF DATA COLLECTED**

126 The types of data collected on participants included questionnaire data, medical records, physical  
127 examination and laboratory findings, and biological specimens. A baseline questionnaire was developed  
128 in 1982 and the questions remained the same for all six examinations. This questionnaire obtained  
129 information on demographics, education, occupation, medical history, study compliance, toxic exposures,  
130 and reproductive history. In general, responses to histories and other questions where the response did  
131 not change over time were obtained in the baseline questionnaire. All veterans who participated in the  
132 1982 baseline examination completed the baseline questionnaire at that time, and a veteran who was new  
133 to the AFHS after 1982 completed the baseline questionnaire when he first participated in the study.

134 In examinations subsequent to the baseline examination, all participants were asked questions to update  
135 their histories since their last interviews. These data were obtained and recorded in an interval  
136 questionnaire. Reported health conditions in the baseline and interval questionnaires were confirmed by a  
137 review of external medical records and classified using International Classification of Diseases, 9<sup>th</sup> and  
138 10<sup>th</sup> Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes.

139 The core content of the interval questionnaire has remained constant since its inception with only minor  
140 modifications. If a veteran participated in the AFHS for the first time in a follow-up examination (1985,  
141 1987, 1992, 1997, or 2002), he was administered a baseline questionnaire to collect historical information  
142 through 1982 and an interval questionnaire to collect updates since 1982. Administering a baseline  
143 questionnaire at the first time of participation in the study and collecting interval updates when a  
144 participant attended a follow-up examination allowed the Air Force to gather histories without  
145 unnecessary repetition.

146 The physical examination portion included laboratory testing, physical examinations, psychological  
147 testing, medical debriefings, and specialized testing (e.g., nerve conduction velocity testing at the 2002  
148 physical examination). The Air Force carefully prescribed the details of the examination in an examiner's

149 handbook, given to each of the examining clinicians. Clinical variations were neither desired nor  
150 authorized; all proposed examination procedural changes were reviewed in detail by Air Force technical  
151 and contractual personnel prior to the start of the examinations. An important objective of the entire  
152 physical examination process was to ensure that bias was not created by any procedural change.

153 The requirement for the clinic staff to be “blinded” to the participant’s group status (i.e., Ranch Hand,  
154 Comparison) was particularly stringent. The clinical staff was prohibited from knowing or seeking  
155 information as to the group identity of any participant. Participants also were instructed not to divulge  
156 their group status to any of the staff members. At the end of his examination, each participant was asked  
157 to note on the evaluation form whether such information was sought by any member of the clinical or  
158 paramedical staff. If necessary, but only rarely, the physician or technician involved was reminded to be  
159 more careful in his or her conversations.

160 The examination content, as designed by the Air Force, emphasized detection of medical endpoints  
161 suspected of being associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. In each  
162 follow-up examination, the Air Force used findings from the previous examination to refine the next  
163 examination.

## 164 **1.6 AFHS PARTICIPATION**

165 Across the 25 years of examinations, participation in the AFHS has been considered excellent for a cohort  
166 of this size and age. The number of Ranch Hands and Comparisons who participated in each of the six  
167 examinations is provided below.

<b>Group/Examination</b>	<b>1982</b>	<b>1985</b>	<b>1987</b>	<b>1992</b>	<b>1997</b>	<b>2002</b>
Eligible to Participate	1,209	1,199	1,188	1,149	1,102	1,043
Ranch Hand Participants	1,046	1,017	996	953	870	777
Percentage of Ranch Hands Who Participated Relative to Those Eligible to Participate	86.5%	84.8%	83.8%	82.9%	78.9%	74.5%
Comparison Participants	1,223	1,292	1,298	1,280	1,251	1,174
<b>Total</b>	<b>2,269</b>	<b>2,309</b>	<b>2,294</b>	<b>2,233</b>	<b>2,121</b>	<b>1,951</b>

168

169 Of the 1,043 Ranch Hands who were eligible to participate in the 2002 follow-up examination, 777 chose  
170 to participate (74.5%). Of the 777 Ranch Hands and 1,174 Comparisons who participated in the 2002  
171 follow-up examination, 671 (86.4%) of the Ranch Hands and 811 (69.0%) of the Comparisons  
172 participated in all six examinations.

## 173 **1.7 REPORT ORGANIZATION**

174 This report is organized as follows:

- 175 • Chapter 1 (Introduction) explains the purpose of the report; provides summary background  
176 information on the AFHS; describes the study design; and discusses mortality and morbidity  
177 components, the types of data collected, statistics on AFHS participation, and the organization  
178 of this report.
- 179 • Chapter 2 (Measures of Exposure) describes the three basic methods for quantifying exposure  
180 to herbicides and dioxin that have been used across the history of the AFHS.

- 181 • Chapter 3 (Interpretive Considerations) discusses specific technical items and issues that may  
182 have affected the interpretations of results found in the AFHS reports and journal articles.
- 183 • Chapter 4 (Illnesses Presumptively Recognized as Agent Orange-Connected) describes  
184 findings in the AFHS population that correspond to the 12 conditions that the Department of  
185 Veterans Affairs presumed were related to exposure to herbicides, such as Agent Orange,  
186 among veterans serving in-country during the Vietnam War.
- 187 • Chapter 5 (Reproductive Outcomes) describes findings from reports and journal articles that  
188 study the health, survival, and reproductive outcomes of Ranch Hands.
- 189 • Chapter 6 (Mortality) presents the results of analyses on the cumulative all-cause and  
190 individual-cause mortality of Ranch Hands.
- 191 • Chapters 7 through 18 present a summary of results found in the statistical analyses that were  
192 conducted on morbidity data collected from the 1982, 1985, 1987, 1992, 1997, and 2002  
193 examinations. These chapters are organized by clinical area and further organized by health  
194 endpoint. The chapters corresponding to the 12 clinical areas are as follows:
- 195 Chapter 7: Cardiovascular Assessment  
196 Chapter 8: Dermatology Assessment  
197 Chapter 9: Endocrinology Assessment  
198 Chapter 10: Gastrointestinal Assessment  
199 Chapter 11: General Health Assessment  
200 Chapter 12: Hematology Assessment  
201 Chapter 13: Immunology Assessment  
202 Chapter 14: Neoplasia Assessment  
203 Chapter 15: Neurology Assessment  
204 Chapter 16: Psychology Assessment  
205 Chapter 17: Pulmonary Assessment  
206 Chapter 18: Renal Assessment.
- 207
- 208 • Chapter 19 (Conclusions) provides an overall summary of the reproductive outcomes,  
209 mortality, and morbidity findings.

210 This report is written in a narrative format with the sparse use of statistical significance metrics. Where  
211 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
212 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized, with only a  
213 brief mention of nonsignificant results. Significant results that appeared consistently across examinations  
214 or have biological meaning are emphasized. Results that are significant, but sporadic, isolated, or  
215 inconsistent, are given less emphasis.

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## 2 MEASURES OF EXPOSURE

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### 2.1 INTRODUCTION

Throughout the 25 years of the Air Force Health Study (AFHS), numerous techniques have been used in attempts to quantify exposure to herbicides. The classic method of comparing “exposed” and “unexposed” veterans have been termed “Group” analyses in the AFHS and have been used in analyses of data from the baseline and all follow-up examinations. By the nature of this two-category classification, however, the magnitude of exposure within the exposed group was not quantified. In the reports based on data collected at the 1982, 1985, and 1987 examinations, an exposure index was constructed based on personnel records and spraying history. During the 1987 physical examination, as the analytical technology became available, the Air Force began a collaborative study with the Centers for Disease Control and Prevention (CDC) to measure dioxin levels directly in the serum of Ranch Hands and Comparisons (1-3). Data collected at the 1987, 1992, 1997, and 2002 follow-up examinations were analyzed using the serum dioxin measurement.

A summary of the measures of exposure used to analyze data from each examination is shown below:

Measure of Exposure/Examination	1982	1985	1987	1992	1997	2002
Group	X	X	X	X	X	X
Exposure Index	X	X	X			
Serum Dioxin Measurement			X	X	X	X

None of these methods is without controversy, and all methods have their advantages and disadvantages. A background and discussion of these three methods are provided in more detail in this chapter. These methods of measuring exposure were used in analyzing mortality, reproductive outcome, and morbidity data, and the subsequent chapters of this report summarize the findings from the analysis.

### 2.2 GROUP STATUS

The exposed population, termed “Ranch Hand,” was defined as those individuals who were formally assigned to the U.S. Air Force organizations responsible for the aerial dissemination of herbicides and insecticides with C-123 aircraft on the Republic of Vietnam (RVN) from 1962 through 1971. These individuals were identified from historical data sources (morning reports, military personnel records, and historical computer tapes) at the National Personnel Records Center, St. Louis, Missouri, and the U.S. Air Force Human Resources Laboratory, Brooks Air Force Base, Texas.

A review of all specialized flight units present in Southeast Asia (SEA) during the Vietnam War revealed that there did not exist an absolutely ideal control group for the Ranch Hand population. Non-Ranch Hand crews flying C-123 aircraft were considered as a comparison group, but the limited size of this population and the subsequent reconfiguration of these aircraft for transport and insecticide missions raised the possibility that a control group from this population might not truly be unexposed. Crewmembers of C-7 aircraft were considered, but the size of this population also was limited and these crewmembers served in the RVN after 1967 only. It finally was decided to use C-130 crewmembers as the control group.

35 The Comparison population was defined as those individuals who were assigned to C-130 aircraft  
36 organizations in SEA during the same time period as the Ranch Hands. Cargo-mission aircrew members  
37 and support personnel were selected because of sufficient population size and similar training and military  
38 background experiences to the Ranch Hand group. The Comparison population was not engaged in the  
39 aerial spraying of herbicides or insecticides. Identification of this population was completed using similar  
40 methods to those used for the Ranch Hand group.

41 Ranch Hands and multiple Comparisons were matched by closest month of birth, race (Black versus non-  
42 Black), and occupational code (categorized as officer-pilot, officer-navigator, officer-other,  
43 enlisted-flying, and enlisted-ground). Matching Ranch Hands and Comparisons on age attempted to  
44 account for the many clinical symptoms and signs associated with advancing age. Matching on race  
45 attempted to account for differences in chronic disease development. Military occupation was strongly  
46 associated with educational background and socioeconomic status.

47 As many as 10 Comparisons were identified for each Ranch Hand. The purpose of identifying multiple  
48 Comparisons was an attempt to maintain the size of the Comparison group when a previously chosen  
49 Comparison declined to participate in a subsequent follow-up examination. A declining study group size  
50 lessens the ability to detect a statistical difference between Ranch Hands and Comparisons. Ranch Hands  
51 could not be replaced because the entire population was asked to participate. Comparisons, however,  
52 could be replaced. A protocol was established to describe the circumstances under which a Comparison  
53 was replaced and the method for replacement.

54 Analyses contrasting the Ranch Hand and Comparison cohort are straightforward, easy to interpret, and  
55 well established in epidemiological studies when a better measure of exposure is not available. Ranch  
56 Hands were coded as “exposed” in these analyses, and Comparisons were coded as “not exposed,”  
57 without regard to the magnitude of the exposure or possible misclassifications.

58 Results of the dioxin assay, which are discussed in more detail later in this chapter, appeared to show a  
59 difference in measured dioxin levels among the three military occupational categories (officers, enlisted  
60 flyers, and enlisted groundcrew). As an attempt to quantify exposure, three contrasts of Ranch Hands and  
61 Comparisons were performed along with the overall Ranch Hand versus Comparison contrast for the  
62 reports on the 1992, 1997, and 2002 follow-up examinations. These contrasts compared Ranch Hands  
63 and Comparisons within the three military occupational categories. As discussed below, the median  
64 levels of exposure to dioxin among Ranch Hands were highest for enlisted groundcrew, followed by  
65 enlisted flyers, then officers.

### 66 **2.3 ORIGINAL AFHS EXPOSURE INDEX**

67 The exposure index as originally described in the AFHS protocol was used for the analysis of data  
68 collected at the 1982 baseline, 1985 follow-up, and 1987 follow-up examinations. The exposure index  
69 was related to the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-containing herbicides: Herbicide Orange,  
70 Herbicide Purple, Herbicide Pink, and Herbicide Green. Archived samples of Herbicide Purple suggested  
71 that the material had a mean TCDD concentration of approximately 33 parts per million (ppm) and  
72 Herbicide Orange had a mean concentration of 2 ppm. Herbicides Pink and Green contained twice the  
73 TCDD of Herbicide Purple and, therefore, have been estimated to contain TCDD at a concentration of  
74 approximately 66 ppm (4, 5).

75 The exposure index used,  $E_i$ , specific to each Ranch Hand subject  $i$ , was  $E_i = W * G_i / N_i$ , where

76  $W$  = TCDD weighting factor

77  $G_i$  = gallons of TCDD-containing herbicide sprayed in the RVN theater during the  $i^{\text{th}}$  subject's  
78 tour of duty, and

79  $N_i$  = number of airmen with subject's duties in the Vietnam theater during the  $i^{\text{th}}$  subject's tour of  
80 duty.

81 The exposure index was, therefore, directly related to the amount of TCDD-containing herbicide sprayed  
82 and inversely related to the number of airmen with similar duties.

83 The TCDD weighting factor was 24 or 1, depending on whether the material sprayed was sprayed before  
84 or after 1 July 1965. The weighting factor of 1 was used for the period after 1 July 1965, as  
85 documentation showed that only Herbicide Orange was disseminated by Air Force-flown, fixed-wing  
86 aircraft at that time. Prior to 1 July 1965, a combination of Herbicides Green, Pink, and Purple were  
87 sprayed by Air Force personnel in the RVN. After analysis of the data and normalization to Agent  
88 Orange concentrations, a weighting factor of 24 was established. Herbicides Blue and White also were  
89 sprayed during these time periods, but these herbicides did not contain TCDD and, therefore, were not  
90 used in determining a TCDD weighting factor.

91 The dates of each subject's tour(s) of duty in the RVN were determined by a review of military records.  
92 Records and reports were used to construct a table of gallons of TCDD-containing herbicide sprayed for  
93 each month during Operation Ranch Hand. Only fixed-wing spray missions were used because Ranch  
94 Hand personnel were not involved with helicopter and other spraying, such as from a backpack. The tour  
95 dates and the amount sprayed were combined to determine the gallons of TCDD-containing herbicide  
96 sprayed in the RVN theater during the  $i^{\text{th}}$  subject's tour of duty.

97 The number of Ranch Hand airmen with the subject's duties in the Vietnam theater during the  $i^{\text{th}}$  subject's  
98 tour of duty was determined relative to the five military occupational categories: officer-pilot, officer-  
99 navigator, officer-other, enlisted-flying, and enlisted-ground. For the purposes of analysis, the first three  
100 categories were combined into a single class called "officers." Navigators and pilots were exposed in the  
101 same manner, and other officers were administrators whose exposure was considered effectively zero. In  
102 addition, all administrative personnel in the enlisted ground category were assigned a zero exposure  
103 value. The number of Ranch Hand airmen in each of the three categories—officer, enlisted-flying, and  
104 enlisted-ground—was used in the calculation of the exposure index.

#### 105 **2.4 SERUM DIOXIN MEASUREMENT**

106 At the 1987 physical examination, the Air Force initiated a collaborative study with the CDC to measure  
107 dioxin levels in the serum of Ranch Hands and Comparisons (1-3). The results of that effort  
108 demonstrated that substantially elevated levels of dioxin could still be found in the serum of some Ranch  
109 Hands (1, 2). Studies of serum dioxin levels have suggested that of all the military personnel who served  
110 in the RVN, the Ranch Hand cohort was one of the most highly exposed to herbicides. If dioxin caused  
111 an adverse health effect, then, based on the principle of dose-response, the Ranch Hands should have  
112 manifested more or earlier evidence of adverse health.

113 The analysis of dose-response relations based on serum assays provided an important enhancement to the  
114 previous AFHS investigations. This was the first large-scale study of dose-response effects based on a  
115 direct measurement of dioxin.

116 At the 1992, 1997, and 2002 follow-up examinations, attempts were made to determine dioxin levels for  
117 new subjects and those who were not previously measured at the 1987 follow-up examination. In  
118 addition, serum samples were taken from selected Ranch Hands at these examinations to provide insight  
119 on dioxin levels and the elimination of dioxin from the body.

120 The measurement of serum dioxin levels led to a statistical evaluation that assessed dose-response  
121 relations between dioxin and health endpoints in 12 clinical areas. The statistical analyses associated with  
122 the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch  
123 Hands. The analyses also contrasted the health of various categories of Ranch Hands having differing  
124 serum dioxin levels with the health of Comparisons having background levels (10 parts per trillion [ppt]  
125 or less) of serum dioxin (6). In particular, three forms of the measure of dioxin were used, referred to as  
126 initial dioxin, categorized dioxin, and 1987 dioxin.

127 The correlation between the original AFHS exposure index and serum dioxin levels was described in the  
128 dioxin analysis of the 1987 physical examination results (6). The exposure index was an indirectly  
129 calculated measure derived solely from personnel records and historical information. The serum dioxin  
130 level was used as a measure of exposure, and dioxin levels in Ranch Hands appeared to be placed  
131 logically relative to cohorts from other dioxin studies. In general, the relation between the measures of  
132 dioxin and the original AFHS exposure index showed weak associations between these alternative  
133 measures of exposure. The analysis reflected the high percentage of veterans who would be misclassified  
134 with regard to dioxin level if the original AFHS exposure index was assumed as the standard. For  
135 example, 77 of 287 (26.8%) Ranch Hand veterans in the original AFHS high exposure index category had  
136 dioxin levels less than 9 ppt.

#### 137 **2.4.1 Initial Dioxin Model**

138 The relation between a health endpoint and an extrapolated initial dioxin measure was examined for  
139 Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. Data on 213 Ranch Hand  
140 veterans with dioxin measured in blood collected in 1982, 1987, 1992, and 1997 produced a half-life  
141 estimate of 7.6 years (7); this estimate was used to extrapolate the 1987 dioxin level back in time to the  
142 end of the tour of duty that qualified a Ranch Hand veteran for inclusion in this study. If a Ranch Hand  
143 did not have a 1987 dioxin level, then the first dioxin measured, either at the 1992, 1997, or 2002 physical  
144 examination, was used to estimate the initial dioxin level. A statistical adjustment for body mass index at  
145 the time of the participant's blood measurement of dioxin was included in this model to account for body  
146 mass index-related differences in elimination rate (7).

147 Regardless of when the dioxin was measured, Ranch Hand veterans with a level less than or equal to 10  
148 ppt were excluded from statistical analyses. Pharmacokinetic studies (7) were restricted to 343 Ranch  
149 Hand veterans with 1987 dioxin greater than 10 ppt because it was thought this value represented an  
150 upper threshold for background exposure (as evidenced by the fact that 10 ppt was the 98<sup>th</sup> percentile of  
151 the Comparison dioxin distribution) and that the ability to extrapolate using the half-life estimate did not  
152 hold at background levels.

153 **2.4.2 Categorized Dioxin Model**

154 The Ranch Hands for whom an initial dioxin was estimated were divided into two categories based on  
155 their initial dioxin measures. These two categories were referred to as “low Ranch Hand” and “high  
156 Ranch Hand.” Two additional categories—Ranch Hands with serum dioxin levels at or below 10 ppt and  
157 Comparisons—were formed and included in the model. Ranch Hands with serum dioxin levels at or  
158 below 10 ppt were assigned to the “background Ranch Hand” category. If a Ranch Hand did not have a  
159 1987 dioxin measurement, the first measured dioxin level was used. Another category was examined by  
160 combining the low and high Ranch Hand categories.

161 Consequently, five categories were used in categorized dioxin analyses:

- 162 • Comparisons
- 163 • Background Ranch Hands (serum dioxin levels at or below 10 ppt)
- 164 • Low Ranch Hands (serum dioxin levels greater than 10 ppt, category cutpoint based on initial  
165 dioxin level but varied by examination, cutpoint specified in the table below)
- 166 • High Ranch Hands (serum dioxin levels greater than 10 ppt, category cutpoint based on initial  
167 dioxin level but varied by examination, cutpoint specified in the table below)
- 168 • Low and high Ranch Hands combined (serum dioxin levels greater than 10 ppt, all Ranch  
169 Hands included).

170 The relation between the health endpoint in each of the four Ranch Hand categories and the health  
171 endpoint in the Comparison category was examined. As with analyses involving initial dioxin, a  
172 statistical adjustment for body mass index at the time of the participant’s blood measurement of dioxin  
173 was included in this model (7).

174 Whereas the extrapolated initial dioxin measure used dioxin in its continuous form for analysis,  
175 categorized dioxin inherently placed a participant in one of the five classifications provided above. Since  
176 1987, the methodology has been refined, the estimate of the half-life has been revised using additional  
177 data, the cohorts attending the follow-up examination have changed, and the nomenclature of the  
178 categories has changed. Below is a list of which participants are included in each of the dioxin categories  
179 for analysis of the 1987, 1992, 1997, and 2002 follow-up examinations:

Dioxin Category	1987 Follow-up Examination	1992 Follow-up Examination	1997 Follow-up Examination	2002 Follow-up Examination
Comparison	≤10 ppt measured dioxin level*	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level	All
Background (Ranch Hands)	≤10 ppt measured dioxin level**	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level
Low (Ranch Hands)	15 ppt < measured dioxin level ≤ 33 ppt	measured dioxin level > 10 ppt, initial dioxin ≤ 143 ppt	measured dioxin level > 10 ppt, initial dioxin ≤ 94 ppt	measured dioxin level > 10 ppt, initial dioxin ≤ 118 ppt
High (Ranch Hands)	measured dioxin level > 33 ppt	measured dioxin level > 10 ppt, initial dioxin > 143 ppt	measured dioxin level > 10 ppt, initial dioxin > 94 ppt	measured dioxin level > 10 ppt, initial dioxin > 118 ppt
Low and High (Ranch Hands)	measured dioxin level > 15 ppt	measured dioxin level > 10 ppt	measured dioxin level > 10 ppt	measured dioxin level > 10 ppt

180

181 \*called “Background” in the 1987 follow-up examination report

182 \*\*called “Unknown” in the 1987 follow-up examination report

### 183 2.4.3 1987 Dioxin Model

184 The relation between the health endpoint and dioxin levels, as measured in 1987, was examined for all  
 185 Ranch Hands with a dioxin measurement. If a Ranch Hand did not have a 1987 dioxin measurement, the  
 186 first dioxin level obtained, either in 1992, 1997, or 2002, was extrapolated to the date of the 1987  
 187 physical examination. If the first dioxin level was not obtained in 1987 and was less than or equal to  
 188 10 ppt, it was not extrapolated to 1987 level, but used at the measured value. This measure was termed  
 189 “current dioxin” in the 1987 and 1992 follow-up examination reports and “1987 dioxin” in the 1997 and  
 190 2002 follow-up examination reports.

191 When 1987 dioxin levels were examined for Comparisons, the vast majority of levels (approximately  
 192 98%) were below 10 ppt (8). The median 1987 dioxin level for Ranch Hands, however, was 11 ppt, and  
 193 there was a distinct difference among military occupation categories. The median dioxin level was 24 ppt  
 194 for enlisted groundcrew, 16 ppt for enlisted flyers, and 7 ppt for officers. The patterns within military  
 195 occupation appeared to agree with Ranch Hand crew chief interviews conducted before the results of the  
 196 assay became available to AFHS participants (9).

197 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 198 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 199 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 200 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 201 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 202 18.6 years (referred to as the “earlier” tour of duty throughout this report) and whose difference was at  
 203 most 18.6 years (referred to as the “later” tour of duty throughout this report).

204 Analyses performed using earlier and later tours of duty allowed investigation of the 1987 dioxin relation  
 205 with health in relation to time. For example, if there were no relation between a measure of health and  
 206 dioxin in the first few years after exposure, and a strong relation many years after exposure, there may be  
 207 no association for Ranch Hands with later tours and an association for Ranch Hands with earlier tours. It  
 208 is important to note that an effect of this kind could be due to the passage of time or to a higher initial  
 209 dioxin level received by Ranch Hands with earlier tours, or both.

210 **2.5 THE ORIGINAL AFHS EXPOSURE INDEX VERSUS SERUM DIOXIN MEASUREMENTS**

211 In the first three AFHS reports, summarizing results of physical examinations conducted in 1982, 1985,  
212 and 1987, the potential relation between health endpoints and herbicide exposure in Ranch Hand veterans  
213 was assessed using the original AFHS exposure index. Six different herbicides were used in the RVN by  
214 Operation Ranch Hand to defoliate by aerial spraying from C-123 aircraft. From 1962 through 1965,  
215 small quantities of Agents Purple (2,4-D; 2,4,5-T), Blue (cacodylic acid), Pink (2,4,5-T), and Green  
216 (2,4,5-T) were sprayed. From 1965 through 1970, more than 11 million gallons of Agent Orange (2,4-D,  
217 2,4,5-T) and smaller quantities of White (2,4-D, picloram) and Blue were sprayed; from 1970 through  
218 1971 only Agents White and Blue were used for defoliation purposes (10). The exposure index was only  
219 an estimate of dioxin exposure because the actual concentration of dioxin in the herbicides varied with  
220 type and lot and because exposure varied with individual work habits and duties. The calculation of the  
221 index was necessary because direct measures of dioxin exposure were not available at that time.

222 The original AFHS exposure index was based on the untested assumption that the exposure of an  
223 individual decreased as the number of men available increased. The calculation was performed for each  
224 month of an individual's tour of duty, and the monthly results were summed to produce a single exposure  
225 index for each Ranch Hand veteran. Each veteran was then assigned to a low, medium, or high exposure  
226 category. These categories were of nearly equal size, and the cutpoints for these categories were different  
227 for the three military occupational categories (officer, enlisted flyer, or enlisted groundcrew).

228 Subsequent to 1987, all outcomes in this study were assessed with group contrasts and the dioxin body  
229 burden measured in serum. The 1987 results were analyzed twice, first using the original AFHS exposure  
230 index (11), and then using the dioxin body burden as the measure of exposure (6).

231 The Ranch Hand Advisory Committee and the AFHS investigators believed the serum dioxin level was  
232 the most appropriate measure of exposure in this study because of the following:

- 233 • It was a direct measurement of the contaminant.
- 234 • It has been accurately measured (12).
- 235 • It correlated with reported skin exposure to herbicides among enlisted Ranch Hand veterans  
236 (9).
- 237 • Its elimination in Ranch Hand veterans followed a plausible pharmacokinetic pattern (7).
- 238 • It has been found to be plausibly associated with health conditions in this study and in other  
239 studies (13).

240 Both measures, the original AFHS exposure index and the serum dioxin measurement, have limitations.  
241 The exposure index was approximate in that the number of gallons sprayed used the totals across all bases  
242 rather than at a specific base. In addition, the assumption that exposure decreased as the number of men  
243 available increased may not have been reasonable. Interviews with Ranch Hand groundcrew in 1989  
244 revealed that as the workload increased, more men were added to the job, resulting in more men  
245 becoming exposed rather than each man becoming less exposed. Finally, the spectrum of behaviors,  
246 skills, duties, weather-related work stoppages, work surges due to war conditions, and other factors (some  
247 known, some unknown) were not included in the calculation. For example, some Ranch Hand  
248 groundcrew had direct contact with bulk quantities of herbicide by filling the tanks and servicing the  
249 equipment, while others drove trucks or forklifts. The index did not distinguish between these two kinds  
250 of exposure patterns. In addition, some Ranch Hands were assigned to administrative duties, which were  
251 indicated in their military records. The original AFHS exposure index was defined as zero for those  
252 assigned to administrative duties.

253 The serum dioxin measurement is also limited as a measure of exposure. Although the half-life of dioxin  
254 is long (7.6 years), pharmacokinetic studies of Ranch Hand veterans suggested that the half-life varies  
255 with body fat (7). Thus, some veterans may eliminate dioxin quickly and others more slowly. Variation  
256 of the dioxin half-life with body fat contributed to variation in the extrapolated initial dose at the time of  
257 exposure. In addition, more than 45 percent of Ranch Hand veterans had background levels, precluding  
258 extrapolation. Some of those with background levels may have had elevated levels while in the RVN,  
259 while others may not have been occupationally exposed at all. The exposure status of Ranch Hands with  
260 background levels cannot be resolved with available data. Furthermore, no validated model exists to  
261 assess the adequacy of the estimated initial dose as an estimate of actual exposure among those with  
262 dioxin levels above background in 1987, 1992, 1997, or 2002. Use of serum dioxin measurements as a  
263 measure of exposure in the RVN is further confounded by the other possible sources of dioxin exposure.  
264 These sources include industrial exposure and environmental factors, such as burning of plastics and fish  
265 consumption.

266 Throughout the 1987, 1992, 1997, and 2002 follow-up examination reports, dioxin levels were used as  
267 measures of both exposure to dioxin itself and exposure to dioxin-contaminated herbicides, including  
268 Agent Orange. Direct contrasts of Ranch Hand and Comparison veterans (group analyses) addressed the  
269 hypothesis of health effects attributable to any herbicide exposure experienced by Ranch Hand veterans  
270 during Operation Ranch Hand. Models involving dioxin measurements addressed the hypothesis that  
271 health effects change with the amount of exposure. Dioxin measurements were used as a measure of  
272 exposure to dioxin-contaminated herbicides because it was expected that as exposure to such herbicides  
273 increased, dioxin levels should increase. Therefore, the dioxin measurement served as a direct biomarker  
274 of exposure to dioxin-contaminated herbicides. No other direct measure or estimate of herbicide  
275 exposure was available with which to address hypothetical dose-response relations with health. Some  
276 indirect measures, such as self-report of skin contact among enlisted groundcrew, or simply being a  
277 Ranch Hand enlisted groundcrew member, are valuable alternatives because dioxin measures suggest that  
278 enlisted groundcrew experienced the heaviest exposures. Reported skin exposure was not addressed, but  
279 enlisted groundcrew status was addressed in contrasts of Ranch Hands and Comparisons. The use of  
280 dioxin as a measure of exposure to dioxin-contaminated herbicides was consistent with the goal of the  
281 study, which was to determine whether adverse health effects exist and can be attributed to occupational  
282 exposure to Agent Orange (14).

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## 3 INTERPRETIVE CONSIDERATIONS

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### 3.1 INTRODUCTION

In interpreting results from any epidemiological study, no single result should be evaluated in isolation or out of context. Rather, interpretations should be addressed in the context of the overall study design, the data collection procedures, the data analysis methods, dose-response effects, strength of association, temporal relation, biological plausibility, and internal and external consistency. This especially applies to the Air Force Health Study (AFHS). This effort was a large-scale prospective observational study in which thousands of measurements and diagnoses were compiled on each participant. Those measurements and diagnoses were subjected to extensive statistical analyses, testing thousands of individual hypotheses. Each positive result should be scrutinized relative to findings in other studies, and relative to the statistical methods used and the medical and biological 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 possibly incorrect assertion that there is no effect. In addition, no epidemiological study can establish that there is no effect; i.e., that dioxin is safe (1). Critical considerations in the evaluation of results from this study are reviewed in this chapter.

### 3.2 STUDY DESIGN AND MODELING CONSIDERATIONS

Biased results will be produced if the assumptions underlying any of the statistical models are violated. As in any epidemiological study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis of no exposure effect because of possible exposure misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Recent dioxin data indicate that 45 percent of the Ranch Hands have only background serum dioxin levels. Either these Ranch Hands were never exposed or their initially elevated serum dioxin levels may have decreased to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether Ranch Hands who have background dioxin levels had elevated levels in the past because there was no method of measuring dioxin in blood prior to 1987 and because no blood was collected and saved prior to 1982.

Analyses of the association between health endpoints and extrapolated initial dioxin levels also are vulnerable to bias because they directly depend on two unvalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life. If dioxin elimination is first-order, but some Ranch Hands have a shorter half-life than others do, then there would have been misclassification of initial dioxin levels.

The half-life of dioxin was found to change with body mass index in 213 Ranch Hand veterans with up to four dioxin measurements, derived from serum drawn in 1982, 1987, 1992, and 1997 (2). The half-life increased with higher levels of obesity. A constant half-life was used in each report and was an estimate derived without adjustment for body mass index (2). As a partial solution to the observed relation between half-life and obesity, analyses using categorized dioxin or initial dioxin were adjusted for body mass index at the time of the blood measurement of dioxin. A study of dioxin elimination in 20 men exposed during the accident in Seveso, Italy, has validated the first-order model (3), which was the basis for the half-life estimate used in this report. Validated models of dioxin elimination adjusted for body mass index or changes in body mass index, however, have not yet been derived.

41 To account for the possible misclassification of exposure between groups, the statistical model using  
42 categorized dioxin classifies Ranch Hands into three levels of exposure: background levels of lipid-  
43 adjusted dioxin and low and high levels of estimated initial dioxin. Each Ranch Hand dioxin category  
44 was contrasted with all Comparisons. Although this model was less dependent on the accuracy of the  
45 initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the  
46 classification of the Ranch Hands is subject to bias if the half-life and first-order dioxin elimination  
47 assumptions are not true. In addition, the Ranch Hands with background levels of lipid-adjusted serum  
48 dioxin may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels  
49 have decreased to background levels. This will result in a bias toward the null hypothesis of no dioxin  
50 effect on the health endpoint.

51 The model that analyzes the association between a 1987 dioxin measurement and health endpoints may be  
52 less subject to bias than other models that use dioxin as an exposure measure; however, recent dioxin  
53 levels may not be a good measure of exposure if serum dioxin elimination rates differed among  
54 individuals. Serum dioxin levels were extrapolated from 1992 measurements to 1987 for Ranch Hand  
55 veterans without serum dioxin levels measured in 1987. Serum dioxin levels also were extrapolated from  
56 1997 measurements to 1987 for Ranch Hand veterans without levels measured in 1987 or 1992. In  
57 addition, serum dioxin levels were extrapolated from 2002 measurements to 1987 for Ranch Hand  
58 veterans without levels measured in 1987, 1992, or 1997. These extrapolations were performed only if  
59 the most recent measurement was greater than 10 parts per trillion (ppt). Therefore, these 1987 dioxin  
60 measurements are subject to bias from a possible violation of the half-life and first-order elimination  
61 assumptions that may affect the initial dioxin estimates. It is recognized that the serum dioxin level may  
62 have been greater than 10 ppt in 1987, but measurements taken from 1992, 1997, or 2002 may have been  
63 at 10 ppt or less and may eliminate individuals whose levels were above 10 ppt during the prior years,  
64 resulting in misclassification.

### 65 **3.3 INFORMATION BIAS**

66 Information bias, represented by the over- or under-reporting of disease symptoms, was minimized by  
67 verifying all diseases and conditions with medical records. It is possible that conditions in Ranch Hands  
68 may be more verifiable because they may have been seen by physicians more often than Comparisons.  
69 This would be revealed by group differences in the quantity and content of medical records. Because  
70 there is no way to quantify these aspects, this potential source of bias remains unexplored. This bias, if it  
71 existed, would affect only the models contrasting Ranch Hands and Comparisons (group analyses and  
72 categorized dioxin analyses). Information bias due to errors in the data introduced through data entry or  
73 machine error was negligible. All laboratory results were subject to strict quality control procedures,  
74 historical data were verified completely by medical records review, and medical data were subjected to  
75 strict quality control standards.

### 76 **3.4 CONSISTENCY OF RESULTS**

77 All statistically significant findings in the baseline and follow-up reports were subjected to clinical  
78 review, ensuring internal consistency throughout the report. In addition, these findings were compared to  
79 published results from other studies to ensure external consistency.

80 **3.5 STRENGTH OF ASSOCIATION**

81 A strong adverse association between exposure and a disease condition, if it exists, would be revealed by  
82 an increased relative risk. Some authors have suggested that a statistically significant relative risk greater  
83 than 2.0 is cause for concern (4). Statistically significant relative risks less than 2.0 are generally  
84 considered to be less important than larger risks because relative risks less than 2.0 can arise more easily  
85 because of unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this  
86 concern. The numbers 2.0 and 5.0 are epidemiological guidelines regarding analyses of association  
87 between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general  
88 guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as  
89 cholesterol) versus continuously distributed exposure (such as extrapolated initial dioxin estimates or  
90 serum dioxin measurements).

91 Statistical power is also an issue in a study with a population this size. A study with a population of the  
92 approximately 2,000 veterans who completed physical examinations lacks power to determine increases  
93 in relative risks for rare events (such as soft tissue sarcoma) because such events are unlikely to occur in  
94 large numbers in a group this small. While certain occupational toxins have a clear diagnostic pathology  
95 (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually nonexistent in the  
96 absence of the causative agent, other toxins merely increase the risk of nondiagnostic pathology. For  
97 example, the AFHS would likely not discern an increase in the relative risk for a rare tumor that does not  
98 have a clear diagnostic pathology. By assessing the pathology observed in association with other known  
99 environmental risk factors (e.g., tobacco use, alcohol use), it is sometimes possible to provide a limit in  
100 the magnitude of effect missed; however, this study has inherent bounds in detecting modest increases in  
101 relative risk for infrequent pathology.

102 **3.6 RESULTS BASED ON INDIRECT MEASURES OF THE VIETNAM EXPERIENCE AND**  
103 **HERBICIDE EXPOSURE**

104 Interpretations of cohort contrasts in this study have been limited because, by design, both cohorts  
105 comprised veterans of the Vietnam War. Thus, the study was not designed to assess directly the  
106 Southeast Asia (SEA) or Vietnam experience but rather the effect, if any, of occupational exposures to  
107 herbicides, with specific emphasis on Agent Orange, in Ranch Hand veterans relative to other Vietnam  
108 veterans who were not occupationally exposed. A “Vietnam” effect, if equally expressed by Ranch Hand  
109 and Comparison veterans, would not be detectable in this study.

110 The primary focus of this study was the potential effects of herbicide/dioxin exposure on health  
111 outcomes. The flexibility of the statistical methodology and the comprehensive nature of the data  
112 collected, however, permitted the analysis of other factors, as allowed for in the AFHS protocol (5).  
113 Because it was impossible to know exactly the kind and amount of herbicide or other chemical exposures  
114 experienced during the Vietnam War by AFHS veterans, indirect measures of the Vietnam experience and  
115 herbicide exposure based on general knowledge of the Vietnam War, as derived from published accounts,  
116 have been considered. Morbidity analyses of cancer incidence, in which the Ranch Hand and  
117 Comparison cohorts were stratified by time spent in the SEA region and the percentage of SEA service  
118 spent in Vietnam, have been performed. Analyses of cancer incidence using the national population as a  
119 reference, with and without restriction to dates of tour, also have been conducted.

120 Stratifications of AFHS participants that have been analyzed include (a) restriction of length of tour of  
121 duty to at most 2 years, and (b) restriction to Ranch Hand veterans with 100 percent of their SEA service  
122 spent in the Republic of Vietnam (RVN) and Comparison veterans with 0 percent of their SEA service  
123 spent in the RVN. These stratifications were attempts to maximize the Agent Orange exposure

124 opportunity among Ranch Hand veterans and minimize it among Comparison veterans. Categorizing  
125 veterans by the amount of time spent in SEA approximated categorization by the percentage of SEA  
126 service spent in Vietnam. Stratification by the percentage of SEA service in Vietnam gave a clearer  
127 dichotomy on the Vietnam experience.

128 Results of cancer incidence analyses using these restrictions have been described in a 2004 journal article  
129 by Akhtar et al. (6). Analyses found that the incidence of melanoma and prostate cancer was increased  
130 among white Ranch Hand veterans after restriction to participants whose tour of duty occurred between  
131 1966 and 1970, the period of heaviest Agent Orange spraying. Among Ranch Hands who spent at most 2  
132 years in SEA, the risk of cancer at any site was increased in the low and high dioxin categories relative to  
133 Comparisons who spent at most 2 years in SEA. Among Ranch Hands who spent 100 percent of their  
134 SEA tour(s) of duty in Vietnam, the risk of cancer at any site was increased in the low and high dioxin  
135 categories relative to Comparisons who spent 0 percent of their SEA tour(s) of duty in Vietnam.

136 Analyses of this type demonstrate that effects not observed in the entire population may be seen in  
137 subgroups of AFHS veterans. In addition, analyses based on stratification by operational factors, rather  
138 than nonmedical risk factors, may yield results in certain subgroups. Stratification, however, can limit the  
139 ability to detect a difference because of the inherent reduction in sample size. The series of reports for the  
140 AFHS have focused on analyses based on standard epidemiological models that use known medical and  
141 demographic risk factors, but additional analysis on subpopulations with alternative risk factors may yield  
142 different results.

### 143 **3.7 BIOLOGICAL PLAUSIBILITY**

144 The assessment of biological plausibility requires consideration of a biological mechanism relating the  
145 exposure and effect of interest. While a lack of biological plausibility or even a contradiction of  
146 biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism  
147 may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological  
148 mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological  
149 explanation of results must be interpreted with caution. In the AFHS, statistically significant results were  
150 subjected to medical review and comparison with previously published results to identify consistent and  
151 biologically plausible results.

### 152 **3.8 INTERPRETATION OF NONSIGNIFICANT RESULTS**

153 In this study, a lack of significant results relating dioxin to a particular disease only means that the study  
154 was unable to detect a relation between dioxin and health. This does not imply that a relation may not  
155 exist, but that if it does exist, it was not detected. A lack of significant results does not mean that dioxin  
156 is safe or that there is no relation between dioxin and health. The AFHS was not designed to establish  
157 safety; rather, this study was designed to determine whether a hazard existed for the exposed personnel.  
158 Determination of safety would require a study at least 10 times as large, as determined in a 1985 study  
159 presenting minimal sample size criteria for proof of safety and hazard in studies of environmental and  
160 occupational exposures (1).

### 161 **3.9 EXTRAPOLATION TO ARMED FORCES GROUND TROOPS**

162 Extrapolation of the serum dioxin results to the general population of ground troops who served in  
163 Vietnam is problematic because Ranch Hand and ground troop exposure situations were very different

164 from one another. Based on serum dioxin testing results obtained by the Centers for Disease Control and  
165 Prevention (7) and others (8), nearly all ground troops tested had 1987 levels of dioxin similar to  
166 background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had 1987  
167 dioxin levels similar to those in men who never left the United States (with mean dioxin levels of 4.2 ppt  
168 and 4.1 ppt, respectively). There is little scientific basis for an extrapolation of these results to the larger  
169 population of Vietnam veterans. The possibility that a limited number of veterans could have been  
170 exposed to levels of dioxin comparable to the Ranch Hand veterans cannot be excluded, but because  
171 blood or adipose tissue were not collected immediately after their return from Vietnam, the actual  
172 exposures of these veterans cannot be known. Others may have received long-term low-dose exposure.  
173 These possibilities and a multitude of factors, including differential elimination and exposures to other  
174 persistent organic pollutants, suggest that existing data do not provide an adequate basis for extrapolation.

### 175 **3.10 CONSIDERATIONS FOR SUMMARIZING RESULTS**

176 A study of this scope with a multitude of endpoints demands, and at the same time defies, meaningful  
177 summary tabulation. Such summaries can be misleading because they ignore correlations between the  
178 endpoints, correlations between examination results, and the nonquantifiable medical importance of each  
179 endpoint. In fact, some endpoints were indices developed from combining multiple endpoints. Other  
180 endpoints, such as psychological scales, may be highly associated with other similar endpoints. In  
181 addition, such tabulations combine endpoints that are not medically or biologically comparable. For  
182 example, diminished sense of smell may be of less medical importance than the presence of a malignant  
183 neoplasm. Summaries can be misleading and must be interpreted carefully—an elementary tally of  
184 significant, or nonsignificant, results is not appropriate.

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## 4 ILLNESSES PRESUMPTIVELY RECOGNIZED AS AGENT ORANGE-CONNECTED

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### 4.1 INTRODUCTION

Any veteran who served in Vietnam between January 9, 1962, and May 7, 1975, and has one or more of the following conditions is presumed by the Department of Veterans Affairs to have been exposed to Agent Orange, and, therefore, presumptively recognized that his condition is service-connected (1, 2):

- Acute and subacute transient peripheral neuropathy (must appear within 1 year of exposure and resolve within 2 years of date of onset)
- Chloracne (must occur within 1 year of exposure)
- Chronic lymphocytic leukemia
- Hodgkin's disease
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Porphyria cutanea tarda (PCT) (must occur within 1 year of exposure)
- Prostate cancer
- Respiratory cancers, including cancers of the lung, larynx, trachea, and bronchus
- Soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma)
- Spina bifida (in children of Vietnam veterans born after the veteran's tour in Vietnam) (except spina bifida occulta)
- Type 2 diabetes.

Congress directed the Secretary of Veterans Affairs in Public Law 102-4, signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam War. In 1994, the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides published its first report (4). This report classified evidence of an association between a health problem and exposure to herbicides as "sufficient," "limited/suggestive," or "inadequate/insufficient." The evidence regarding association was drawn from occupational, environmental, and veterans studies in which individuals were exposed to the herbicides used in Vietnam, to their components, or to their contaminants. Since this report, the IOM has published five biennial updates—1996, 1998, 2000, 2002, and 2004—incorporating results from additional studies (5-9). The work of this committee has provided the Department of Veterans Affairs

33 with the necessary information to create the list of compensable conditions described above. The  
34 recommendations from this committee are included in further discussion of these conditions in this  
35 chapter.

36 In the subsequent descriptions of the compensable conditions given above, summaries of Ranch Hands in  
37 each of the dioxin categories (background, low, or high) are often provided. Ranch Hands in the  
38 background dioxin category had a measured dioxin level of 10 parts per trillion (ppt) or less. Ranch  
39 Hands in the low dioxin category had a measured dioxin level of greater than 10 ppt and an estimated  
40 initial dioxin level of 118 ppt or less. Ranch Hands in the high dioxin category had a measured dioxin  
41 level of greater than 10 ppt and an estimated initial dioxin level of greater than 118 ppt.

42 A dioxin measurement was available for 1,027 of the 1,197 Ranch Hands for whom medical records were  
43 available. Of these 1,027 Ranch Hands, 452 were in the background dioxin category, 287 were in the low  
44 dioxin category, and 288 were in the high dioxin category. Of the 170 Ranch Hands for whom a dioxin  
45 level was not available, 148 did not participate in the Air Force Health Study (AFHS) after the 1985  
46 follow-up examination, and the serum dioxin measurement was not available until the 1987 follow-up  
47 examination.

48 A dioxin measurement was available for 1,524 of the 1,855 Comparisons for whom medical records were  
49 available. Of these 1,524 Comparisons, 1,489 Comparisons had a measured dioxin level of 10 ppt or less  
50 and 35 Comparisons had a measured dioxin level of more than 10 ppt. Of the 331 Comparisons for whom  
51 a dioxin level was not available, 305 did not participate in the AFHS after the 1985 follow-up  
52 examination, and the serum dioxin measurement was not available until the 1987 follow-up examination.

53 Findings from the AFHS for these conditions are described in the remainder of this chapter. Descriptions  
54 of each of these conditions have been taken from the April 2005 Veterans Affairs' *Agent Orange Review*  
55 (3). The term "compound of interest" in the discussions includes 2,4-dichlorophenoxyacetic acid (2,4-D),  
56 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin  
57 (TCDD, or dioxin), cacodylic acid, and picloram.

## 58 **4.2 ACUTE AND SUBACUTE TRANSIENT PERIPHERAL NEUROPATHY**

59 Peripheral neuropathy is a nervous system condition that causes numbness, tingling, and muscle  
60 weakness. This condition affects only the peripheral nervous system, that is, only the nervous system  
61 outside the brain and spinal cord. Only the transient (short-term) acute and subacute forms of this  
62 condition, not the chronic persistent forms, have been associated with herbicide exposure.

63 No Ranch Hands or Comparisons were observed with acute or subacute transient peripheral neuropathy in  
64 the AFHS.

65 In the 1996 *Veterans and Agent Orange* update (5), the Committee to Review the Health Effects in  
66 Vietnam Veterans of Exposure to Herbicides concluded that there is "limited/suggestive" evidence of an  
67 association between exposure to certain herbicides used in Vietnam and the development of early onset  
68 (previously termed "acute and "subacute") transient peripheral neuropathy. This conclusion remained  
69 unaltered in the 2004 *Veterans and Agent Orange* update (9). In this report, however, the committee  
70 added that there was inadequate or insufficient "evidence to determine an association between exposure to  
71 compounds of interest and delayed or persistent peripheral neuropathy."

72 **4.3 CHLORACNE**

73 Chloracne is a skin condition that looks like common forms of acne seen in teenagers. The first sign of  
74 chloracne may be excessive oiliness of the skin. This is accompanied or followed by numerous  
75 blackheads. In mild cases, the blackheads may be limited to the areas around the eyes extending to the  
76 temples. In more severe cases, blackheads may appear in many places, especially over the cheekbone and  
77 other facial areas, behind the ears, and along the arms. If chloracne appears, however, it is usually after a  
78 short interval of exposure to dioxin, without a long latency period, and usually persists for a maximum of  
79 2 to 3 years.

80 No Ranch Hands or Comparisons were observed with chloracne in the AFHS.

81 In the first *Veterans and Agent Orange* report in 1994 published by the IOM, the Committee to Review  
82 the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there is sufficient  
83 evidence of an association between exposure to dioxin and chloracne (4). This conclusion remained  
84 unaltered in the 2002 *Veterans and Agent Orange* update (8); however, the committee added a notation  
85 that chloracne would appear shortly after dioxin exposure and not after a long latency (8). The 2004  
86 *Veterans and Agent Orange* update concurred with previous reports (9).

87 **4.4 CHRONIC LYMPHOCYTIC LEUKEMIA**

88 Chronic lymphocytic leukemia is a disease that progresses slowly with increasing production of excessive  
89 numbers of white blood cells. In the 2004 *Veterans and Agent Orange* update, the epidemiologic  
90 evidence was considered by the Committee to Review the Health Effects in Vietnam Veterans of  
91 Exposure to Herbicides to be “sufficient” concerning chronic lymphocytic leukemia, and “exposure to at  
92 least one compound of interest (9).”

93 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, five Ranch  
94 Hands and six Comparisons had chronic lymphocytic leukemia. Three of the Ranch Hands with chronic  
95 lymphocytic leukemia were in the background dioxin category, one of the Ranch Hands was in the low  
96 dioxin category, and one Ranch Hand did not have a dioxin measurement. The six Comparisons with  
97 chronic lymphocytic leukemia had a measured dioxin level less than 10 ppt.

98 In 2004, the AFHS staff and colleagues published one journal article related to cancers of the  
99 lymphopoietic system, where lymphomas, multiple myeloma, and leukemia were combined because of a  
100 sparse number of occurrences (10). No adverse effects to Ranch Hands were noted in this analysis.

101 **4.5 HODGKIN’S DISEASE**

102 Hodgkin’s disease is a malignant lymphoma characterized by progressive enlargement of the lymph  
103 nodes, liver, and spleen, and by progressive anemia. The IOM, as reported in the first *Veterans and Agent  
104 Orange* book in 1994 on the health effects of herbicides used in Vietnam (4), concluded that there is  
105 “sufficient” evidence to establish an association, although not a causal relation, between dioxin exposure  
106 and the occurrence of Hodgkin’s disease (4). The 2004 *Veterans and Agent Orange* update stated that an  
107 association existed between exposure to at least one of the compounds of interest and Hodgkin’s disease  
108 (9).

109 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, one Ranch  
110 Hand and three Comparisons had Hodgkin’s disease. The Ranch Hand with Hodgkin’s disease was in the

111 background dioxin category. The three Comparisons with Hodgkin’s disease had a measured dioxin level  
112 less than 10 ppt.

#### 113 **4.6 MULTIPLE MYELOMA**

114 Multiple myeloma is a cancer of specific bone marrow cells that is characterized by bone marrow tumors  
115 in various bones of the body. The evidence for an association, although not a causal relation, between  
116 dioxin exposure and the occurrence of multiple myeloma was considered “limited/suggestive” by the  
117 IOM Committee in the first *Veterans and Agent Orange* report and all updates (4-9).

118 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, four  
119 Ranch Hands and one Comparison had multiple myeloma. One of the Ranch Hands with multiple  
120 myeloma was in the background dioxin category and three were in the low dioxin category. The one  
121 Comparison with multiple myeloma had a measured dioxin level less than 10 ppt.

#### 122 **4.7 NON-HODGKIN’S LYMPHOMA**

123 Non-Hodgkin’s lymphoma is a group of malignant tumors that affect the lymph glands and other  
124 lymphatic tissue. These tumors are relatively rare compared to other types of cancer, and although  
125 survival rates have improved during the past 2 decades, these diseases tend to be fatal.

126 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, two Ranch  
127 Hands and seven Comparisons had non-Hodgkin’s lymphoma. One of the Ranch Hands with non-  
128 Hodgkin’s lymphoma was in the background dioxin category and one was in the high dioxin category.  
129 Six of the seven Comparisons with non-Hodgkin’s lymphoma had a measured dioxin level; one of these  
130 six Comparisons had a measured dioxin level greater than 10 ppt.

131 The IOM, as reported first in their 1994 book on the health effects of herbicides used in Vietnam (4),  
132 concluded that there is “sufficient” evidence to establish an association, although not a causal relation,  
133 between dioxin exposure and the occurrence of non-Hodgkin’s lymphoma (4-9). In the 2004 *Veterans  
134 and Agent Orange* update, the committee concluded there was sufficient evidence to conclude that an  
135 association existed between exposure to at least one compound of interest and non-Hodgkin’s lymphoma  
136 (9).

#### 137 **4.8 PORPHYRIA CUTANEA TARDA (PCT)**

138 PCT is a disorder characterized by liver dysfunction and by thinning and blistering of the skin in sun-  
139 exposed areas. The IOM, as reported first in their 1994 book on the health effects of herbicides used in  
140 Vietnam (4), concluded that there is “sufficient” evidence to establish an association, although not a  
141 causal relation between herbicides or dioxin and PCT. In the 1996 report, the association with PCT was  
142 downgraded from “sufficient” to “suggestive” evidence, based on studies completed since the first IOM  
143 report (5). The 2004 *Veterans and Agent Orange* update continued to support a finding of  
144 “limited/suggestive” evidence between herbicides and PCT (9).

145 No Ranch Hands or Comparisons were observed with PCT in the AFHS.

146 **4.9 PROSTATE CANCER**

147 The IOM Committee concluded that there is “limited/suggestive” evidence to establish an association,  
148 although not a causal relation, between dioxin exposure and the occurrence of prostate cancer in the first  
149 *Veterans and Agent Orange* report and all updates (4-9).

150 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, 63 Ranch  
151 Hands and 93 Comparisons had prostate cancer. Of the 63 Ranch Hands with prostate cancer, 25 Ranch  
152 Hands were in the background dioxin category, 27 were in the low dioxin category, 10 were in the high  
153 dioxin category, and 1 Ranch Hand did not have a dioxin measurement. Of the 93 Comparisons, 90 had a  
154 measured dioxin level, and 1 of these 90 Comparisons had a measured dioxin level greater than 10 ppt.

155 The AFHS staff and colleagues published three journal articles related to cancer, which include prostate  
156 cancer as one of the categories analyzed (10-12). A further discussion of these articles is found in  
157 Chapter 14 – Neoplasia Assessment.

158 **4.10 RESPIRATORY CANCERS, INCLUDING CANCERS OF THE LUNG, LARYNX, TRACHEA,  
159 AND BRONCHUS**

160 The evidence for an association, although not a causal relation, between dioxin exposure and the  
161 occurrence of respiratory cancers was considered “limited/suggestive” by the IOM Committee (4-9).

162 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, 44 Ranch  
163 Hands and 59 Comparisons had respiratory cancer. Of the 44 Ranch Hands with respiratory cancer, 14  
164 Ranch Hands were in the background dioxin category, 14 were in the low dioxin category, 2 were in the  
165 high dioxin category, and 14 Ranch Hands did not have a dioxin measurement. Of the 59 Comparisons,  
166 42 had a measured dioxin level, and 1 of these 42 Comparisons had a measured dioxin level greater than  
167 10 ppt.

168 **4.11 SOFT TISSUE SARCOMA (OTHER THAN OSTEOSARCOMA, CHONDROSARCOMA,  
169 KAPOSÍ'S SARCOMA, OR MESOTHELIOMA)**

170 Soft tissue sarcoma is a group of different types of malignant tumors that arise from body tissues, such as  
171 muscle, fat, blood and lymph vessels, and connective tissues (not in hard tissue such as bone and  
172 cartilage). These cancers are in the soft tissue that occurs with and between organs.

173 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, one Ranch  
174 Hand and five Comparisons had a soft tissue sarcoma. The Ranch Hand with a soft tissue sarcoma was in  
175 the background dioxin category. All five Comparisons with a soft tissue sarcoma had a measured dioxin  
176 level, and one of these five Comparisons had a measured dioxin level greater than 10 ppt.

177 The IOM Committee, as reported first in their 1994 book on the health effects of herbicides used in  
178 Vietnam (4), concluded that there is “sufficient” evidence to establish an association, although not a  
179 causal relation, between dioxin exposure and the occurrence of soft tissue sarcoma (4). This conclusion  
180 has remained unchanged in all *Veterans and Agent Orange* updates (5-9).

181 **4.12 SPINA BIFIDA (IN CHILDREN OF VIETNAM VETERANS) (EXCEPT SPINA BIFIDA**  
182 **OCCULTA)**

183 Spina bifida is a neural tube birth defect that results from the failure of the bony portion of the spine to  
184 close properly in the developing fetus during early pregnancy. Among 792 live-born infants to Ranch  
185 Hand fathers and 981 live-born infants to Comparison fathers, four children from Ranch Hand fathers and  
186 zero children from Comparison fathers had spina bifida or anencephaly, which were both neural tube  
187 defects (13). Two of the Ranch Hands were in the low dioxin category and two Ranch Hands were in the  
188 high dioxin category (14). This result, along with two other epidemiological studies, led the IOM to  
189 conclude that there was limited/suggestive evidence of an association between exposure to herbicides and  
190 spina bifida in the offspring of exposed individuals, as reported in the 1996 *Veterans and Agent Orange*  
191 update (5). This conclusion remained the same in subsequent *Veterans and Agent Orange* updates in  
192 1998, 2000, 2002, and 2004 (6-9).

193 **4.13 TYPE 2 DIABETES**

194 Type 2 diabetes, or diabetes mellitus, is characterized by high blood sugar levels resulting from the  
195 body's inability to respond properly to the hormone insulin.

196 Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, 188 Ranch  
197 Hands and 309 Comparisons had type 2 diabetes. Of the 188 Ranch Hands with type 2 diabetes, 49  
198 Ranch Hands were in the background dioxin category, 60 were in the low dioxin category, 69 were in the  
199 high dioxin category, and 10 Ranch Hands did not have a dioxin measurement. Of the 309 Comparisons  
200 with type 2 diabetes, 293 had a measured dioxin level, and 9 of these 293 Comparisons had a measured  
201 dioxin level greater than 10 ppt.

202 The AFHS staff and colleagues published nine journal articles related to diabetes and glucose control (15-  
203 23). A further discussion of these articles is found in Chapter 9 – Endocrinology Assessment.

204 Epidemiologic studies suggested that any increased risk of Type 2 diabetes from herbicide or dioxin  
205 exposure is small when compared to the known predictors—family history, obesity, physical inactivity—  
206 for diabetes. Based on its comprehensive review of the literature, the IOM found limited or suggestive  
207 evidence of an association between exposure to herbicides, including 2,4,5-trichlorophenoxyacetic acid  
208 (2,4,5-T) and its contaminant dioxin, and Type 2 diabetes (7, 24). This conclusion remained unchanged  
209 in the 2002 and 2004 *Veterans and Agent Orange* updates (8, 9).

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## 5 REPRODUCTIVE OUTCOMES

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### 5.1 INTRODUCTION

The possibility of an increased risk in birth defects in children of Vietnam veterans has caused veterans, the general public, and federal and state legislatures concern about possible dioxin exposure received by veterans during the Vietnam War. At the Air Force Health Study (AFHS) baseline examination in 1982, reproductive outcome information was collected and the results of the analysis of these data were included as part of the report for this examination. The data were based on birth defects reported by the mothers of the children and supplemented by information from the father as needed. At the time of analysis in 1984, this reported information had not yet been verified. Records necessary for verification were located and obtained, beginning in 1985. During the same period, analytical chemists at the Centers for Disease Control and Prevention (CDC) developed an assay for dioxin in serum and demonstrated its suitability as a substitute for the assay of dioxin in adipose tissue obtained by biopsy. Subsequent analysis of reproductive outcomes related birth defects to paternal serum dioxin levels (1-3).

A section of the 1982 baseline examination report described reproductive outcomes based on spouse-reported information. A supplemental technical report (4) was written based on the 1982 baseline report (5), but the supplemental report was updated and based on verified outcomes rather than self-reported information. A report in 1992 (6) presented the results of reanalysis based on verified information in conjunction with paternal serum dioxin levels. A series of journal articles were written based on the 1992 report. The findings described in these reports and articles are summarized below.

### 5.2 1982 BASELINE EXAMINATION

Analysis performed for the 1982 baseline examination revealed no difference between Ranch Hands and Comparisons for infertility, sperm count, or sperm abnormalities, based on semen collected from the participants at this examination (5). The conception outcomes of miscarriage, stillbirth, induced abortion, and live birth also were not different between spouses or partners of Ranch Hands and Comparisons. An association between increasing herbicide exposure and miscarriage was identified in Ranch Hand officers, but this effect was not seen for other military occupations (i.e., enlisted flyers, enlisted groundcrew).

An increase in the post-Southeast Asia (SEA) live birth outcomes of physically handicapped, all birth defects, and neonatal death for children of Ranch Hands was found based on data provided by participants and spouses in separate questionnaires administered at the baseline examination. An association between increasing herbicide exposure and birth defects was observed in Ranch Hand officers and enlisted flyers.

These birth defect findings at the baseline examination required further evaluation of the data. The analyses for the baseline report relied heavily on unverified spouse reports. The techniques used for collecting data stressed biologically born children, but the collection inadvertently resulted in information on multiple adopted and stepchildren in addition to the biologically born children. Subsequent analysis was conducted using birth certificates and medical records to verify fertility and reproductive outcomes.

36 **5.2.1 Analysis of Live Birth Outcomes - Update**

37 Since the release of the baseline morbidity report in February 1984, birth defects and neonatal deaths  
38 reported by study participants and their spouses during the administration of the baseline questionnaire  
39 were verified by a review of records. This verification was accomplished by the review of birth and other  
40 medical records, birth certificates, and death certificates. An update of this 1984 report was published as  
41 an Air Force technical report (4).

42 The percentage of reported neonatal deaths that was verified was not different among Ranch Hands,  
43 Original Comparisons, and all Comparisons; therefore, bias in the reporting of responses between groups  
44 did not appear to be present.

45 The results that were found based on verified data were comparable to the results based on self-reported  
46 data. There was a change in the relation between birth defects and group (i.e., Ranch Hand, Comparison),  
47 depending on whether the conception was prior to or after the father's service in SEA. More verified  
48 birth defects for conceptions prior to the father's service in SEA were found for Comparisons than for  
49 Ranch Hands, but more verified birth defects for conceptions after the father's service in SEA were found  
50 for Ranch Hands than for Comparisons. Reviewers from the Advisory Committee on Phenoxy  
51 Herbicides have questioned the relevance of these pre-SEA birth defect findings (7).

52 A change was also indicated in the relation between neonatal deaths and group, depending on whether the  
53 death was prior to or after the father's service in SEA. The percentage of neonatal deaths was similar in  
54 Ranch Hands and Comparisons for births prior to the father's service in SEA, but after the father's service  
55 in SEA, more neonatal deaths occurred among the children of Ranch Hand fathers than of Comparison  
56 fathers.

57 **5.3 1992 REPRODUCTIVE OUTCOMES REPORT**

58 The uncertainties surrounding unverified participant and spouse reports prompted the verification of  
59 reproductive outcomes. Participants and spouses separately reported fertility information at the 1982,  
60 1985, and 1987 examinations. A review of birth certificates, newborn clinic records, health records, and  
61 death certificates was conducted. The health status of each child was verified through the age of 18. A  
62 total of 1,098 Ranch Hands and 1,549 Comparisons fathered 8,263 pregnancies and 6,792 live births. In  
63 addition, serum dioxin levels became available in 1986 (see Chapter 2) as an estimate of exposure for a  
64 subset of these veterans. A dioxin level had been determined by August 1991 for 791 Ranch Hands and  
65 942 Comparisons; 5,489 pregnancies and 4,514 live births were fathered by these veterans. A report was  
66 released in August 1992 that described the results of the analysis of reproductive outcomes in conjunction  
67 with serum dioxin levels (6).

68 The analysis of birth defects in the AFHS baseline report found that the Ranch Hand rate of reported  
69 pre-SEA birth defects was less than the Comparison rate, and the Ranch Hand rate of reported post-SEA  
70 birth defects was greater than the Comparison rate. Reanalysis using verified data found similar results.  
71 Additional analyses, however, indicated no relation between paternal dioxin levels (initial, categorized, or  
72 1987 dioxin) and the differential rates of pre-SEA and post-SEA birth defects.

73 The association between the father's dioxin level and sperm count and the percentage of abnormal sperm  
74 was assessed based on semen specimens collected during the 1982 baseline examination. No significant  
75 association was found between dioxin and sperm count or the percentage of abnormal sperm.

76 Miscarriages and adverse outcomes increased with increasing 1987 dioxin in conceptions fathered by  
77 Ranch Hands with late tours of duty, but decreased with increasing 1987 dioxin in conceptions fathered  
78 by Ranch Hands with earlier tours of duty. The highest number of post-SEA conceptions was found in  
79 Ranch Hands in the high dioxin category. The authors concluded that the results were mixed and  
80 biologically implausible and appear nonsupportive of a relation between dioxin and miscarriages.

81 The rate of abnormally low birth weights among children born after the Ranch Hand father's service in  
82 SEA was greater than the rate of abnormally low birth weights among children born prior to the Ranch  
83 Hand father's service in SEA. There was a decrease of a similar magnitude, however, in the rate of  
84 abnormally low birth weights children born after the Comparison father's service in SEA relative to  
85 children born prior to the Comparison father's service in SEA. The parallel increase in the rate of low  
86 birth weights in children of Ranch Hand fathers and the decrease in the rate of low birth weights in  
87 children of Comparison fathers relative to service in SEA lacked a biological explanation. When  
88 examining the birth weight itself, instead of the rate of abnormally low birth rates, the birth weight  
89 decreased with dioxin (initial, categorized, or 1987 dioxin) in some strata and increased in others. The  
90 mixed results of the birth weight analysis did not appear to suggest that birth weight was adversely  
91 associated with dioxin.

92 Few associations were found between dioxin and 13 individual categories of birth defects. Those  
93 associations that were noted, total congenital anomalies and musculoskeletal deformities, did not show  
94 increasing risks with increasing dioxin.

95 Major birth defects were defined, according to CDC definitions, as those defects that potentially can  
96 affect survival, result in marked physical or psychological handicaps, or interfere with a child's prospects  
97 for a productive and fulfilling life. No consistent patterns of association were found between the major  
98 birth defects and dioxin. In some analyses, the highest rates of major birth defects were found in children  
99 born to Ranch Hands with intermediate categorized dioxin levels, while the lowest rates were found in  
100 children born to Ranch Hands with the highest categorized dioxin levels. The results suggested no  
101 evidence that birth defect severity was adversely associated with dioxin.

102 Twelve specific birth defects and four developmental anomalies were investigated. There were only  
103 enough occurrences to permit statistical analysis on specific delays in development and hyperkinetic  
104 syndrome. Findings were few for both specific delays in development and hyperkinetic syndrome and  
105 often were in the direction opposite of what would have been expected with a dose-response relation.

106 Among 792 live-born infants to Ranch Hand fathers and 981 live-born infants to Comparison fathers, four  
107 children from Ranch Hand fathers and zero children from Comparison fathers had spina bifida or  
108 anencephaly, which are both neural tube defects. Two of the Ranch Hands were in the low dioxin  
109 category (extrapolated initial dose at or below 110 parts per trillion [ppt]) and two Ranch Hands were in  
110 the high dioxin category (extrapolated initial dose above 110 ppt) (1).

111 Of 1,772 births after the father's service in SEA, 57 had multiple birth defects that could not be attributed  
112 to recognized syndromes. The rate of multiple birth defects in children of Ranch Hands with the highest  
113 categorized dioxin levels was not elevated. The data did not support an association between dioxin and  
114 multiple birth defects.

115 Among children born after the Ranch Hand father's service in SEA, the rate of neonatal deaths (childhood  
116 death within 28 days of birth) was higher in children of Ranch Hands with the highest categorized dioxin  
117 levels than in children of Comparisons. Corresponding data, however, showed the same pattern among

118 children born before the Ranch Hand father's service in SEA. Therefore, the findings appeared to be due  
119 to chance rather than to paternal dioxin exposure.

120 In summary, the lack of an association between dioxin and total conceptions and between dioxin and  
121 sperm count or sperm abnormalities did not support the idea that dioxin was adversely related to the  
122 ability to father children. Dioxin also was unrelated to miscarriage, total adverse outcomes, birth weight,  
123 all 13 categories of birth defects, and neonatal death, and thus did not support the possibility of an adverse  
124 relation between dioxin and reproductive outcomes. The few positive associations that were found  
125 between dioxin and reproductive outcomes were generally weak, inconsistent, or biologically  
126 implausible.

### 127 **5.3.1 AFHS Journal Articles Based on 1992 Reproductive Outcomes Report**

128 The analyses for this report generated a series of journal articles on reproductive outcomes. The analysis  
129 reported in these journal articles were restricted to conceptions and children of veterans with dioxin  
130 results who were conceived during or after the father's service in SEA. A summary of these articles,  
131 which report similar findings to the 1992 reproductive outcomes report, is described below.

132 Few associations were found between dioxin and semen abnormalities, inability to conceive, prematurity,  
133 neonatal deaths, birth defects, birth defect severity, and developmental abnormalities (1). Associations  
134 were generally weak, inconsistent, or biologically implausible. There was no meaningful elevation in risk  
135 for spontaneous abortion or stillbirth.

136 There were some elevations in risk in some birth defect organ system categories, which, after review of  
137 the clinical descriptions, were not considered biologically meaningful. An increase in nervous system  
138 defects in children of Ranch Hands with increased paternal dioxin was observed, but it was based on  
139 sparse data. There was no indication of increased birth defect severity, delays in development, or  
140 hyperkinetic syndrome with paternal dioxin.

141 Verification of the existence, lineage, birth weight, gestation, and vital status of live births was attempted  
142 (2). No association was seen between paternal dioxin level and intrauterine growth retardation. The risk  
143 of infant death was increased among children of Ranch Hands whose fathers had the highest dioxin levels  
144 and among children whose fathers had background dioxin levels, but the pattern of results implied that the  
145 outcomes might not be related to paternal dioxin level.

146 Additional follow-up analyses on testosterone, follicle-stimulating hormone, luteinizing hormone,  
147 testicular abnormalities, and testicular volume were conducted on participants who attended the 1992  
148 follow-up physical examination. No consistent or meaningful associations between serum dioxin levels  
149 and any of these outcome variables were observed. Analyses of testosterone in its continuous form  
150 indicated that there might have been a subclinical relation between dioxin and testosterone, but the  
151 association, if it existed, was too weak to be clinically meaningful (3).

## 152 **5.4 CONCLUSION**

153 The lack of an association between dioxin and total conceptions and between dioxin and any examined  
154 semen characteristics did not support the idea that dioxin was adversely related to the ability to father  
155 children. Dioxin also was unrelated to miscarriage, total adverse outcomes, birth weight, all 13 categories  
156 of birth defects, and neonatal death, and thus did not support the possibility of an adverse relation  
157 between dioxin and reproductive outcomes. The few positive associations that were found between  
158 dioxin and reproductive outcomes were generally weak, inconsistent, or biologically implausible.

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## 6 MORTALITY

### 6.1 INTRODUCTION

The Air Force Health Study (AFHS) protocol specified that the mortality of Ranch Hand and Comparison subjects be examined across the 20-year period of the AFHS. The United States Air Force (USAF) Military Personnel Center records, the Veterans Administration Death Beneficiary Identification and Record Location System, and the Internal Revenue Service database of active social security account numbers were used to determine the subjects' deaths. Death certificates were ordered from the vital statistics department of the appropriate state or foreign country. The underlying cause of death was classified according to National Center for Health Statistics decision tables. Veterans killed in action during the Vietnam War were excluded because the immediate effects of herbicide exposure were not thought to cause Ranch Hand combat deaths.

The AFHS protocol specified that up to 10 Comparisons were to be matched to each Ranch Hand according to date of birth, rank, race, and occupation, and that 5 Comparisons from each matched set were to be randomly chosen and used as the Comparison cohort for mortality studies. There were concerns that this randomly chosen Comparison cohort might not be representative of the mortality of all matched Comparisons. Data analyses performed prior to the 1989 Mortality Update (1) suggested that the mortality experience of the randomly chosen Comparison cohort was, purely by chance, not representative of the mortality experience of the entire matched Comparison cohort. After the concurrence of the Advisory Committee appointed by the Agent Orange Working Group, the Comparison cohort was expanded to include all matched Comparisons after the 1986 Mortality Update (2) and prior to the 1989 Mortality Update (1). No differences in the conclusions were seen in the 1989 Mortality Update (1), regardless of whether the randomly selected Comparisons or the entire Comparison cohort were used.

The published reports or articles displayed in the table below concern mortality in the AFHS population. A brief summary of these reports and articles is contained in the next section.

Report or Article	Verified Deaths through	Deaths (Population Size)	
		Ranch Hand	Comparison
Baseline Mortality Study Results (30 June 1983)	31 December 1982	50 (1,247)	250 (6,171)
Mortality Update – 1984 (10 December 1984)	31 December 1983	54 (1,256)	265 (6,171)
Mortality Update – 1985 (29 November 1985)	31 December 1984	55 (1,257)	285 (6,171)
Mortality Update – 1986 (26 December 1986)	31 December 1985	59 (1,257)	312 (6,171)
Mortality Update – 1989 (17 April 1989)	31 December 1987	74 (1,261)	376 (6,250)
Health Status of Air Force Veterans Occupationally Exposed to Herbicides in Vietnam 2. Mortality (in <i>The Journal of the American Medical Association</i> )	31 December 1987	74 (1,261)	1,039 (19,101)*
	31 December 1987	74 (1,261)	1,038 (19,101)*
Mortality Update – 1991 (15 October 1991)	31 December 1989	91 (1,261)	1,241 (19,080)*
Mortality Update – 1993 (October 1993)	31 December 1991	106 (1,261)	1,439 (19,080)*
Mortality Update – 1994 (13 September 1994)	31 December 1992	111 (1,261)	1,545 (19,080)*
Mortality Update – 1996 (July 1996)	31 December 1993	118 (1,261)	1,672 (19,080)*

Report or Article	Verified Deaths through	Deaths (Population Size)	
		Ranch Hand	Comparison
Postservice Mortality of U.S. Air Force Veterans Occupationally Exposed to Herbicides in Vietnam: 15-Year Follow-up (25 March 1998) (in <i>American Journal of Epidemiology</i> )	31 December 1993	118 (1,261)	1,672 (19,080)*
Post-service mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War (May 2005) (in <i>Military Medicine</i> )	31 December 1999	186 (1,262)	2,330 (19,078)*

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\*: Comparison deaths based on all Comparisons; previous results were based on a randomly chosen cohort of five matched Comparisons.

Note: One additional death was verified between 1 April 1988 (cutoff date for verified deaths in *The Journal of American Medicine Association* article [3]) and 15 June 1988 (cutoff date for verified deaths in the 1989 Mortality Update [1]). This accounts for the difference in Comparison deaths between the two publications.

34 **6.2 1983 BASELINE MORTALITY STUDY**

35 As reported in the 1983 Baseline Mortality Study Results report (4), 50 Ranch Hand and 250  
36 Comparisons had died as of 31 December 1982. Analyses showed that the mortality experience of the  
37 Ranch Hand group was nearly identical to that of the Comparison group. The authors cautioned,  
38 however, that this mortality report could in no way be regarded as conclusively negative because the  
39 study population may not have reached the latency period in which attributable fatal disease might have  
40 been expected and detected. The cohort of deaths at that time was small, and both the Ranch Hand and  
41 Comparison groups were young and relatively healthy.

42 **6.3 1984 MORTALITY UPDATE**

43 As of 31 December 1983, 54 Ranch Hands and 265 Comparisons had died. As described in the 1984  
44 Mortality Update (5), no differences between Ranch Hand and Comparison mortality were found. Cause-  
45 specific analyses did not show any increased Ranch Hand mortality for accidents, suicide, homicide,  
46 malignancy, or circulatory system disease. No relation was found between mortality in Ranch Hands and  
47 the Air Force herbicide exposure index (described in Chapter 2). Continued mortality surveillance was  
48 recommended because the study groups were still relatively young and healthy.

49 **6.4 1985 MORTALITY UPDATE**

50 As of 31 December 1984, 55 Ranch Hands and 285 Comparisons had died. The analyses described in the  
51 1985 Mortality Update (6) found no differences between Ranch Hand and Comparison mortality. Cause-  
52 specific analyses did not show any increased Ranch Hand mortality for accidents, suicide, homicide,  
53 malignancy, or circulatory system disease. No relation was found between mortality in Ranch Hands and  
54 the herbicide exposure index. An interaction involving age and military occupation, however, was  
55 discovered in these analyses. Older Ranch Hand officers (older than 35 years of age) experienced fewer  
56 deaths than older Comparison officers, but younger Ranch Hand officers (35 years of age or younger)

57 experienced more deaths than younger Comparison officers. Continued mortality surveillance was again  
58 recommended because the study groups were still relatively young and healthy.

### 59 **6.5 1986 MORTALITY UPDATE**

60 As of 31 December 1985, 59 Ranch Hands and 312 Comparisons had died, as reported in the 1986  
61 Mortality Update (2). The conclusions and recommendations remained unchanged from the 1985  
62 Mortality Update.

### 63 **6.6 1989 MORTALITY UPDATE**

64 The next AFHS Mortality Update was published in 1989 (1). A subsequent article in *The Journal of the*  
65 *American Medical Association* (3) also presented the results of this update. As of 31 December 1987, 74  
66 Ranch Hands and 376 Comparisons had died, based on using the original Comparison cohort. For this  
67 update, the Comparison cohort was expanded to include the entire Comparison population who flew or  
68 serviced C-130 cargo aircraft in Southeast Asia (SEA) during the same calendar period that the Ranch  
69 Hand unit was active in Vietnam. This change in the Comparison cohort resulted in 74 Ranch Hands and  
70 1,039 Comparison deaths as of 31 December 1987 (verified as of 15 June 1988).

71 As in previous updates, no differences between Ranch Hand and Comparison mortality were found in the  
72 1989 Mortality Update (1). No difference between the observed and the expected number of deaths in  
73 Ranch Hands was seen when the cumulative mortality from all causes was examined. Cause-specific  
74 analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, homicide,  
75 malignancy, or circulatory disease. Digestive system deaths were more frequent in Ranch Hands than  
76 expected. Five of the six digestive system deaths, however, were attributable to alcohol consumption; the  
77 finding was considered to be unrelated to herbicide exposure. No relation was found between mortality in  
78 Ranch Hands and the herbicide exposure index.

### 79 **6.7 1991 MORTALITY UPDATE**

80 As of 31 December 1989, 91 Ranch Hands and 1,241 Comparisons had died (using the entire Comparison  
81 population). The 1991 Mortality Update (7) was also the first report in which analysis of mortality in  
82 relation to serum dioxin levels was available (see Chapter 2). Prior to this report, the herbicide exposure  
83 index was used to assess dose-response trends within Ranch Hands.

84 Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide,  
85 malignancy, or circulatory disease. The increase of digestive system deaths in Ranch Hands continued;  
86 nine Ranch Hands died from digestive diseases. There was an excess of deaths from circulatory disease  
87 among Ranch Hand enlisted groundcrew personnel. The authors were concerned about this increase  
88 because Ranch Hand enlisted groundcrew had a higher median dioxin level than enlisted flyers or  
89 officers, and because dioxin levels were associated with diabetes and lipid abnormalities. Whereas there  
90 was no association between dioxin and cardiovascular disease in living Ranch Hands, it was considered  
91 possible that an increase in circulatory disease deaths could be dioxin-related through its association with  
92 diabetes and serum lipids.

93 **6.8 1993 MORTALITY UPDATE**

94 An evaluation of the cumulative Ranch Hand mortality from all causes through 31 December 1991 found  
95 no difference in the observed number of deaths from what was expected of a cohort of this size and age,  
96 as reported in the 1993 Mortality Update (8). As of this date, 106 Ranch Hands and 1,439 Comparisons  
97 had died. There was an increasing trend in death from all causes in Ranch Hand enlisted flyers during the  
98 1989 to 1991 period. Of the seven Ranch Hand enlisted flyers who died during that period, five were due  
99 to a malignant neoplasm. This trend was not seen in Ranch Hand enlisted groundcrew, who were more  
100 heavily exposed to dioxin on average. The trend in enlisted flyers was a source of concern, but if these  
101 deaths were caused by exposure, a corresponding trend in enlisted groundcrew would have been  
102 expected.

103 Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide,  
104 homicide, deaths due to infectious or parasitic diseases, deaths due to a malignant neoplasm, deaths due to  
105 endocrine disease, or deaths due to circulatory disease. The increase in digestive system deaths in Ranch  
106 Hands continued, as did the increase in deaths from circulatory disease among Ranch Hand enlisted  
107 groundcrew personnel.

108 For 872 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no  
109 difference in the mean 1987 dioxin levels between 856 Ranch Hands who were still alive and the 16  
110 Ranch Hands who were deceased as of 31 December 1991. There also was no relation between survival  
111 time and dioxin levels.

112 **6.9 1994 MORTALITY UPDATE**

113 As reported in the 1994 Mortality Update (9), no difference between the observed and the expected  
114 number of deaths in Ranch Hands was seen when the cumulative mortality from all causes through 31  
115 December 1992 was examined. As of this date, 111 Ranch Hands and 1,545 Comparisons had died.  
116 Cause-specific analyses found no increase in overall Ranch Hand mortality from accidental deaths,  
117 suicides, homicides, deaths due to infectious and parasitic diseases, deaths due to malignant neoplasms,  
118 deaths due to endocrine disease, or deaths due to circulatory diseases. As with previous updates, the  
119 increase in digestive system deaths in Ranch Hands and deaths from circulatory disease among Ranch  
120 Hand enlisted groundcrew personnel was observed. A new finding on deaths due to ill-defined or  
121 unknown causes, however, was seen for the first time in this update. The number of deaths due to ill-  
122 defined or unknown causes increased among Ranch Hand enlisted flyers.

123 For 988 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no  
124 difference in the mean 1987 dioxin levels between 968 Ranch Hands who were still alive and the 20  
125 Ranch Hands who were deceased as of 31 December 1992. There also was no relation between survival  
126 time and 1987 dioxin levels.

127 **6.10 1996 MORTALITY UPDATE**

128 No difference between the observed and the expected number of deaths in Ranch Hands was seen when  
129 the cumulative mortality from all causes through 31 December 1993 was examined. As reported in the  
130 1996 Mortality Update (10), 118 Ranch Hands and 1,672 Comparisons had died. Cause-specific analyses  
131 found no increase in overall Ranch Hand mortality from accidental deaths, suicides, homicides, deaths  
132 due to infectious and parasitic diseases, deaths due to malignant neoplasms, deaths due to endocrine  
133 disease, deaths due to respiratory disease, deaths due to circulatory disease, or deaths due to ill-defined or  
134 unknown causes. An increase in deaths due to digestive disease was no longer seen, and an increase in

135 deaths in Ranch Hand enlisted flyers was no longer present. There were 30 deaths due to malignant  
136 neoplasms, but they did not appear to aggregate in an unusual pattern relative to what would have been  
137 expected. The increase in deaths from circulatory disease among Ranch Hand enlisted groundcrew that  
138 was reported since the 1991 Mortality Update (7) was still present, although no new circulatory disease  
139 deaths in this cohort were reported since the 1994 Mortality Update (9). Further analysis of circulatory  
140 disease deaths in enlisted groundcrew revealed that more than 65 percent of these deaths were due to  
141 atherosclerotic heart disease.

142 For 991 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no  
143 difference in the mean 1987 dioxin levels between 968 Ranch Hands who were still alive and the 23  
144 Ranch Hands who were deceased as of 31 December 1993. There also was no relation between survival  
145 time and 1987 dioxin levels.

146 Further analysis was performed and reported in a 1998 journal article (11) describing the mortality of  
147 AFHS veterans. In particular, in the subgroup of Ranch Hand veterans that had survived more than 20  
148 years since their military service in SEA, no increase in the risk of death due to cancer at all sites was  
149 found. When investigating cancer deaths according to primary anatomic site, a small increase in the  
150 number of deaths caused by cancer of the bronchus and lung was seen.

#### 151 **6.11 MORTALITY THROUGH 1999**

152 As described in a journal article published in 2005 (12), as of 31 December 1999, 186 Ranch Hands and  
153 2,330 Comparisons had died. The risk of death caused by cancer was not increased, but the risk of death  
154 caused by circulatory system diseases was increased in enlisted groundcrew. When circulatory disease  
155 was divided into five categories—atherosclerotic heart disease, cardiomyopathy, cerebrovascular disease,  
156 hypertensive disease, and other circulatory diseases—the strongest association between group and  
157 circulatory system disease was because of atherosclerotic heart disease. The cumulative all-cause  
158 mortality experience of Ranch Hands was not statistically greater than Comparisons (relative risk=1.15,  
159 95% confidence interval: (1.0, 1.3), but this trend bears further monitoring to confirm the increased risk  
160 suggested by these results.

161 To examine cancer mortality in a way that accounts for latency, the risk was evaluated among those  
162 subjects who survived at least 20 years after entry into follow-up. No differences were found in this  
163 subset, as was also the case with cancer mortality within 20 years of service in SEA.

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## 7 CARDIOVASCULAR ASSESSMENT

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### 7.1 INTRODUCTION

Cardiac disease and peripheral vascular disease are not recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin. Both bradycardia and tachycardia have been suggested following acute heavy exposures to the 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) components, but the cardiovascular effects after chronic low-dose exposure are essentially unknown. To assess cardiovascular function and exposure to herbicides, the Air Force Health Study (AFHS) collected data by questionnaire and physical examination to identify a number of cardiac endpoints.

Analyses were performed to assess the cardiovascular function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). The analyses of the cardiovascular assessment were based on medical records verification of the data collected from questionnaires and the physical examination findings.

The questionnaire captured data on the occurrence of heart conditions. Medical records reviews confirmed reported heart conditions and identified any unreported conditions for each participant. As a result, a history of essential hypertension, heart disease (excluding essential hypertension), myocardial infarction, and stroke or transient ischemic attack was determined for each participant.

The physical examination assessed the central cardiac function by measurements of systolic blood pressure, diastolic blood pressure, heart sounds (by auscultation), and an electrocardiograph (ECG). The standard 12-lead ECG was performed and rhythm strips were obtained for all participants. The ECG findings were analyzed at each of the six physical examinations. The following components of the ECG have been analyzed since the 1985 follow-up examination: (1) right bundle branch block (RBBB), (2) left bundle branch block, (3) nonspecific ST- and T-wave changes, (4) bradycardia (a resting pulse rate less than 50 beats per minute), (5) tachycardia (a resting pulse rate greater than 100 beats per minute), (6) arrhythmia, (7) evidence of a prior myocardial infarction, and (8) other diagnoses (ventricular aneurysm and Wolff-Parkinson-White syndrome).

The peripheral vascular function was assessed during the cardiovascular examination by funduscopic examination of small vessels of the eyes, the presence or absence of carotid bruits, and the examination of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. In 1982, 1985, and 1987, manual techniques were used to examine peripheral pulses. In 1985, the Doppler technique also was introduced to make these measurements and replaced the manual method for the 1992 through 2002 examinations.

The Doppler procedure for examining pulses involved a set of measurements designed to determine whether a pulse abnormality existed, where the obstruction was most likely located, and whether it had functional implications. Pulses were considered abnormal if no arterial flow or a monophasic arterial flow was present on either side.

In addition, two pulse indices were constructed from the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulse measurements, as follows:

- Peripheral pulses: radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses

39           • Leg pulses: femoral, popliteal, dorsalis pedis, and posterior tibial pulses.

40 In addition, the assessment of all pulses combined the carotid pulse with peripheral pulses and was  
41 analyzed for the 1982, 1985, and 1987 examinations. Each of these indices was considered normal if all  
42 components were normal, and abnormal if one or more pulses were abnormal.

43 Other measurements to assess the peripheral vascular function included a measure of intermittent  
44 claudication and vascular insufficiency based on participant responses in the health questionnaire; a  
45 kidney, urethra, and bladder (KUB) x-ray assessment; a resting blood pressure index; and two hyperemic  
46 indices used as measures of intermittent claudication.

47 As a self-reported assessment of claudication, each participant was asked the following questions as part  
48 of the questionnaire:

- 49           • Do you get a pain in either or both of your legs while walking?
- 50           • Does this pain ever begin when you are standing still or sitting?
- 51           • Do you get this pain in either or both of your calf muscles?

52 The answers were used to detect intermittent claudication and vascular insufficiency (yes, no), which  
53 indicate an insufficient oxygen supply to the leg muscles. A participant was judged to have intermittent  
54 claudication and vascular insufficiency if he answered “yes” to the first and third questions and “no” to  
55 the second question. This self-reported determination of intermittent claudication was analyzed for the  
56 1992, 1997, and 2002 follow-up examinations.

57 At the 1992 follow-up examination, a KUB x-ray assessment was accomplished to detect hardening of the  
58 arteries and vascular disease. Kidney stones, as detected from this assessment, were analyzed separately  
59 in the renal assessment, but if other abnormalities existed, the KUB x-ray assessment was defined as  
60 abnormal.

61 Three indices of claudication using peripheral blood pressure measurements were analyzed at the 2002  
62 follow-up examination. Right and left brachial (upper arm) blood pressures were taken during the  
63 vascular examination using the Doppler technique. After brachial pressures were recorded, the right and  
64 left supine ankle pressures were measured. A resting pressure index was calculated from the resting ankle  
65 systolic pressure and the brachial systolic pressure. Post-exercise pressures were obtained at the ankle  
66 and the brachial arteries at the site of the highest pressures before exercise. Brachial and ankle pressures  
67 were obtained at 1 minute post-exercise and 2 minutes post-exercise, and two hyperemic pressure indices  
68 of claudication were calculated from these measurements after exercise.

69 The first Institute of Medicine (IOM) *Veterans and Agent Orange* report in 1994 (8) concluded that there  
70 is “inadequate or insufficient” evidence to establish an association between dioxin exposure and the  
71 occurrence of specific circulatory disorders, including coronary artery disease, myocardial infarction,  
72 stroke and hypertension, or circulatory diseases in general. The findings remained unchanged in all  
73 subsequent *Veterans and Agent Orange* updates (9-13).

### 74 **7.1.1 Chapter Structure**

75 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
76 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
77 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
78 results that appeared consistently across examinations or have biological meaning are emphasized,

79 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
 80 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
 81 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
 82 the parameter and either group or dioxin are not discussed.

83 The results discussed below that were discovered as part of further analysis based on a statistical  
 84 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
 85 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
 86 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
 87 baseline examination. Older participants were defined as those born before 1942.

88 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 89 Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 90 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 91 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 92 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 93 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at  
 94 most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this  
 95 stratification based on the participant's tour of duty is given in Chapter 2.

96 The following chart lists the variables that were analyzed for the cardiovascular assessment and at which  
 97 physical examination they were analyzed. The variables appearing in bold type are discussed  
 98 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>All Pulses</b>	X	X	X	X			
<b>Carotid Bruits</b>	X	X	X	X	X	X	X
<b>Diastolic Blood Pressure</b>	X	X	X	X	X	X	X
<b>Dorsalis Pedis Pulses</b>	X	X	X	X	X	X	X
<b>ECG: Arrhythmia</b>		X	X	X	X	X	X
<b>ECG: Bradycardia</b>		X	X	X	X	X	X
<b>ECG: Evidence of Prior Myocardial Infarction</b>					X	X	X
ECG: LBBB		X	X	X	X	X	X
<b>ECG: Nonspecific ST- and T-wave Changes</b>		X	X	X	X	X	X
<b>ECG: Other Diagnoses</b>		X	X	X	X	X	X
<b>ECG: Overall</b>	X	X	X	X	X	X	X
<b>ECG: RBBB</b>		X	X	X	X	X	X
<b>ECG: Tachycardia</b>		X	X	X	X	X	X
<b>Essential Hypertension</b>		X	X	X	X	X	X
<b>Femoral Pulses</b>	X	X	X	X	X	X	X
<b>Funduscopy Examination</b>	X	X	X	X	X	X	X
<b>Heart Disease (Excluding Essential Hypertension)</b>	X	X	X	X	X	X	X
Heart Sounds	X	X	X	X	X	X	X
Hyperemic Pressure Index (1 minute post-exercises)							X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Hyperemic Pressure Index (2 minutes post-exercise)							X
Intermittent Claudication and Vascular Insufficiency Index					X	X	X
<b>KUB X-ray Assessment (Excluding Kidney Stones)</b>					X		
<b>Leg Pulses</b>	X	X	X	X	X	X	X
<b>Myocardial Infarction</b>		X	X	X	X	X	X
<b>Peripheral Pulses</b>	X	X	X	X	X	X	X
<b>Popliteal Pulses</b>	X	X	X	X	X	X	X
<b>Posterior Tibial Pulses</b>	X	X	X	X	X	X	X
Radial Pulses	X	X	X	X	X	X	X
Resting Pressure Index							X
Stroke or Transient Ischemic Attack						X	X
<b>Systolic Blood Pressure</b>	X	X	X	X	X	X	X

99 **7.2 ESSENTIAL HYPERTENSION**

100 The prevalence of essential hypertension after service in Southeast Asia (SEA) increased as 1987 dioxin  
101 levels increased, based on data collected at the 1992 follow-up examination and again on data collected at  
102 the 1997 follow-up examination.

103 **7.3 HEART DISEASE (EXCLUDING ESSENTIAL HYPERTENSION)**

104 The prevalence of heart disease after service in SEA was increased in Ranch Hands based on data at the  
105 1985 follow-up examination.

106 The prevalence of heart disease after service in SEA, based on data collected at the 1997 follow-up  
107 examination, was increased in Ranch Hands and, in particular, in Ranch Hand enlisted flyers. In addition,  
108 Ranch Hands in the background dioxin category had a greater prevalence of heart disease than  
109 Comparisons.

110 Ranch Hand enlisted flyers had a greater prevalence of heart disease after service in SEA than  
111 Comparison enlisted flyers, based on data collected at the 2002 follow-up examination.

112 **7.4 MYOCARDIAL INFARCTION**

113 Among participants with a low differential cortisol response, Ranch Hands in the low dioxin category had  
114 a greater prevalence of myocardial infarction after service in SEA than Comparisons, based on data  
115 collected at the 1987 follow-up examination.

116 The analysis of myocardial infarction after service in SEA, based on data collected at the 1992 follow-up  
117 examination, found that among nonobese (approximate body mass index less than 30) participants, Ranch  
118 Hands in the high dioxin category had a greater prevalence of myocardial infarction than Comparisons.

119 **7.5 SYSTOLIC BLOOD PRESSURE**

120 Among participants with type B personalities (14) who had later tours of duty, the percentage of  
121 participants with abnormally high systolic blood pressure values (>140 mm Hg) at the 1987 follow-up  
122 examination increased with increasing 1987 dioxin levels. In addition, the analysis showed that among  
123 younger participants, Ranch Hands in the low dioxin category had a greater prevalence of abnormally  
124 high systolic blood pressure values than Comparisons.

125 **7.6 DIASTOLIC BLOOD PRESSURE**

126 Among the youngest participants, Ranch Hands had a higher average diastolic blood pressure than  
127 Comparisons at the 1987 follow-up examination. Among participants with type B personalities, diastolic  
128 blood pressure values increased with increasing initial dioxin levels. Among participants with type B  
129 personalities and a family history of heart disease, Ranch Hands in the low dioxin category had a higher  
130 average diastolic blood pressure than Comparisons. In addition, among participants with type B  
131 personalities and no family histories of heart disease, Ranch Hands in the high dioxin category had a  
132 greater average diastolic blood pressure than Comparisons.

133 Among officers, diastolic blood pressure values at the 1992 follow-up examination increased as initial  
134 dioxin levels increased.

135 Analysis of 2002 follow-up examination data showed that Ranch Hands in the high dioxin category had a  
136 greater percentage of participants with abnormal diastolic blood pressure readings (>90 mm Hg) than  
137 Comparisons.

138 **7.7 ECG**

139 **7.7.1 Overall**

140 Among participants with normal cholesterol levels ( $\leq 200$  mg/dL) at the 1992 follow-up examination, the  
141 percentage of Ranch Hands with abnormal overall ECG results increased with increasing levels of initial  
142 dioxin, as well as with increasing levels of 1987 dioxin.

143 **7.7.2 Arrhythmia**

144 For participants with later tours of duty, the occurrence of arrhythmias increased as 1987 dioxin levels  
145 increased at the 1987 follow-up examination. The prevalence of arrhythmia increased with increasing  
146 initial dioxin levels for participants with type A personalities (14).

147 Among participants who had never smoked, the percentage of Ranch Hands at the 1992 follow-up  
148 examination with arrhythmias increased with increasing levels of initial dioxin and 1987 dioxin. Among  
149 participants with low high-density lipoprotein (HDL) cholesterol levels (0-35 mg/dL), Ranch Hands in  
150 the high dioxin category had a greater prevalence of arrhythmias than Comparisons.

151 **7.7.3 Evidence of Prior Myocardial Infarction**

152 Among nondiabetic Ranch Hands, the percentage of participants with evidence of a prior myocardial  
153 infarction at the 1992 follow-up examination, as determined from the ECG, increased with increasing  
154 initial dioxin. In addition, evidence of prior myocardial infarction in Ranch Hands increased with  
155 increasing 1987 dioxin levels.

156 The percentage of Ranch Hands at the 1997 follow-up examination with evidence of a prior myocardial  
157 infarction increased with increasing initial dioxin levels.

#### 158 **7.7.4 Bradycardia**

159 Ranch Hand enlisted flyers at the 1992 follow-up examination had a greater occurrence of bradycardia  
160 than Comparison enlisted flyers. Ranch Hands in the background dioxin category had a greater  
161 prevalence of bradycardia than Comparisons, primarily among participants with type B personalities.

#### 162 **7.7.5 Tachycardia**

163 Ranch Hands in the high dioxin category had a greater prevalence of tachycardia than Comparisons at the  
164 1997 follow-up examination.

#### 165 **7.7.6 Right Bundle Branch Block (RBBB)**

166 Among moderate lifetime smokers (no more than 10 pack-years), the prevalence of RBBB at the 1992  
167 follow-up examination increased with increasing initial dioxin. Analysis of 1992 follow-up examination  
168 data also found that the percentage of Ranch Hands with RBBB increased with increasing 1987 dioxin  
169 levels.

#### 170 **7.7.7 Nonspecific ST- and T-Wave Changes**

171 Based on data collected for the 1992 follow-up examination, the presence of nonspecific ST- and T-wave  
172 changes increased with increasing 1987 dioxin levels.

#### 173 **7.7.8 Other Diagnoses**

174 Analyses for the 1987 and 1997 follow-up examinations showed Ranch Hands in the high dioxin category  
175 had a greater occurrence of other ECG diagnoses than Comparisons.

176 Among Ranch Hand enlisted flyers, the prevalence of other ECG diagnoses at the 1992 follow-up  
177 examination increased with increasing 1987 dioxin levels.

### 178 **7.8 FUNDUSCOPIC EXAMINATION**

179 The 1992 follow-up examination analysis showed that the percentage of Ranch Hands with an abnormal  
180 funduscopic examination increased with increasing 1987 dioxin levels.

### 181 **7.9 CAROTID BRUI TS**

182 Among the heaviest drinkers throughout their lifetimes in the 1992 follow-up examination (greater than  
183 40 drink-years), Ranch Hands in the background and high dioxin categories had a greater prevalence of  
184 carotid bruits than Comparisons.

185 **7.10 PULSES**

186 **7.10.1 All Pulses/Peripheral Pulses**

187 When examining all pulses collectively, analysis of data from the 1987 follow-up examination revealed  
188 interactions between initial dioxin and age as well as between 1987 dioxin and lifetime smoking history.  
189 The percentage of Ranch Hand pulse abnormalities increased with increasing initial dioxin, primarily  
190 among older participants. Among Ranch Hands who were the heaviest lifetime smokers (greater than 10  
191 pack-years) with later tours of duty, the prevalence of pulse abnormalities increased with increasing 1987  
192 dioxin. A greater percentage of pulse abnormalities was seen among Ranch Hands in the low dioxin  
193 category and Ranch Hands in the high dioxin category than among Comparisons.

194 For 1987 follow-up examination data, the analysis of all pulses collectively included the carotid pulse in  
195 addition to peripheral pulses (radial, femoral, popliteal, dorsalis pedis, and posterior tibial). Exclusion of  
196 carotid pulses from the determination did not change the results described above.

197 In addition, peripheral pulses were examined at the 1982 baseline examination. Ranch Hands at the 1982  
198 baseline examination had a greater percentage of abnormal peripheral pulses than Comparisons.

199 Analysis of diabetics at the 1992 follow-up examination showed that the percentage of diabetic Ranch  
200 Hands with abnormal peripheral pulses increased with increasing 1987 dioxin levels among Ranch Hands  
201 with no family history of heart disease. In addition, a higher percentage of Ranch Hand diabetics in the  
202 high dioxin category than Comparisons had abnormal peripheral pulses.

203 **7.10.2 Leg Pulses**

204 Leg pulses (peripheral pulses, with the exception of the radial pulses) at the 1987 follow-up examination  
205 mirrored the analysis of all pulses and peripheral pulses. Interactions between initial dioxin and age, as  
206 well as between 1987 dioxin and lifetime smoking history, were found. A greater percentage of leg pulse  
207 abnormalities was seen among Ranch Hands in the low dioxin category and Ranch Hands in the high  
208 dioxin category than among Comparisons.

209 At the 1992 follow-up examination, analysis showed the prevalence of abnormal leg pulses in diabetic  
210 Ranch Hands in the high dioxin category was greater than diabetic Comparisons.

211 **7.10.3 Femoral Pulses**

212 Analysis of data from the 1987 follow-up examination showed that a greater percentage of Ranch Hands  
213 (in particular, Ranch Hands in the high dioxin category) had abnormal femoral pulses than Comparisons.  
214 In addition, among participants with type A personalities, the prevalence of femoral pulse abnormalities  
215 increased with increasing initial dioxin levels.

216 Ranch Hands in the low dioxin category had a greater prevalence of abnormal femoral pulses than  
217 Comparisons at the 1992 follow-up examination.

218 **7.10.4 Popliteal Pulses**

219 A greater percentage of Ranch Hands (in particular, Ranch Hands in the high dioxin category) than  
220 Comparisons had abnormal popliteal pulses at the 1992 follow-up examination. In addition, among  
221 officers, the prevalence of popliteal pulse abnormalities increased with increasing 1987 dioxin levels.

222 **7.10.5 Dorsalis Pedis Pulses**

223 Analysis of 1987 follow-up examination data showed that the prevalence of dorsalis pedis pulse  
224 abnormalities increased with increasing 1987 dioxin among Ranch Hands with later tours of duty.  
225 Similarly, the prevalence of dorsalis pedis pulse abnormalities increased as initial dioxin levels increased.

226 Among older participants and diabetic participants at the 1992 follow-up examination, Ranch Hands in  
227 the high dioxin category had a greater prevalence of dorsalis pedis pulse abnormalities than Comparisons.

228 **7.10.6 Posterior Tibial Pulses**

229 Ranch Hands had a greater percentage of posterior tibial pulse abnormalities than Comparisons at the  
230 1985 follow-up examination, as measured by manual palpation rather than Doppler methods.

231 The 1987 follow-up examination analysis found that Ranch Hands in the low dioxin category had a  
232 higher prevalence of abnormal posterior tibial pulses than Comparisons.

233 A greater percentage of Ranch Hands in the high dioxin category had posterior tibial pulse abnormalities  
234 than Comparisons at the 1992 follow-up examination. In addition, among moderate current cigarette  
235 smokers (no more than 20 cigarettes per day, on average), Ranch Hands in each of the dioxin categories  
236 (background, low, and high) had a greater percentage of posterior tibial pulse abnormalities at the 1992  
237 follow-up examination than Comparisons.

238 **7.11 KIDNEY, URETHRA, AND BLADDER (KUB) X-RAY ABNORMALITIES**

239 Among non-Black participants, the percentage of Ranch Hands with KUB x-ray abnormalities at the 1992  
240 follow-up examination increased with increasing 1987 dioxin levels.

241 **7.12 AFHS CARDIOVASCULAR MORTALITY THROUGH 1999**

242 As described in a 2005 article “Post-service Mortality of Air Force Veterans Occupationally Exposed to  
243 Herbicides during the Vietnam War” (15), as of 31 December 1999, 186 Ranch Hands and 2,330  
244 Comparisons have died. The risk of death caused by circulatory system diseases was increased in enlisted  
245 groundcrew, which may suggest an association with dioxin. Of the 186 Ranch Hands who had died, 40  
246 were enlisted groundcrew who had died from circulatory diseases. Of the 2,330 Comparisons who had  
247 died, 393 were enlisted groundcrew who had died from circulatory diseases.

248 **7.13 CONCLUSION**

249 After 25 years of observation in the AFHS, the prevalence of cardiovascular disease did not appear to be  
250 associated with dioxin exposure. Abnormal pulses appeared to be related to dioxin in earlier phases of  
251 the study, but not in the 2002 follow-up examination. The increase in the number of deaths caused by  
252 diseases of the circulatory system for Ranch Hand nonflying enlisted personnel, however, does point to  
253 the possibility of an association with dioxin.

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## 8 DERMATOLOGY ASSESSMENT

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### 8.1 INTRODUCTION

The dermatology assessment of participants in the Air Force Health Study (AFHS) included the occurrence of self-reported acne and physical examination at the 1982, 1985, 1987, 1992, and 2002 examinations (1-6). Of particular interest was the detection of chloracne after exposure to herbicides and dioxin. Chloracne is recognized as a consequence of exposure to high levels of chlorophenols.

Chloracne may persist for at most 2 to 3 years. Therefore, primary lesions were not expected to be noted at the physical examinations. No biopsies to confirm the diagnosis of chloracne were deemed necessary by the examining dermatologists. Analysis was therefore limited to secondary lesions, such as scarring, hyperpigmentation, and depigmentation. If secondary lesions had been observed, chloracne might be suggested if the lesions had been found in the typical distribution areas of chloracne. In addition, the occurrence, duration, and location of acne were studied because of the absence of chloracne in AFHS veterans. This was the only objective way to assess for potential cases of chloracne.

During the health interview conducted as part of the questionnaire, each study participant was asked about occurrences of acne on the face since the date of the last health interview. This information was used to update data gathered from previous examinations. Information regarding the date and location of each acne occurrence also was collected. The analysis of acne was based on participant-reported occurrences rather than data from medical records verification because it was expected that the majority of participants who reported acne did not visit a physician for the acne.

Questions regarding the presence of acne emphasized acne on the temples, eyes, or ears, as acne on these locations may have been related to chloracne. Total duration of acne was determined by adding the duration of each reported occurrence of acne from all AFHS questionnaires. A review of medical records did not find any documented cases of chloracne among AFHS participants.

Six dermatologic conditions noted at the physical examination and a composite dermatologic index were analyzed. The following conditions were analyzed: acneiform lesions, acneiform scars, comedones, inclusion cysts, depigmentation, and hyperpigmentation of the skin. Depigmentation and hyperpigmentation were defined as areas of skin that were less or more pigmented relative to the rest of the skin. The dermatology index was created by combining results from the examination for comedones, acneiform lesions, acneiform scars, and inclusion cysts.

Other dermatologic evaluation abnormalities were analyzed as a group for the 1982, 1985, 1987, and 1992 physical examinations. The types of abnormalities are given in Section 8.6 of this chapter.

Some possible neoplasms were discovered by the physicians at the physical examinations. Contingent upon participant authorization, suspicious skin lesions were biopsied and the pathology determined. Abnormalities relating to skin malignancies are discussed in Chapter 14, Neoplasia Assessment.

The article written by AFHS authors, titled "Serum dioxin, chloracne, and acne in veterans of Operation Ranch Hand," studied the relation between categorized dioxin and the prevalence of acne for participants who attended the 1992 follow-up examination (7). None of the Ranch Hand veterans was diagnosed with chloracne and, therefore, analyses were restricted to acne. Acne was investigated both with and without

39 regard to anatomic location. No meaningful or consistent association between dioxin exposure and  
40 prevalence of acne was observed. Results suggested that exposure of Ranch Hand veterans to dioxin was  
41 insufficient for the production of chloracne, or perhaps the exposure may have caused chloracne that  
42 resolved and currently was undetectable.

43 In the 1994 *Veterans and Agent Orange* report published by the Institute of Medicine (IOM), the  
44 Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that  
45 there is sufficient evidence of an association between exposure to dioxin and chloracne (8). This  
46 conclusion remained unaltered in the 2002 and 2004 IOM *Veterans and Agent Orange* updates (9, 10);  
47 however, the committee added a notation in this report that chloracne would appear shortly after dioxin  
48 exposure and not after a long latency (9).

### 49 **8.1.1 Chapter Structure**

50 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
51 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
52 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
53 results that appeared consistently across examinations or have biological meaning are emphasized,  
54 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
55 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
56 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
57 the parameter and either group or dioxin are not discussed.

58 The results discussed below that were discovered as part of further analysis based on a statistical  
59 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
60 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
61 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
62 baseline examination. Older participants were defined as those born before 1942.

63 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
64 Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987  
65 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
66 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
67 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
68 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at  
69 most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this  
70 stratification based on the participant's tour of duty is given in Chapter 2.

71 The following chart lists the variables that were analyzed for the dermatology assessment and at which  
72 physical examination they were analyzed. The variables appearing in bold type are discussed  
73 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Acne - Self-reported Occurrence and Duration)</b>	X	X	X	X	X	Analysis not performed	X
<b>Acneiform Lesions</b>	X	X	X	X			X
<b>Acneiform Scars</b>	X	X	X	X			X
Any Dermatologic Evaluation Abnormality	X						
Comedones	X	X	X	X			X
Depigmentation		X	X	X			X
<b>Dermatology Index</b>	X	X	X	X	X		X
Duration of Acne	X	X	X				X
<b>Hyperpigmentation</b>	X	X	X	X			X
Inclusion Cysts	X	X	X	X			X
Location of Post-SEA Acne (excluding participants with pre-SEA acne)		X	X	X	X		X
<b>Other Dermatologic Evaluation Abnormalities</b>	X	X	X	X	X		

74 **8.2 ACNE – SELF-REPORTED OCCURRENCE AND DURATION**

75 The occurrence, location, and duration of acne were reported by the participants at each physical  
76 examination and combined to construct a lifetime history of acne. Based on the compilation of all  
77 examinations, the analyses performed for the 2002 follow-up examination showed that the occurrence of  
78 reported acne after service in Southeast Asia (SEA) increased in Ranch Hand enlisted groundcrew, the  
79 subgroup with the highest median dioxin levels. The occurrence and duration of reported acne since SEA  
80 service increased in the background, low, and high Ranch Hand dioxin categories. In examining whether  
81 the occurrence of acne prior to service in SEA had an effect, it was discovered that the associations with  
82 dioxin were found only in participants who did not report acne prior to service in SEA. No relation was  
83 found in participants who did report acne prior to service in SEA.

84 **8.3 ACNEIFORM LESIONS**

85 The prevalence of acneiform lesions at the 2002 follow-up examination was greater for Ranch Hands in  
86 the background dioxin category than for Comparisons.

87 **8.4 ACNEIFORM SCARS**

88 As 1987 dioxin levels increased in Ranch Hands with later tours of duty, the occurrence of acneiform  
89 scars at the 1987 follow-up examination increased.

90 **8.5 HYPERPIGMENTATION**

91 Among older participants, the prevalence of hyperpigmentation at the 1987 follow-up examination  
92 increased as initial dioxin levels increased. In addition, as 1987 dioxin levels increased in Ranch Hands  
93 with later tours of duty, the occurrence of hyperpigmentation at the 1987 follow-up examination  
94 increased.

95 **8.6 OTHER DERMATOLOGIC EVALUATION ABNORMALITIES**

96 An endpoint named “other abnormalities,” which was the combination of vitiligo, jaundice, spider  
97 angiomas, palmar erythema, palmar keratosis, actinic keratosis, petechia, ecchymosis, conjunctival  
98 abnormality, oral mucosal abnormality, fingernail abnormality, toenail abnormality, dermatographia, cutis  
99 rhomboidalis, nevus, and other nonspecific abnormalities, was created for the purpose of analysis for the  
100 1992 follow-up examination. This variable was considered abnormal if at least one of the above  
101 conditions was present and normal if all of the conditions were absent. For participants who reported  
102 acne prior to their tour of duty in SEA, the percentage of participants who had these other abnormalities  
103 increased as initial dioxin increased.

104 **8.7 DERMATOLOGY INDEX**

105 A dermatology index was created by combining results for comedones, acneiform lesions, acneiform  
106 scars, and inclusion cysts. A participant was defined as abnormal for this dermatology index if any of  
107 these conditions was present and defined as normal if none was present. Younger Ranch Hands in the  
108 background dioxin category had an abnormal dermatology index more often than younger Comparisons  
109 in the analysis of data collected at the 1992 follow-up examination.

110 **8.8 CONCLUSION**

111 Chloracne is a skin condition recognized as a consequence of exposure to high levels of dioxin and other  
112 cyclic organochlorine compounds. It usually appears without long latency after a short interval of  
113 exposure to dioxin and persists for about 2 to 3 years. Primary lesions of chloracne were not expected to  
114 persist and be noted upon physical examination. Chloracne might be suggested if the secondary lesions  
115 such as scarring, hyperpigmentation, and depigmentation had been observed in the typical distribution  
116 areas of chloracne around eyes, temples, and ears. No evidence of chloracne was found.

117 The dermatology assessment included the occurrence of self-reported acne and physical examination. An  
118 increased frequency of reported acne after service in SEA in Ranch Hand enlisted groundcrew was  
119 observed, along with an increase between the occurrence and duration of reported acne since SEA service  
120 in the background, low, and high Ranch Hand dioxin categories. The association between the occurrence  
121 and frequency of dioxin were found only in participants who did not report acne prior to service in SEA.  
122 No associations were found in participants who did report acne prior to service in SEA.

123 The interpretation of the increased frequency of reported acne after service in SEA in Ranch Hand  
124 enlisted groundcrew was observed, but is of uncertain meaning because secondary lesions that were  
125 observed revealed no association with herbicide or dioxin exposure.

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## 9 ENDOCRINOLOGY ASSESSMENT

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### 9.1 INTRODUCTION

The human endocrine system generally is not believed to be a primary target of dioxin or dioxin-like exposure, although large doses of dioxin are known to produce a variety of metabolic phenomena in a number of species of experimental animals. Several sites of endocrine activity, including the pancreas, thyroid gland, and hypothalamic-pituitary-testis axis have been evaluated for dioxin toxicity in animal and human studies. Special emphasis has been placed on the parameters associated with diabetes in the Air Force Health Study (AFHS), due to the associations found in the analysis of the 1987, 1992, 1997, and 2002 follow-up examinations.

The two most important hormones secreted by the pancreas are insulin and glucagon. Insulin stimulates liver cells to take up glucose from the blood and convert it into glycogen. Glucagon stimulates the conversion of glycogen into glucose, which is then released into the blood. The production of insulin is regulated by blood glucose concentrations; high blood glucose concentrations combined with insulin deficiency results in diabetes. Type 2 diabetes, the diagnosis given to approximately 90 percent of all diabetes cases in the general population, describes a combination of insulin resistance, insulin deficiency, and glucose overproduction. The epidemiologic studies suggest that any increased risk of type 2 diabetes from herbicide or dioxin exposure is small when compared to known risk factors, such as family history, obesity, and physical inactivity.

The thyroid gland produces thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ), hormones that are released in response to thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. To maintain thyroid hormone homeostasis, the pituitary is stimulated to release more TSH when circulating  $T_3$  and  $T_4$  levels are low. Conversely, high levels of circulating  $T_3$  and  $T_4$  trigger the pituitary to reduce TSH production. Disruptions in this feedback loop can lead to diseases such as hypothyroidism and hyperthyroidism.

The hypothalamic-pituitary-testis axis produces several hormones affecting gonadal function. The hypothalamus releases gonadotropin-releasing hormone that subsequently signals the pituitary to release luteinizing hormone (LH), the hormone that regulates growth and development of eggs and sperm. Within the testis, LH stimulates testosterone production in the Leydig cells. Testosterone from the testes, as well as follicle-stimulating hormone (FSH) released by the pituitary, stimulates production of sperm. Excess testosterone converts to estradiol by the aromatase enzyme. Male-mediated adverse reproductive effects can be due to any number of imbalances in gonadal hormones produced via the hypothalamic-pituitary-testis axis.

The AFHS endocrinology assessment for the 1982, 1985, 1987, 1992, 1997, and 2002 follow-up examinations (1-7) included medical records verification of questionnaire responses, physical examination results, and laboratory findings.

The AFHS health interview questionnaires posed a general screening question on thyroid function and disease. Each participant was asked the following question during the in-person health interview: "Since the date of the last interview, has a doctor told you for the first time that you had thyroid problems?" Medical records review was accomplished to confirm self-reported problems with thyroid function and to

40 identify any unreported thyroid conditions. At each physical examination, a history of thyroid disease  
41 was constructed for each participant.

42 Similar information was asked of each participant regarding diabetes. This information also was verified  
43 and combined with previously collected information. For the 2002 follow-up examination, the American  
44 Diabetes Association's (ADA) revised definition of a diabetic was used (8). According to the ADA, a  
45 diabetic was defined as an individual with a 2-hour postprandial glucose level of 200 mg/dL or greater on  
46 two separate occasions, or a fasting glucose level of 126 mg/dL or greater on two separate occasions, or  
47 one 2-hour postprandial glucose level of 200 mg/dL or greater and a fasting glucose level of 126 mg/dL  
48 or greater on separate occasions. In addition, any participant diagnosed as a diabetic prior to the 2002  
49 examination was included in the analysis.

50 Participants were considered diabetics at previous AFHS examinations if they had a 2-hour postprandial  
51 glucose level of 200 mg/dL or greater at that physical examination or a verified history of diabetes prior  
52 to that examination.

53 As part of the health interview questionnaire, questions were asked of diabetics regarding the use of  
54 insulin, oral diabetes medication, and diet. This self-reported information was verified and a diabetic  
55 control index was constructed and analyzed for all participants. This index was categorized as "requiring  
56 insulin," "oral hypoglycemics," "diet and exercise," or "no treatment" for diabetics and "no diabetes" for  
57 nondiabetics.

58 A variable that was termed "time to diabetes onset" was analyzed. This variable combined both diabetics  
59 and nondiabetics. For the purposes of statistical analyses, time to diabetes onset was the number of years  
60 between the date of diagnosis of diabetes and the end date of the last qualifying tour of duty in Southeast  
61 Asia (SEA) for diabetics. For nondiabetics, this variable was the number of years between the date of the  
62 AFHS physical examination and the end date of the last qualifying tour of duty in SEA.

63 The physical examination of endocrine function included manual palpation of the thyroid gland and  
64 testes. Thyroid abnormalities consisted of enlarged gland, tenderness, presence of nodules, or a  
65 thyroidectomy. Testicular abnormalities consisted of atrophied or testes surgically removed after SEA.  
66 Testicular volume (minimum and total) was determined using ultrasound techniques for the 1992 follow-  
67 up examination. Diabetic retinopathy and neuropathy (presence or absence) also were assessed for the  
68 1992 follow-up examination.

69 Laboratory measurements for anti-thyroid antibodies (presence or absence), TSH ( $\mu$ IU/mL), free T<sub>4</sub>  
70 (ng/dL), T<sub>4</sub> ( $\mu$ g/dL), T<sub>3</sub> uptake (percent), total testosterone (ng/dL), free testosterone (pg/mL), LH  
71 (mIU/mL), FSH (mIU/mL), estradiol (pg/mL), glucagon (pg/mL), and sex hormone-binding globulin  
72 (SHBG) (nmol/L) were collected and analyzed for all participants in the endocrinology assessment. A  
73 free thyroxine index, which is a mathematical computation from T<sub>4</sub> and T<sub>3</sub> uptake that estimates how  
74 much thyroid hormone is free in the blood stream to work on the body, and a total testosterone to SHBG  
75 ratio were analyzed for the 1982 and 1992 AFHS examinations, respectively.

76 Glucose (mg/dL), urinary glucose (presence or absence), and serum insulin ( $\mu$ IU/mL) (fasting for all  
77 participants and 2-hour postprandial for nondiabetics) were analyzed. Participants classified as diabetic  
78 were tested for hemoglobin A1c (percent), C-peptide (ng/mL), proinsulin (pmol/L), and glutamic acid  
79 decarboxylase antibodies (GADA) (presence or absence).

80 Two cortisol measurements, taken 2 hours apart, were obtained from all participants at the 1985 follow-  
81 up examination as a general indicator of the integrity of the endocrine system and as a secondary risk

82 factor for coronary heart disease. The two measurements, as well as the difference between the  
83 measurements, were analyzed.

84 The following journal articles on diabetes and glucose control were written by AFHS staff and their  
85 colleagues:

- 86 • Diabetes versus dioxin body burden in veterans of Operation Ranch Hand (9)
- 87 • Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand (10) and a follow-up  
88 letter to the editor (11)
- 89 • Letter to the Editor: Weight history, glucose intolerance, and insulin levels in middle-aged  
90 Swedish men (12)
- 91 • Serum dioxin, insulin, fasting glucose and sex hormone-binding globulin in veterans of  
92 Operation Ranch Hand (13)
- 93 • Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background  
94 levels of exposure (14)
- 95 • Dioxin and diabetes mellitus: An analysis of the combined NIOSH and Ranch Hand data (15)
- 96 • Diabetes mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin elimination in veterans of Operation  
97 Ranch Hand (16)
- 98 • Insulin sensitivity following Agent Orange exposure in Vietnam veterans with high blood  
99 levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (17).

100 The following journal article on the thyroid function was written by AFHS staff and their colleagues:

- 101 • Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels and thyroid function in Air Force  
102 veterans of the Vietnam War (18).

103 The following journal articles on testosterone, FSH, LH, testicular abnormalities, sperm count, sperm  
104 abnormalities, and testicular volume were written by AFHS staff and their colleagues:

- 105 • Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand (19)
- 106 • [Follow-up] Letter to the editor (20).

107 These articles are discussed later in this chapter.

108 Based on a comprehensive review of the literature, the 2000 Institute of Medicine (IOM) Committee to  
109 Review the Health Effects in Vietnam Veterans of Exposure to Herbicides found limited or suggestive  
110 evidence of an association between exposure to herbicides, including 2,4,5-trichlorophenoxyacetic acid  
111 (2,4,5-T) and its contaminant dioxin, and type 2 diabetes (21). A separate report also was written  
112 describing the findings between type 2 diabetes and herbicide and dioxin exposure (22). This conclusion  
113 remained unchanged in the 2004 *Veterans and Agent Orange* update (23).

114 In 2002, the IOM (24) concluded that there is inadequate or insufficient evidence to determine if an  
115 association exists between Agent Orange and other herbicides used in Vietnam and altered thyroid  
116 function. This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (23).

117 Based on the 2004 *Veterans and Agent Orange* update (23), “the lack of data on the association between  
118 exposure to the chemicals of interest and altered sperm characteristics or infertility, coupled with the lack

119 of exposure information on Vietnam veterans, precludes quantification of any possible increase in their  
 120 risk.”

### 121 **9.1.1 Chapter Structure**

122 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
 123 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
 124 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
 125 results that appeared consistently across examinations or have biological meaning are emphasized,  
 126 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
 127 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
 128 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
 129 the parameter and either group or dioxin are not discussed.

130 The results discussed below that were discovered as part of further analysis based on a statistical  
 131 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
 132 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
 133 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
 134 baseline examination. Older participants were defined as those born before 1942.

135 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 136 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 137 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 138 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 139 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 140 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at  
 141 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
 142 stratification based on the participant’s tour of duty is given in Chapter 2.

143 The following chart lists the variables that were analyzed for the endocrinology assessment and at which  
 144 physical examination they were analyzed. The variables appearing in bold type are discussed  
 145 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
2-hour Cortisol		X					
<b>2-hour Postprandial Glucose</b>	X	X	X	X	X	X	X
<b>2-hour Postprandial Urinary Glucose</b>					X	X	X
<b>Anti-thyroid Antibodies</b>					X	X	X
<b>C-peptide</b>					X		X
<b>Diabetes</b>		X	X	X	X	X	X
<b>Diabetic Control</b>					X	X	X
Diabetic Neuropathy					X		
Diabetic Retinopathy					X		
<b>Differential Cortisol</b>		X					
<b>Estradiol</b>					X	X	X
<b>Fasting Glucose</b>				X	X	X	X
<b>Fasting Urinary Glucose</b>					X	X	

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Free T <sub>4</sub>							X
<b>Free Testosterone</b>					X	X	X
Free Thyroxine Index	X						
<b>FSH</b>			X	X	X	X	X
GADA							X
<b>Glucagon</b>					X		
<b>Hemoglobin A1c</b>					X	X	X
Initial Cortisol		X					
<b>Insulin</b>					X	X	X
<b>LH</b>					X	X	X
<b>Proinsulin</b>					X		X
SHBG					X		
T <sub>3</sub> Uptake	X	X	X	X			
<b>T<sub>4</sub></b>	X				X	X	
<b>Testicular Examination</b>		X	X	X		X	X
<b>Testicular Volume (Minimum and Total)</b>					X		
<b>Thyroid Disease</b>		X	X	X	X	X	X
Thyroid Gland		X	X	X	X	X	X
<b>Time to Diabetes Onset</b>					X	X	X
<b>Total Testosterone</b>	X	X	X	X	X	X	X
Total Testosterone to SHBG Ratio					X		
<b>TSH</b>		X	X	X	X	X	X

146

147 Because of the nature of the endocrine function, this chapter has been organized into three sections:  
148 diabetes and glucose control, thyroid gland, and hypothalamic-pituitary-testis axis.

## 149 **9.2 DIABETES AND GLUCOSE CONTROL**

### 150 **9.2.1 Prevalence of Diabetes**

151 A higher percentage of Ranch Hands in the high dioxin category than Comparisons were diabetic in the  
152 analysis of the 1987 follow-up examination data. This difference was seen primarily in older participants.  
153 The percentage of diabetic Ranch Hands also increased with increasing initial and 1987 dioxin levels.

154 Among officers, the analysis of the 1992 follow-up examination data showed a higher prevalence of  
155 diabetes among Ranch Hands in the combined low and high dioxin category than Comparisons. The  
156 prevalence of Ranch Hand diabetics also increased with increasing initial dioxin and 1987 dioxin levels.

157 A higher percentage of Ranch Hands in the high dioxin category than Comparisons were diabetic at the  
158 1997 follow-up examination. The prevalence of Ranch Hand diabetics also increased with increasing  
159 initial dioxin and 1987 dioxin levels.

160 In the analysis of the 2002 follow-up examination data, the percentage of participants classified as  
161 diabetic increased as initial and 1987 dioxin levels increased.

162 **9.2.2 Diabetic Control**

163 Analysis of 1992 follow-up examination data showed that the percentage of Ranch Hands using oral  
164 hypoglycemics to control diabetes increased with increasing initial dioxin levels and with 1987 dioxin  
165 levels, particularly among enlisted flyers and enlisted groundcrew. Ranch Hands in the high dioxin  
166 category had a higher prevalence of oral hypoglycemic use for diabetes than Comparisons. The  
167 percentage of Ranch Hands controlling diabetes through diet only increased with increasing 1987 dioxin  
168 levels, particularly among officers and enlisted flyers.

169 The percentage of Ranch Hands requiring insulin to control diabetes was greater than Comparisons in the  
170 analysis of the 1997 follow-up examination data. The percentage of Ranch Hands in both the low and  
171 high dioxin categories requiring insulin for diabetic control also was greater than Comparisons. The  
172 percentage of Ranch Hands requiring insulin increased with increasing initial dioxin levels. In addition,  
173 the percentage of Ranch Hands using diet only to control diabetes and the percentage of Ranch Hands  
174 using oral hypoglycemics for diabetic control increased with increasing 1987 dioxin levels.

175 Analysis of the 2002 follow-up examination data showed that the percentage of Ranch Hands requiring  
176 insulin increased with increasing initial and 1987 dioxin levels. A higher percentage of Ranch Hands in  
177 the high dioxin category than Comparisons required insulin. In addition, the percentage of Ranch Hands  
178 using oral hypoglycemics for diabetic control increased with increasing 1987 dioxin levels.

179 **9.2.3 Time to Diabetes Onset**

180 The analysis of 1992 follow-up examination data found that the time to diabetes onset decreased (adverse  
181 effect) with increasing 1987 dioxin levels. The time to diabetes onset decreased with increasing initial  
182 and 1987 dioxin levels in the 1997 and 2002 follow-up examination data analyses.

183 **9.2.4 Fasting Glucose**

184 In the analysis of the 1987 follow-up examination data, fasting glucose levels in Ranch Hands increased  
185 with increasing initial and 1987 dioxin levels. Similarly, the percentage of Ranch Hands with abnormally  
186 high fasting glucose levels increased with increasing initial dioxin and with 1987 dioxin levels. The  
187 average fasting glucose level was greater for Ranch Hands in the high dioxin category than for  
188 Comparisons, as was the prevalence of abnormally high fasting glucose levels.

189 The 1992 follow-up examination showed that fasting glucose levels in Ranch Hands increased with  
190 increasing initial dioxin, particularly among officers and enlisted groundcrew. Among only nondiabetic  
191 participants, fasting glucose levels increased with increasing initial dioxin among Ranch Hand officers.  
192 Fasting glucose levels increased with increasing 1987 dioxin when evaluating all Ranch Hands and also  
193 when analysis was restricted to only diabetic Ranch Hands. In addition, the prevalence of abnormally  
194 high fasting glucose levels in Ranch Hands increased with increasing 1987 dioxin. Nondiabetic Ranch  
195 Hands in the background dioxin category had a higher average fasting glucose level than nondiabetic  
196 Comparisons among enlisted groundcrew.

197 Fasting glucose levels and the prevalence of Ranch Hands with abnormally high fasting glucose levels  
198 increased with increasing initial dioxin and 1987 dioxin in the analysis of the 1997 follow-up examination  
199 data.

200 **9.2.5 2-hour Postprandial Glucose**

201 In the analysis of the 1987 follow-up examination data, 2-hour postprandial glucose levels in Ranch  
202 Hands increased with increasing initial dioxin levels and with 1987 dioxin levels in Ranch Hands with  
203 earlier tours. In addition, abnormally high 2-hour postprandial glucose levels were more prevalent among  
204 Ranch Hands in the high dioxin category than among Comparisons.

205 The analysis of 1992 follow-up examination data showed that Ranch Hands had higher average 2-hour  
206 postprandial glucose levels than Comparisons among obese (approximate body mass index of 30 or more)  
207 participants, among obese enlisted groundcrew, and among enlisted groundcrew with no family history of  
208 diabetes. Ranch Hands in the high dioxin category had higher average 2-hour postprandial glucose levels  
209 than Comparisons among obese participants and among participants with no family history of diabetes. A  
210 greater percentage of Ranch Hands in the high dioxin category than Comparisons also had elevated 2-  
211 hour postprandial glucose levels.

212 Two-hour postprandial glucose levels at the 1992 follow-up examination increased with increasing initial  
213 dioxin levels. An increase in 2-hour postprandial glucose levels with increasing 1987 dioxin levels was  
214 observed, as was the prevalence of elevated 2-hour postprandial glucose among non-Black participants.

215 **9.2.6 Fasting Urinary Glucose**

216 The analysis of the 1992 follow-up examination data showed that the percentage of Ranch Hands with  
217 fasting urinary glucose present increased with increasing initial dioxin and with 1987 dioxin, both when  
218 all participants were considered and when diabetic participants only were considered.

219 In the analysis of the 1997 follow-up examination data, the percentage of participants with fasting urinary  
220 glucose present increased with increasing 1987 dioxin.

221 **9.2.7 2-hour Postprandial Urinary Glucose**

222 Based on the analysis of the 1992 follow-up examination data, the prevalence of abnormal 2-hour  
223 postprandial urinary glucose levels in Ranch Hands increased with increasing 1987 dioxin levels.

224 Among officers, a higher percentage of Ranch Hands than Comparisons had 2-hour postprandial urinary  
225 glucose present at the 1997 and 2002 follow-up examination.

226 **9.2.8 Insulin**

227 Based on the analysis of all participants, the 1992 follow-up examination data analysis showed a higher  
228 average insulin level in Ranch Hands than in Comparisons among obese participants and obese officers.  
229 Insulin levels in Ranch Hands increased with increasing 1987 dioxin levels. The prevalence of  
230 abnormally high insulin levels was greater in Ranch Hands than in Comparisons among obese officers  
231 and among obese participants in the background dioxin category.

232 The 1992 follow-up examination analysis of diabetic participants showed that the average serum insulin  
233 level was higher for Ranch Hands in the low dioxin category than for Comparisons. Among older  
234 diabetic participants, the prevalence of abnormally high insulin levels was higher for Ranch Hands in the  
235 low dioxin category than for Comparisons.

236 The 1992 follow-up examination analysis of nondiabetic participants showed a higher average serum  
237 insulin level for Ranch Hands than Comparisons among obese participants. Serum insulin levels for

238 nondiabetic Ranch Hand participants increased with increasing initial and 1987 dioxin levels. The  
239 prevalence of abnormally high serum insulin levels in Ranch Hands increased with increasing 1987  
240 dioxin and also increased with increasing initial dioxin levels, particularly among enlisted flyers. Also  
241 among enlisted flyers, Ranch Hands in the high dioxin category had a higher prevalence of abnormally  
242 high serum insulin levels than Comparisons.

243 Data for both fasting (for all participants) and 2-hour postprandial insulin (for nondiabetics) were  
244 collected for the 2002 follow-up examination data. Fasting insulin levels and the prevalence of  
245 abnormally high fasting insulin levels increased in Ranch Hands as initial dioxin increased. Ranch Hand  
246 enlisted groundcrew had a lower average 2-hour postprandial insulin level than Comparison enlisted  
247 groundcrew.

### 248 **9.2.9 Hemoglobin A1c**

249 Hemoglobin A1c indicates a patient's blood sugar control over the last 2 to 3 months. Hemoglobin A1c is  
250 formed when glucose in the blood binds irreversibly to hemoglobin to form a stable glycated hemoglobin  
251 complex and is not subject to the fluctuations that are seen with daily blood glucose monitoring.

252 Hemoglobin A1c levels increased with increasing initial dioxin levels among Ranch Hand officers and  
253 enlisted groundcrew in the analysis of the 1992 follow-up examination data. The percentage of Ranch  
254 Hand officers with abnormally high hemoglobin A1c levels also increased with increasing initial dioxin  
255 levels. In addition, an increase in hemoglobin A1c levels with increasing 1987 dioxin levels was  
256 observed among all Ranch Hands, older obese Ranch Hands, and diabetic Ranch Hands. Among obese  
257 Ranch Hands, the prevalence of abnormally high hemoglobin A1c levels increased with increasing 1987  
258 dioxin levels.

259 Ranch Hands in the high dioxin category had increased average hemoglobin A1c levels and a greater  
260 prevalence of abnormally high hemoglobin A1c levels than Comparisons when the 1997 follow-up  
261 examination data were analyzed. In addition, hemoglobin A1c levels increased with increasing 1987  
262 dioxin levels in Ranch Hands, and the percentage of Ranch Hands with abnormally high hemoglobin A1c  
263 levels increased with increasing 1987 dioxin levels.

264 In the analysis of the 2002 follow-up examination data, the prevalence of abnormally high hemoglobin  
265 A1c levels in Ranch Hand diabetics increased with increasing 1987 dioxin levels.

### 266 **9.2.10 C-peptide**

267 C-peptide is a subunit of insulin and is measured to differentiate insulin production by the body and  
268 insulin injected into the body. The C-peptide level may be measured in a patient with type 2 diabetes to  
269 see if any insulin is still being produced by the body. It may also be measured in the evaluation of low  
270 blood sugar to see if too much insulin is being produced by a patient.

271 The analysis of the 1992 follow-up examination data showed that Ranch Hands in the low dioxin  
272 category had a higher average C-peptide level than Comparisons among diabetic enlisted groundcrew. In  
273 addition, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high C-peptide  
274 levels than Comparisons, primarily among older diabetic participants.

275 **9.2.11 Glucagon**

276 In the 1992 follow-up examination data analysis, serum glucagon levels increased in Ranch Hands as  
277 1987 dioxin increased, particularly among Ranch Hands with no family history of diabetes. The  
278 percentage of Ranch Hands with an abnormally high glucagon level also increased as 1987 dioxin  
279 increased. Among all participants who treat their diabetes through diet only, and among officers who do  
280 the same, Ranch Hands had a higher average serum glucagon level than Comparisons when diabetic  
281 participants were analyzed separately. When nondiabetics were analyzed separately, serum glucagon  
282 levels increased in Ranch Hands as initial and 1987 dioxin levels increased.

283 **9.2.12 Proinsulin**

284 Proinsulin is a precursor of insulin with minimal hormonal activity and is converted into insulin by  
285 enzymatic action.

286 The 1992 follow-up examination analysis of diabetic Ranch Hands showed that the percentage of Ranch  
287 Hand officers with abnormally high serum proinsulin levels increased with increasing 1987 dioxin levels.

288 **9.2.13 Diabetes Versus Dioxin Body Burden in Veterans of Operation Ranch Hand**

289 An analysis based on veterans who participated in the 1987 physical examination and who had a dioxin  
290 measurement was conducted to investigate glucose intolerance and diabetes versus dioxin levels (9). A  
291 history of diabetes, time to diabetes onset, and how diabetes is being treated or controlled were analyzed  
292 versus dioxin. Associations with initial dioxin were observed for fasting glucose and diabetes. Both  
293 associations were consistent with a dose-response effect. An effect also was present between diabetes and  
294 categorized dioxin and between time to diabetes onset and categorized dioxin, consistent with a dose-  
295 response effect within Ranch Hands. Ranch Hands in the high dioxin category experienced diabetes  
296 sooner than Comparisons. A greater percentage of Ranch Hands in the high dioxin category required diet  
297 control, oral medications, or insulin to treat their diabetes than Comparisons.

298 **9.2.14 Serum Dioxin and Diabetes Mellitus in Veterans of Operation Ranch Hand**

299 The prevalence of diabetes, use of oral medications to control diabetes, and time-to-diabetes onset were  
300 studied, based on participants who had a dioxin measurement and attended the 1982, 1985, 1987, or 1992  
301 AFHS examination (10). Analysis was also conducted on glucose levels and serum glucose abnormalities  
302 based on participants at the 1992 physical examination who had a dioxin measurement. Each Ranch  
303 Hand veteran was assigned to the background, low, or high dioxin exposure category on the basis of a  
304 measurement of dioxin body burden. Glucose abnormalities, diabetes prevalence, and the use of oral  
305 medications to control diabetes increased, and time-to-diabetes-onset decreased, with dioxin exposure.  
306 Serum insulin abnormalities for Ranch Hands in the high dioxin category were increased in nondiabetics.  
307 The results indicated a possible relation between dioxin exposure and diabetes mellitus, glucose  
308 metabolism, and insulin production.

309 Subsequent to the publication of the above article, the possibility of an interaction between plasma lipid  
310 fractions, diabetes, and total serum dioxin levels was raised. The concern was that dioxin may be more  
311 heavily concentrated in the triglyceride fraction of total lipids, which would contribute to the finding of  
312 increased risk of diabetes mellitus in participants with high dioxin levels because diabetes is associated  
313 with increased triglycerides. The AFHS authors conducted further analysis and found no evidence to  
314 support concern (11).

315 **9.2.15 Letter to the Editor: Weight History, Glucose Intolerance, and Insulin Levels in Middle-**  
316 **aged Swedish Men**

317 A 1998 article described the relation between impaired glucose tolerance and type 2 diabetes mellitus and  
318 the length of time that a subject had been overweight (25). Duration of overweight was studied as an  
319 independent risk factor for impaired glucose tolerance and type 2 diabetes mellitus using data from the  
320 1992 AFHS follow-up examination (12). The relation of body mass index and waist circumference to  
321 risk of impaired glucose tolerance or diabetes mellitus generally agreed between the two articles.  
322 Duration of being overweight, however, was not seen as an independent risk factor.

323 **9.2.16 Serum Dioxin, Insulin, Fasting Glucose and Sex Hormone-Binding Globulin in Veterans of**  
324 **Operation Ranch Hand**

325 Insulin, fasting glucose, and SHBG were analyzed in relation to dioxin based on participants at the 1992  
326 physical examination who had a dioxin measurement (13). Each Ranch Hand veteran was assigned to  
327 one of three dioxin categories—background, low, and high—based on his dioxin level. Among  
328 nondiabetic veterans, insulin was increased for Ranch Hands in the high dioxin category. Insulin  
329 decreased as SHBG increased among young (age 53 or less), lean (body mass index < 30), nondiabetic  
330 veterans in the high category. The findings suggest a compensatory metabolic relation between dioxin  
331 and insulin regulation.

332 **9.2.17 Serum Dioxin Level in Relation to Diabetes Mellitus among Air Force Veterans with**  
333 **Background Levels of Exposure**

334 Data from several epidemiologic studies suggest that exposure to unusually high amounts of dioxin  
335 increases the risk of diabetes mellitus, and experimental data suggest that the mechanism for this is  
336 decreased cellular glucose uptake. To investigate the dose response relation more closely, the association  
337 of serum dioxin level with prevalence of diabetes mellitus and with levels of serum insulin and glucose  
338 was examined among 1,197 veterans in the AFHS who never had contact with dioxin-contaminated  
339 herbicides and whose serum dioxin level was within the range of background exposure typically seen in  
340 the United States ( $\leq 10$  ng/kg lipid) (14). The prevalence of diabetes was increased for those veterans who  
341 were in the highest quartile of dioxin levels ( $\geq 5.2$  ng/kg lipid), as compared to veterans in the first quartile  
342 of dioxin levels ( $< 2.8$  ng/kg lipid). The association was slightly weaker after adjusting for serum  
343 triglycerides drawn at the same time of the dioxin measurement. A positive relation existed between  
344 glucose and insulin levels and serum dioxin; adjustment for serum triglycerides again weakened most of  
345 the associations. Whether adjustment for serum triglycerides was appropriate, however, could not be  
346 determined with the available data. The association of background-level dioxin exposure with the  
347 prevalence of diabetes in these data may well be due to reasons other than causality, although a causal  
348 contribution cannot be wholly dismissed.

349 **9.2.18 Dioxin and Diabetes Mellitus: An Analysis of the Combined NIOSH and Ranch Hand Data**

350 In an attempt to reconcile disparate results, analysis was conducted in a similar manner from combined  
351 AFHS and National Institute for Occupational Safety and Health (NIOSH) data sets, the two principal  
352 studies of dioxin and diabetes. A uniform approach to outcome definition, data analysis, and covariate  
353 control was adopted, and results were described in a 2001 journal article (15). This article reanalyzed  
354 data from 990 Ranch Hands and 1,275 Comparisons and a NIOSH population of 267 chemical workers  
355 and 227 referents. The Ranch Hand veterans had lower concentrations of lipid-adjusted serum dioxin  
356 (median 12 parts per trillion [ppt]) than the NIOSH workers (median 75 ppt). The combined exposed  
357 groups did not differ markedly from the combined nonexposed groups for prevalence of diabetes, with no

358 evidence of a difference of exposure effect between studies. In addition, virtually no difference was  
359 found between combined exposed and nonexposed groups in average fasting serum glucose, and there  
360 was little evidence in either study of a dose-response trend for fasting serum glucose. An increasing trend  
361 was found in prevalence of diabetes with increased dioxin among the Ranch Hand population, with  
362 excess risk largely confined to the highest 8 percent of the exposed group (>78 ppt serum dioxin) versus  
363 those with less than 10 ppt dioxin. No such positive dose-response was found in the NIOSH population.  
364 The reason for the difference in diabetes dose-response trends between the two studies was unknown.

365 Reviewers of AFHS results on diabetes hypothesized that the association between diabetes and dioxin  
366 concentration reflects an association between diabetes and the dioxin elimination rate. Individuals with  
367 slow elimination rates may retain dioxin for a longer period of time, have a long dioxin half-life, and,  
368 consequently, may be at an increased risk for diabetes. Individuals with quick elimination rates may  
369 retain dioxin for a shorter period of time, have a relatively short dioxin half-life, and may be at a  
370 decreased risk for diabetes.

### 371 **9.2.19 Diabetes Mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin Elimination in Veterans of** 372 **Operation Ranch Hand**

373 Results of AFHS analyses to examine this hypothesis were reported in a 2003 journal article (16). No  
374 relation was found between the rate of dioxin elimination and the occurrence or time to onset of diabetes.  
375 Without adjustment for age, body mass index, family history of diabetes, and smoking history, the time to  
376 onset of diabetes decreased and the risk of diabetes increased with a diminished elimination rate. After  
377 adjustment for age, body mass index, family history of diabetes, and smoking history, diabetes time to  
378 onset and occurrence were not associated with dioxin elimination. No difference was found between the  
379 average elimination rates of diabetic and nondiabetic veterans, without or with adjustment for risk factors.

### 380 **9.2.20 Insulin Sensitivity Following Agent Orange Exposure in Vietnam Veterans with High Blood** 381 **Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin**

382 Studies to determine whether insulin sensitivity was related to dioxin were performed and reported in a  
383 2004 journal article (17). Ranch Hand and Comparison subjects were matched by age, body mass index,  
384 race, and a family history of diabetes. Insulin sensitivity was measured using a frequently sampled  
385 intravenous glucose tolerance test in a matched study of 29 Ranch Hand-Comparison pairs of veterans  
386 and a quantitative insulin sensitivity check index based on fasting glucose and fasting insulin in 71  
387 matched pairs. There were no differences in an insulin sensitivity index, a quantitative insulin sensitivity  
388 check index, tumor necrosis factor alpha (TNF $\alpha$ ), adiponectin, and two measures of insulin secretion  
389 between Ranch Hands and Comparisons. The difference in the insulin sensitivity index and the  
390 quantitative insulin sensitivity check index between the Ranch Hand member and the Comparison  
391 member of the pair decreased as the difference in dioxin increased. These data suggested that high blood  
392 dioxin levels may promote an insulin-resistant state, but the magnitude of this effect appeared to be small,  
393 such that an 18-fold increase in dioxin due to increased exposure resulted in only a 10 percent change in  
394 the insulin sensitivity index in the 29 matched pairs.

## 395 **9.3 THYROID**

### 396 **9.3.1 Thyroid Disease**

397 In the 1992 follow-up examination analysis of thyroid disease, among participants with type A  
398 personalities (26), a higher percentage of Ranch Hands in the background dioxin category had a history of  
399 thyroid disease than Comparisons.

400 **9.3.2 Anti-thyroid Antibodies**

401 Ranch Hands in the combined low and high dioxin category had a higher prevalence of anti-thyroid  
402 antibodies than Comparisons, based on analysis of the 1992 follow-up examination data.

403 **9.3.3 Thyroid-stimulating Hormone (TSH)**

404 A higher average TSH level in Ranch Hands than Comparisons was observed at the 1985 follow-up  
405 examination.

406 Ranch Hands in the high dioxin category had a higher average TSH level than Comparisons at the 1987  
407 follow-up examination.

408 Based on data from the 1997 follow-up examination, a greater percentage of Ranch Hand enlisted  
409 groundcrew than Comparison enlisted groundcrew had an abnormally high TSH value.

410 The analysis of the 2002 follow-up examination data showed that the average TSH level was higher for  
411 Ranch Hands than Comparisons, primarily among officers. Ranch Hands in the background dioxin  
412 category also had a higher average TSH level than Comparisons.

413 **9.3.4 Thyroxine (T<sub>4</sub>)**

414 In the analysis of the 1992 follow-up examination data, the percentage of abnormally high T<sub>4</sub> levels  
415 increased with increasing initial and 1987 dioxin levels.

416 **9.3.5 Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Levels and Thyroid Function in Air  
417 Force Veterans of the Vietnam War**

418 Potential health effects of dioxin concentration on total T<sub>4</sub>, TSH, T<sub>3</sub> uptake, the free thyroxine index, and  
419 thyroid diseases were examined in an AFHS article published in 2003 (18). Data for 1,009 Ranch Hand  
420 and 1,429 Comparison veterans compliant to any of the AFHS examinations in 1982, 1985, 1987, 1992,  
421 and 1997 were analyzed. Each veteran was assigned to one of four dioxin categories: Comparison,  
422 background Ranch Hand, low Ranch Hand, or high Ranch Hand. The 1982, 1985, 1987, 1992, and 1997  
423 AFHS examinations showed a trend of increasing TSH that was not accompanied by changes in  
424 circulating T<sub>4</sub> or in the percentage of T<sub>3</sub>, which was measured only in 1982 and 1985. Ranch Hands in  
425 the low and high dioxin categories had a greater TSH average than Comparisons, and a trend test showed  
426 a linear increase across the Comparison, background, low, and high dioxin categories. There was no  
427 evidence of changes in clinical thyroid disease, and no changes in microsomal or anti-thyroidal antibodies  
428 were observed. These findings suggest that dioxin may affect thyroid hormone metabolism and function  
429 in Ranch Hand veterans.

430 **9.4 HYPOTHALAMIC-PITUITARY-TESTIS AXIS**

431 **9.4.1 Differential Cortisol**

432 Younger Black Ranch Hands had a lower mean differential cortisol level than their Comparison  
433 counterparts at the 1985 follow-up examination.

434 **9.4.2 Testicular Examination**

435 In the analysis of the 1987 follow-up examination data, the percentage of Ranch Hands with an abnormal  
436 testicular examination increased with increasing initial and 1987 dioxin levels. In addition, more Ranch  
437 Hands in the high dioxin category had an abnormal testicular examination than Comparisons.

438 **9.4.3 Testicular Volume (Minimum and Total)**

439 In the 1992 follow-up examination data analysis, the minimum testicular volume, using ultrasound  
440 techniques, decreased as 1987 dioxin levels increased among Ranch Hand enlisted flyers. Total testicular  
441 volume, using ultrasound techniques, decreased with increasing levels of initial and 1987 dioxin among  
442 Ranch Hand enlisted flyers.

443 **9.4.4 Total Testosterone**

444 The analysis of the 1987 follow-up examination data found that testosterone levels decreased (adverse  
445 effect) with increasing 1987 dioxin levels in Ranch Hands with later tours of duty. Testosterone levels  
446 also decreased with increasing initial dioxin levels, particularly among Ranch Hands with type A  
447 personalities. In addition, Ranch Hands in the high dioxin category had a lower average testosterone  
448 level than Comparisons. Among participants with type A personalities, the prevalence of abnormally low  
449 testosterone levels was greater in Ranch Hands in the high dioxin category than in Comparisons.

450 In the analysis of 1992 follow-up examination data, testosterone levels decreased with increasing 1987  
451 dioxin among all Ranch Hands, and among officers and enlisted flyers, in particular. Among Ranch  
452 Hands with type A personalities, testosterone levels decreased with increasing initial dioxin levels. The  
453 percentage of Ranch Hand officers with abnormally low testosterone levels increased as initial and 1987  
454 dioxin levels increased. In addition, among participants with type A personalities, Ranch Hands in the  
455 background and low dioxin categories had a greater percentage of abnormally low testosterone levels than  
456 Comparisons.

457 **9.4.5 Free Testosterone**

458 In the 2002 follow-up examination data analysis, Ranch Hand officers were found to have had a higher  
459 percentage of abnormally low free testosterone levels than Comparison officers.

460 **9.4.6 Estradiol**

461 The analysis of the 1992 follow-up examination data found that the percentage of abnormally high  
462 estradiol levels increased with increasing 1987 dioxin levels among Ranch Hand enlisted groundcrew.

463 **9.4.7 Follicle-stimulating Hormone (FSH)**

464 The 1987 follow-up examination data analysis showed that FSH levels increased with increasing 1987  
465 dioxin levels among Ranch Hands with later tours of duty. In the analysis of the 1992 follow-up  
466 examination data, a higher percentage of Ranch Hand officers had abnormally high FSH levels relative to  
467 Comparison officers.

468 **9.4.8 Luteinizing Hormone (LH)**

469 The percentage of Ranch Hands at the 1992 follow-up examination with abnormal high LH levels  
470 increased with increasing initial dioxin levels. In addition, Ranch Hands in the low dioxin category had a  
471 higher average LH level than Comparisons.

472 In the analysis of 2002 follow-up examination data, Ranch Hand officers had a higher average LH level  
473 than Comparison officers. Ranch Hands in the low dioxin category also had a higher average LH level  
474 than Comparisons.

475 **9.4.9 Serum Dioxin, Testosterone, and Gonadotropins in Veterans of Operation Ranch Hand**

476 Using data from the 1982, 1987, and 1992 examinations, the relations between dioxin and current  
477 testosterone, FSH, LH, testicular abnormalities, sperm count, sperm abnormalities, and testicular volume  
478 were studied (19). No consistent or meaningful association between dioxin levels and any of these  
479 outcome variables were found. The authors noted that, if adverse effects did exist, the Ranch Hand  
480 exposure in Southeast Asia was insufficient to produce detectable associations comparable with those  
481 seen in industrial workers with heavier exposure.

482 Reviewers of the aforementioned article commented that analyses on testosterone, FSH, and LH in their  
483 continuous form were not mentioned. In a follow-up letter to the editor (20), the AFHS authors  
484 confirmed that analyses had been conducted. Findings from these analyses were weak and inconsistent  
485 with known exposure differences in Ranch Hands by military occupation. The authors noted that there  
486 may be a subclinical relation between dioxin and testosterone but the association, if it exists, was too  
487 weak to be clinically meaningful.

488 **9.5 CONCLUSION**

489 Results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent and potentially  
490 meaningful adverse relation between dioxin levels and diabetes. Although the prevalence of diabetes was  
491 comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the  
492 possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. A  
493 dioxin-related increase in severity, a decrease in the time from exposure to first diagnosis, and an increase  
494 in fasting glucose and hemoglobin A1c supported the dioxin relation with the occurrence of diabetes.  
495 Increased risks of diabetes were found with initial dioxin, in the high dioxin category, and with 1987  
496 dioxin levels. An increase in severity, a decrease in the time from exposure to first diagnosis, and an  
497 increase in fasting glucose and hemoglobin A1c also were observed as initial and 1987 dioxin levels  
498 increased.

499 Sporadic associations between dioxin levels and thyroid or gonadal hormone abnormalities appeared  
500 unlikely to be clinically important.

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## 10 GASTROINTESTINAL ASSESSMENT

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### 10.1 INTRODUCTION

There is a wealth of dioxin research data available in animal models, but there is relatively little information about the effects of dioxin on the human digestive system. The liver is a major target organ for dioxin and dioxin-like chemicals following single high-dose and continued low-dose exposure in laboratory animals. Porphyria cutanea tarda (PCT) is a suspected clinical endpoint following moderate to high level exposure. Although the discussions in this chapter deal with the gastrointestinal function, the focus of the chapter is on liver function and associated diseases.

Analyses were performed in the gastrointestinal assessment of Air Force Health Study (AFHS) participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7), based on medical records verification of the data collected from questionnaires, physical examination, and laboratory findings. During the health interviews for each AFHS examination, each participant was asked about the occurrence of hepatitis, jaundice, cirrhosis, enlarged liver, and other liver conditions. Medical records reviews confirmed reported conditions and identified any unreported conditions for each participant. Data from all AFHS examinations were combined to form a history of liver conditions for each participant. These verified results were grouped into the following eight categories of disorders for analysis: (1) uncharacterized hepatitis (non-A, non-B, and non-C), (2) jaundice (unspecified, not of the newborn), (3) chronic liver disease and cirrhosis (alcohol-related), (4) chronic liver disease and cirrhosis (nonalcohol-related), (5) liver abscess and sequelae of chronic liver disease, (6) enlarged liver (hepatomegaly), (7) acute and subacute necrosis of the liver, and (8) other disorders of the liver. The purpose of the uncharacterized hepatitis (non-A, non-B, and non-C) category was to define a category that was neither clearly A nor B nor C, so that liver disease misdiagnosed as “viral hepatitis” could be detected.

During the administration of the questionnaire, each participant was asked the following three questions: (1) “Have you had patches of your skin change color?”; (2) “Have you had easier bruising of the skin than usual?”; and (3) “Have you had skin that was extra sensitive or seemed to hurt for no reason?” Participant-reported responses to these questions on skin bruises, patches, or sensitivity were analyzed. Positive responses to the presence of skin bruises, patches, or sensitivity were considered as a surrogate measure for a possible symptom of PCT. This variable was analyzed at the 1982, 1985, and 1987 follow-up examinations.

The presence of gastric, duodenal, peptic, or gastrojejunal ulcers, as verified by a review of medical records, was analyzed.

Current hepatomegaly was assessed by the AFHS examining physician.

Laboratory variables analyzed included alanine aminotransferase (ALT in U/L), aspartate aminotransferase (AST in U/L), gamma glutamyltransferase (GGT in U/L), alkaline phosphatase (U/L), creatine phosphokinase (U/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), lactate dehydrogenase (LDH in U/L), cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), cholesterol-HDL ratio, triglycerides (mg/dL), stool hemoccult, prothrombin time (seconds), serum amylase (U/L), and 10 components (in mg/dL) in a protein profile (prealbumin, albumin,  $\alpha$ -1-acid glycoprotein,  $\alpha$ -1-

40 antitrypsin,  $\alpha$ -2-macroglobulin, apolipoprotein B, C3 complement, C4 complement, haptoglobin, and  
41 transferrin).

42 Serological evidence of prior hepatitis A, B, C, and D, as well as current hepatitis B infection, were  
43 analyzed.

44 Analyses were conducted and described for d-glucaric acid, which is considered to be a reliable index of  
45 hepatic microsomal activity. The analyses were based on urine collected at the 1985 follow-up  
46 examination and stored at -70 °C.

47 PCT is a disorder of porphyrin metabolism that leads to massive overproduction and excretion of  
48 uroporphyrin. Uroporphyrin and coproporphyrin were analyzed, as was d-aminolevulinic acid, the first  
49 compound in the porphyrin synthesis pathway.

50 The following journal article on the relation of hepatic abnormalities and indices of hepatic function to  
51 dioxin was written by AFHS staff and their colleagues:

- 52 • Dioxin and hepatic abnormalities in veterans of Operation Ranch Hand (8).

53 This article is discussed later in this chapter.

54 The Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of  
55 Exposure to Herbicides reported in their 1994 publication, *Veterans and Agent Orange* (9), that there was  
56 “sufficient” evidence to establish an association between PCT and herbicides or dioxin, although not a  
57 causal relation. In the 1996 *Veterans and Agent Orange* update, the association with PCT was changed to  
58 “limited or suggestive” (10). This was also the conclusion in the 2004 *Veterans and Agent Orange*  
59 update (11).

### 60 **10.1.1 Chapter Structure**

61 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
62 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
63 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
64 results that appeared consistently across examinations or have biological meaning are emphasized,  
65 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
66 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
67 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
68 the parameter and either group or dioxin are not discussed.

69 The results discussed below that were discovered as part of further analysis based on a statistical  
70 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
71 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
72 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
73 baseline examination. Older participants were defined as those born before 1942.

74 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
75 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
76 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
77 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
78 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
79 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at

80 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
 81 stratification based on the participant’s tour of duty is given in Chapter 2.

82 The following chart lists the variables that were analyzed for the gastrointestinal assessment and at which  
 83 physical examination they were analyzed. The variables appearing in bold type are discussed  
 84 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Acute and Subacute Necrosis of the Liver			X	X	X	X	X
<b>Albumin</b>					X	X	X
<b>Alkaline Phosphatase</b>	X	X	X	X	X	X	X
<b>ALT</b>	X	X	X	X	X	X	X
<b>Apolipoprotein B</b>					X	X	X
<b>AST</b>	X	X	X	X	X	X	X
<b>C3 Complement</b>					X	X	X
<b>C4 Complement</b>					X	X	X
<b>Cholesterol</b>	X	X	X	X	X	X	X
<b>Cholesterol-HDL Ratio</b>			X	X	X	X	X
Chronic Liver Disease and Cirrhosis (Alcohol-related)	X	X	X	X	X	X	X
Chronic Liver Disease and Cirrhosis (Nonalcohol-related)	X	X	X	X	X	X	X
Coproporphyrin	X	X					
<b>Creatine Phosphokinase</b>			X	X	X	X	X
Current Hepatitis B						X	
Current Hepatomegaly	X	X	X	X	X	X	X
d-aminolevulinic acid	X						
d-glucuric acid				X			
<b>Direct Bilirubin</b>	X	X	X	X	X	X	X
Enlarged Liver (Hepatomegaly)		X	X	X	X	X	X
<b>GGT</b>	X	X	X	X	X	X	X
<b>Haptoglobin</b>					X	X	X
<b>HDL Cholesterol</b>			X	X	X	X	X
Jaundice (unspecified)	X	X	X	X	X	X	X
<b>LDH</b>	X	X	X	X	X	X	X
Liver Abscess and Sequelae of Chronic Liver Disease			X	X	X	X	X
<b>Other Liver Disorders</b>	X	X	X	X	X	X	X
<b>Prealbumin</b>					X	X	X
Prior Hepatitis A					X	X	X
Prior Hepatitis B					X	X	X
Prior Hepatitis C					X	X	X
Prior Hepatitis D						X	
Prothrombin Time				X	X	X	X
Serum Amylase					X	X	X
<b>Skin Bruises, Patches, or Sensitivity</b>	X	X	X	X			

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Stool Hemocult</b>					X	X	X
Total Bilirubin	X	X	X	X	X	X	X
Transferrin					X	X	X
<b>Triglycerides</b>	X	X	X	X	X	X	X
Ulcer		X	X	X			
<b>Uncharacterized Hepatitis</b>	X	X	X	X	X	X	X
Uroporphyrin	X	X					
<b><math>\alpha</math>-1-Acid Glycoprotein</b>					X	X	X
<b><math>\alpha</math>-1-Antitrypsin</b>					X	X	X
<b><math>\alpha</math>-2-Macroglobulin</b>					X	X	X

85 **10.2 HEPATITIS**

86 **10.2.1 Uncharacterized Hepatitis (Non-A, Non-B, Non-C)**

87 Data from the 1987 follow-up examination showed an increase in the prevalence of uncharacterized  
88 hepatitis as initial dioxin levels increased and as 1987 dioxin levels increased (for those with earlier tours  
89 of duty). Ranch Hands in the high dioxin category also had a greater occurrence of uncharacterized  
90 hepatitis than Comparisons.

91 **10.2.2 Prior Hepatitis B**

92 Among enlisted flyers, the occurrence of prior hepatitis B infection at the time of the 1992 follow-up  
93 examination increased with increasing 1987 dioxin levels.

94 **10.3 LIPIDS**

95 **10.3.1 Cholesterol**

96 Ranch Hands at the 1987 follow-up examination showed an increase in cholesterol with increasing initial  
97 dioxin levels, as well as with increasing 1987 dioxin levels for those in earlier tours of duty. Ranch  
98 Hands in the high dioxin category had a greater average cholesterol level than Comparisons, and Ranch  
99 Hands in the background dioxin category had a greater percentage of abnormally high cholesterol values  
100 than Comparisons.

101 Among moderate lifetime drinkers (no more than 40 drink-years at the time of the examination), Ranch  
102 Hands in the background dioxin category had a greater average cholesterol value at the 1992 follow-up  
103 examination than Comparisons. Among lifetime nondrinkers, Ranch Hands in the high dioxin category  
104 had a greater average cholesterol value than Comparisons. Among Ranch who did not report exposure to  
105 degreasing chemicals, cholesterol values and the percentage of Ranch Hands with abnormally high  
106 cholesterol values increased with increasing initial dioxin levels.

107 Among heaviest current drinkers (more than four drinks per day) at the time of the 1992 follow-up  
108 examination, a greater percentage of Ranch Hands than Comparisons had abnormally high cholesterol  
109 values. Among the heaviest current drinkers, Ranch Hands in the background dioxin category had a  
110 greater percentage of abnormally high cholesterol values than Comparisons. Among moderate current  
111 drinkers (no more than four drinks per day), a greater percentage of Ranch Hands in the low dioxin

112 category than Comparisons had abnormally high cholesterol values. Cholesterol levels and the  
113 percentage of abnormally high cholesterol levels for Ranch Hands (in particular, Ranch Hand officers) at  
114 the 1992 follow-up examination increased with increasing 1987 dioxin levels.

### 115 **10.3.2 High-density Lipoprotein (HDL) Cholesterol**

116 Among Ranch Hands who did not report exposure to degreasing chemicals, HDL cholesterol at the 1987  
117 follow-up examination decreased with increasing initial dioxin levels. HDL cholesterol levels decreased  
118 with increasing 1987 dioxin levels.

119 A greater percentage of Ranch Hands (primarily officers) at the 1992 follow-up examination had  
120 abnormally low HDL cholesterol values relative to Comparison officers. Among the heaviest lifetime  
121 drinkers (more than 40 drink-years prior to the 1992 examination), a greater percentage of Ranch Hands  
122 in the background dioxin category than Comparisons had abnormally low HDL cholesterol values.

123 Among moderate lifetime drinkers (no more than 40 drink-years prior to the 1992 examination), HDL  
124 cholesterol values at the 1992 follow-up examination decreased and the percentage of Ranch Hands with  
125 abnormally low HDL cholesterol values increased with increasing 1987 dioxin levels. Similarly, HDL  
126 cholesterol values decreased as 1987 dioxin levels increased among Ranch Hands who were light or  
127 moderate drinkers (more than four drinks per day) at the time of the 1992 examination.

128 As seen at the 1997 follow-up examination, a greater percentage of Ranch Hands in the background  
129 dioxin category than Comparisons had abnormally low HDL cholesterol values.

### 130 **10.3.3 Cholesterol-HDL Ratio**

131 Ranch Hands in the 1987 follow-up examination showed an increase in the cholesterol-HDL ratio with  
132 increasing initial dioxin levels. Ranch Hands in the high dioxin category had a greater average  
133 cholesterol-HDL ratio than Comparisons.

134 Ranch Hands with earlier tours of duty (in particular, those who did not report exposure to industrial  
135 chemicals) showed an increase in cholesterol-HDL ratio at the 1987 follow-up examination. The  
136 percentage of Ranch Hands with an abnormally high cholesterol-HDL ratio value also increased as 1987  
137 dioxin levels increased. In addition, the percentage of abnormally high cholesterol-HDL ratio values  
138 among all Ranch Hands, among Ranch Hands who did not report exposure to degreasing chemicals, and  
139 among older Ranch Hands who did report exposure to degreasing chemicals, increased with increasing  
140 initial dioxin levels.

141 An increase in the cholesterol-HDL ratio, and an increase in the percentage of abnormally high  
142 cholesterol-HDL ratio values in Ranch Hands as 1987 dioxin levels increased, were observed at both the  
143 1992 and 1997 follow-up examinations.

### 144 **10.3.4 Triglycerides**

145 Among the oldest participants in the 1985 follow-up examination, Ranch Hands had a greater average  
146 triglyceride value than Comparisons.

147 The 1987 follow-up examination showed that triglyceride values and the prevalence of abnormally high  
148 triglyceride values in Ranch Hands increased with increasing initial dioxin levels. Triglyceride values in  
149 Ranch Hands increased with increasing 1987 dioxin levels. The prevalence of abnormally high

150 triglyceride values also increased with increasing 1987 dioxin levels in Ranch Hands with later tours of  
151 duty.

152 Among officers, triglyceride values at the 1992 follow-up examination increased with increasing initial  
153 dioxin levels. As 1987 dioxin levels increased in Ranch Hands (as a group, and for officers who were  
154 moderate or heavy drinkers), an increase in triglyceride values was observed. In addition, an increase in  
155 the percentage of Ranch Hands with abnormally high triglyceride values was seen as 1987 dioxin levels  
156 increased. Ranch Hand officers had a greater average triglyceride value and a greater percentage of  
157 abnormally high triglyceride values than Comparison officers. Ranch Hands in the high dioxin category  
158 had a greater average triglyceride value and a greater percentage of abnormally high triglyceride values  
159 than Comparisons.

160 Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater occurrence of  
161 abnormally high triglyceride values than Comparison enlisted groundcrew. Ranch Hands in the high  
162 dioxin category had a greater average triglyceride value and a greater percentage of abnormally high  
163 triglyceride values than Comparisons. In addition, as 1987 dioxin levels increased, triglyceride values  
164 and the prevalence of abnormally high triglyceride values in Ranch Hands increased.

165 The 2002 follow-up examination found that Ranch Hands (primarily enlisted groundcrew) had a greater  
166 occurrence of abnormally high triglyceride values than Comparisons. Similarly, Ranch Hands in the low  
167 and high dioxin categories had a greater occurrence of abnormally high triglyceride values than  
168 Comparisons. An increase in the prevalence of triglyceride abnormalities in Ranch Hands also was seen  
169 as 1987 dioxin levels increased.

## 170 **10.4 LIVER ENZYMES**

### 171 **10.4.1 Alanine Aminotransferase (ALT)**

172 Ranch Hands (in particular, younger Ranch Hands) had increased ALT values at the 1987 follow-up  
173 examination with increasing initial dioxin levels. Among light alcohol drinkers (less than one drink per  
174 day) at the time of the 1987 examination and Ranch Hands who did not report exposure to degreasing  
175 chemicals, the percentage of abnormally high ALT values increased with increasing initial dioxin levels.  
176 In addition, among lighter alcohol drinkers at the time of the 1987 dioxin examination, ALT levels  
177 increased with increasing 1987 dioxin for Ranch Hands with earlier tours of duty. Ranch Hands in the  
178 high dioxin category had a greater average ALT value than Comparisons.

179 The analysis of ALT at the 1992 follow-up examination showed that ALT values in Ranch Hands and the  
180 percentage of Ranch Hands with abnormally high ALT values increased with increasing 1987 dioxin  
181 levels.

182 The 1997 follow-up examination analysis of ALT found that the percentage of Ranch Hands with  
183 abnormally high ALT values increased with increasing initial and 1987 dioxin levels. ALT values in  
184 Ranch Hands also increased with increasing 1987 dioxin levels. In addition, Ranch Hands in the low and  
185 high dioxin categories combined had a greater average ALT value than Comparisons.

### 186 **10.4.2 Aspartate Aminotransferase (AST)**

187 Among moderate alcohol drinkers at the 1985 follow-up examination (one to four drinks per day), Ranch  
188 Hands had a greater average AST value than Comparisons.

189 Among moderate drinkers at the time of the 1992 follow-up examination, AST values increased with  
190 increasing initial dioxin levels. Among heaviest drinkers at the time of the examination (more than four  
191 drinks per day), AST values increased with increasing initial dioxin levels and 1987 dioxin levels.

192 The 1997 follow-up examination analysis showed that AST values and the percentage of abnormally high  
193 AST values increased with increasing 1987 dioxin. In addition, Ranch Hands in the high dioxin category  
194 had a greater average AST value than Comparisons.

#### 195 **10.4.3 Gamma Glutamyltransferase (GGT)**

196 GGT values at the 1987 follow-up examination increased with increasing initial dioxin levels. Similarly,  
197 the percentage of abnormally high GGT values increased with increasing initial dioxin levels for all  
198 Ranch Hands and specifically among Ranch Hands who did not report exposure to degreasing chemicals.  
199 Ranch Hands in both the low and high dioxin categories had a greater average GGT value and a greater  
200 prevalence of abnormally high GGT values than Comparisons. Among participants who did not report  
201 exposure to degreasing chemicals, a greater percentage of Ranch Hands in the high dioxin category than  
202 Comparisons had abnormally high GGT values. GGT values increased with increasing 1987 dioxin  
203 levels for Ranch Hands with later tours of duty.

204 Among Ranch Hands who did not report exposure to degreasing chemicals, GGT values at the 1992  
205 follow-up examination increased with increasing initial dioxin. Also among participants who did not  
206 report exposure to degreasing chemicals, Ranch Hands in the high dioxin category had a greater average  
207 GGT value and a greater percentage of abnormally high GGT values than Comparisons. Ranch Hands  
208 (primarily officers and enlisted flyers) showed an increase in GGT values as 1987 dioxin levels increased.  
209 The percentage of abnormally high GGT values increased with increasing 1987 dioxin levels.

210 The 1997 follow-up examination found that Ranch Hands in the high dioxin category had a greater  
211 average GGT value than Comparisons. GGT values and the percentage of abnormally high GGT values  
212 in Ranch Hands increased with increasing 1987 dioxin levels.

#### 213 **10.4.4 Alkaline Phosphatase**

214 Analysis of 1985 follow-up examination data found that Ranch Hands had a greater average alkaline  
215 phosphatase value than Comparisons. Among those participants who did not report exposure to industrial  
216 chemicals, Ranch Hands also had a greater average alkaline phosphatase value than Comparisons.

217 Ranch Hands at the 1987 follow-up examination (in particular, Ranch Hands in the high dioxin category)  
218 had a greater average alkaline phosphatase value than Comparisons. Black Ranch Hands also had a  
219 greater average alkaline phosphatase value than Black Comparisons. Alkaline phosphatase levels  
220 increased with increasing initial dioxin levels in Ranch Hands. In addition, the percentage of Ranch  
221 Hands with abnormally high alkaline phosphatase values increased with increasing 1987 dioxin among  
222 Ranch Hands with earlier tours of duty.

223 Among all participants, non-Black participants, younger participants, and participants who did not report  
224 exposure to degreasing chemicals, all Ranch Hands and Ranch Hand enlisted groundcrew had a greater  
225 average alkaline phosphatase value at the 1992 follow-up examination. Among all participants and those  
226 who did not report exposure to degreasing chemicals, Ranch Hands in the background dioxin category  
227 and Ranch Hands in the low dioxin category had a greater average alkaline phosphatase value than  
228 Comparisons.

229 In addition, Ranch Hand enlisted groundcrew had a greater percentage of abnormally high alkaline  
230 phosphatase values than Comparison enlisted groundcrew at the 1992 follow-up examination. Similarly,  
231 Ranch Hands in the background dioxin category had a greater percentage of abnormally high alkaline  
232 phosphatase values than Comparisons. Alkaline phosphatase levels increased with increasing 1987  
233 dioxin levels among Black Ranch Hands.

234 The 1997 follow-up examination analysis found that for all participants and for enlisted groundcrew,  
235 Ranch Hands had a greater average alkaline phosphatase value than Comparisons. Ranch Hands in the  
236 background dioxin category also had a greater average alkaline phosphatase value than Comparisons.

237 Ranch Hand enlisted groundcrew at the 2002 follow-up examination had a greater percentage of  
238 abnormally high alkaline phosphatase values than Comparison enlisted groundcrew.

#### 239 **10.4.5 Creatine Phosphokinase**

240 Ranch Hands at the 1992 follow-up examination showed an increase in creatine phosphokinase values as  
241 1987 dioxin levels increased. Similarly, the 1997 follow-up examination analysis showed an increase in  
242 creatine phosphokinase values and an increase in the percentage of Ranch Hands with abnormally high  
243 creatine phosphokinase values as 1987 dioxin levels increased.

#### 244 **10.4.6 Direct Bilirubin**

245 Analysis of 1985 follow-up examination data found that, among participants who did not report exposure  
246 to industrial chemicals, a greater percentage of Ranch Hands than Comparisons had abnormally high  
247 direct bilirubin values.

248 Ranch Hands at the 1987 follow-up examination showed an increase in direct bilirubin values with  
249 increasing initial dioxin levels. In addition, Ranch Hands in the high dioxin category had a greater  
250 average direct bilirubin value than Comparisons.

#### 251 **10.4.7 Lactate Dehydrogenase (LDH)**

252 The 1992 follow-up examination analysis showed that, among enlisted groundcrew who were the heaviest  
253 lifetime drinkers (more than 40 drink-years at the 1992 follow-up examination), Ranch Hands had a  
254 greater average LDH value than Comparisons. Also among the heaviest lifetime drinkers, Ranch Hands  
255 in the background dioxin category had a greater percentage of abnormally high LDH values than  
256 Comparisons.

### 257 **10.5 OTHER LIVER DISORDERS**

258 A greater percentage of Ranch Hands in the high dioxin category than Comparisons had other liver  
259 disorders, based on data collected at the 1987 follow-up examination.

260 At the 1992 follow-up examination, other liver disorders among Ranch Hands increased with increasing  
261 initial and 1987 dioxin levels. Ranch Hands in the high dioxin category had a greater prevalence of other  
262 liver disorders than Comparisons.

263 The occurrence of other liver disorders increased with increasing initial dioxin levels, based on data  
264 collected at the 1997 follow-up examination. As in the 1987 and 1992 follow-up examinations, analysis

265 of 1997 follow-up examination data found that Ranch Hands in the high dioxin category had a greater  
266 prevalence of other liver disorders than Comparisons.

267 Subsequent analysis was conducted to investigate whether the findings for the occurrence of other liver  
268 disorders could be explained by a particular subcategory of liver disorders (12). Five separate  
269 subcategories were explored. Although the associations described above were found when the five  
270 subcategories were combined, no associations were observed when the subcategories were analyzed  
271 individually.

## 272 **10.6 PROTEIN PROFILE**

### 273 **10.6.1 $\alpha$ -1-Acid Glycoprotein**

274 Among lifetime nondrinkers through the 1992 follow-up examination, Ranch Hands in the low dioxin  
275 category had a greater average  $\alpha$ -1-acid glycoprotein value than Comparisons. In addition, younger  
276 Ranch Hands in the low dioxin category had a greater percentage of abnormally high  $\alpha$ -1-acid  
277 glycoprotein values than younger Comparisons. Ranch Hand enlisted flyers had an increase in the  
278 percentage of abnormally high  $\alpha$ -1-acid glycoprotein values at the 1992 follow-up examination as both  
279 initial dioxin and 1987 dioxin levels increased.

280 Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater average  $\alpha$ -1-acid  
281 glycoprotein value than Comparison enlisted groundcrew.

### 282 **10.6.2 $\alpha$ -1-Antitrypsin**

283 Ranch Hands in the background dioxin category had a greater average  $\alpha$ -1-antitrypsin value than  
284 Comparisons, as seen at the 1992 follow-up examination. In addition,  $\alpha$ -1-antitrypsin values in Ranch  
285 Hands decreased with increasing 1987 dioxin levels.

286 Analysis of data from the 1997 follow-up examination revealed that Ranch Hands and Ranch Hand  
287 enlisted groundcrew had a greater average  $\alpha$ -1-antitrypsin value than their Comparison counterparts.  
288 Ranch Hands in both the background and high dioxin categories had a greater average  $\alpha$ -1-antitrypsin  
289 value than Comparisons.

290 The 2002 follow-up examination analysis found that Ranch Hands in the low dioxin category had a  
291 greater percentage of abnormally high  $\alpha$ -1-antitrypsin values than Comparisons.

### 292 **10.6.3 $\alpha$ -2-Macroglobulin**

293 Among older participants,  $\alpha$ -2-macroglobulin values at the 1992 follow-up examination increased with  
294 increasing initial dioxin levels.

295 Ranch Hands at the 1997 follow-up examination showed an increase in the percentage of abnormally high  
296  $\alpha$ -2-macroglobulin values as 1987 dioxin levels increased.

### 297 **10.6.4 Albumin**

298 The 1992 follow-up examination of albumin found that among those who did not report exposure to  
299 industrial chemicals, Ranch Hands in the low dioxin category had a lower average albumin value (adverse  
300 effect) than Comparisons. Among heaviest drinkers at the time of the 1992 examination and among

301 participants who did not report exposure to degreasing chemicals, albumin decreased with increasing  
302 1987 dioxin levels.

### 303 **10.6.5 Apolipoprotein B**

304 Among Ranch Hands (primarily older Ranch Hands), both apolipoprotein B values and the percentage of  
305 abnormally high apolipoprotein B values at the 1992 follow-up examination increased with increasing  
306 initial dioxin levels and 1987 dioxin levels.

### 307 **10.6.6 C3 Complement**

308 The 1992 follow-up examination analysis of C3 complement found that Ranch Hands in the background  
309 dioxin category had a lower average C3 complement value (adverse effect) than Comparisons.

### 310 **10.6.7 C4 Complement**

311 Ranch Hand officers at both the 1997 and 2002 follow-up examinations had a lower average C4  
312 complement value (adverse effect) than Comparison officers. In addition, analysis of 2002 follow-up  
313 examination data indicated that the average C4 complement value decreased and the percentage of  
314 abnormally low C4 complement values increased with increasing initial dioxin.

### 315 **10.6.8 Haptoglobin**

316 For all participants and, specifically, among enlisted groundcrew, Ranch Hands had a greater average  
317 haptoglobin value than Comparisons at the 1992 follow-up examination. Among Ranch Hand officers,  
318 the percentage of abnormally high haptoglobin values increased with increasing initial dioxin levels.

319 Ranch Hands at the 1997 follow-up examination (in particular, enlisted groundcrew) had a greater  
320 average haptoglobin value than Comparisons. The percentage of abnormally high haptoglobin values was  
321 also greater for Ranch Hands than for Comparisons. Ranch Hands in the background dioxin category had  
322 a greater average haptoglobin value and a greater percentage of abnormally high haptoglobin values than  
323 Comparisons. In addition, Ranch Hands in the low and high dioxin categories combined had a greater  
324 average haptoglobin value than Comparisons.

325 As in the 1997 follow-up examination, Ranch Hands in the 2002 follow-up examination had a greater  
326 average haptoglobin value than Comparisons, particularly among enlisted groundcrew.

### 327 **10.6.9 Prealbumin**

328 Among participants who did not report exposure to degreasing chemicals, prealbumin values at the 1992  
329 follow-up examination decreased (adverse effect) with increasing 1987 dioxin levels.

330 Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater percentage of  
331 abnormally low prealbumin values than Comparison enlisted groundcrew. Similarly, Ranch Hands in the  
332 high dioxin category had a greater percentage of abnormally low prealbumin values than Comparisons.

## 333 **10.7 PROTHROMBIN TIME**

334 The 1987 follow-up examination of prothrombin time revealed an increase in prothrombin time as initial  
335 dioxin levels increased among Ranch Hands, and, in particular, among Ranch Hands who were moderate

336 lifetime smokers (no more than 10 pack-years). In addition, the 1987 follow-up examination found  
337 Ranch Hands with later tours of duty had an increased prevalence of prothrombin time abnormalities as  
338 1987 dioxin levels increased.

339 As in the 1987 follow-up examination, the 1992 follow-up examination showed an increase in  
340 prothrombin time with increasing initial dioxin levels.

341 Ranch Hands in the background dioxin category had a higher average prothrombin time than  
342 Comparisons at the 2002 follow-up examination.

### 343 **10.8 SKIN BRUISES, PATCHES, OR SENSITIVITY**

344 The 1987 follow-up examination found that Ranch Hands in each of the background, low, and high  
345 dioxin categories had a greater occurrence of skin bruises, patches, or sensitivity than Comparisons.

### 346 **10.9 STOOL HEMOCCULT**

347 The 1992 follow-up examination showed that among the heaviest lifetime drinkers (in particular, officers  
348 and enlisted groundcrew), a greater percentage of Ranch Hands than Comparisons had positive stool  
349 hemocult results. A greater percentage of Ranch Hands in the low dioxin category than Comparisons  
350 also had positive stool hemocult results.

351 A greater percentage of Ranch Hand officers than Comparison officers had positive stool hemocult  
352 results at the 2002 follow-up examination.

### 353 **10.10 DIOXIN AND HEPATIC ABNORMALITIES IN VETERANS OF OPERATION RANCH HAND**

354 The associations between hepatic abnormalities and indices of hepatic function and dioxin were published  
355 in a journal article appearing in the *Annals of Epidemiology* in 2001 (8). The prevalence of ever having  
356 liver disease through March 1993, and ALT, AST, GGT, LDH, alkaline phosphatase, and total bilirubin,  
357 were examined according to serum dioxin levels. Ranch Hand veterans with the highest dioxin exposure  
358 were more likely than Comparisons to have a history of abnormal serum enzyme levels and liver function  
359 tests. The liver disorders associated with dioxin exposure primarily reflected earlier increases in ALT  
360 (prior to the 1992 follow-up examination) and continued increased levels of GGT. Whether the  
361 associations observed were causal was unclear.

### 362 **10.11 CONCLUSION**

363 Analysis of laboratory data indicated that dioxin was associated with hepatic enzymes such as AST, ALT,  
364 and GGT, and with lipid-related health indices such as cholesterol, HDL, and triglycerides. Although  
365 hepatic enzymes showed an association with dioxin, there was no evidence of an increase in overt liver  
366 disease. These laboratory findings were consistent with significant associations seen for obesity-related  
367 variables in other clinical assessments, such as the body mass index results in the general health  
368 assessment and the diabetes and glucose results noted in the endocrinology assessment. These findings  
369 may represent a dioxin-mediated alteration of biochemical processes or a subtle relation between dioxin  
370 and lipid metabolism.

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## 11 GENERAL HEALTH ASSESSMENT

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### 11.1 INTRODUCTION

Analyses were performed to assess the general health of Air Force Health Study (AFHS) participants at all six examinations (1-7). Measures of general health included an estimate of a participant's body fat; a participant-reported perception of his health; the appearance of the subject as younger than, older than, or the same as his stated age, as observed by a board-certified internist; and an appearance of illness or distress as observed by the internist. Clinicians often employ measures such as these to assess an overall state of health. While these measures may be imperfect and were no doubt influenced by many variables, they do reflect overall health impressions from both self and observer perspectives.

At each examination, a board-certified internist at the examination recorded the appearance of acute illness or distress (yes, no) of the AFHS participant. The appearance of illness was reserved for a relatively low percentage of participants who had significant manifestations of illness, such as cachexia and frailty. No associations between appearance of illness or distress and either group or dioxin levels were observed at the AFHS examinations.

#### 11.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results ( $p$ -value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the general health assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Appearance of Illness or Distress	X	X	X	X	X	X	X
<b>Body Mass Index/Body Fat</b>	X	X	X	X	X	X	X
<b>Relative Age Appearance as Assessed by a Physician</b>	X	X	X	X	X	X	X
<b>Self-perception of Health</b>	X	X	X	X	X	X	X

40 **11.2 BODY MASS INDEX/BODY FAT**

41 Body fat measures and the commonly used body mass index are approximate measures of the percentage  
 42 of a person’s body mass that can be attributable to fat. The body mass index serves as a valuable clinical  
 43 clue to the presence of disease and helps define obesity—an important health risk factor. The estimator of  
 44 body fat and obesity for the AFHS has changed over the years but has always used the ratio of a person’s  
 45 weight to the square of his height.

46 The 1985 follow-up examination found that the average body fat was less for Ranch Hands than for  
 47 Comparisons. Beginning with the dioxin measurements in 1987, analyses showed increased body fat  
 48 with increasing dioxin within Ranch Hands. This relation was evident for initial dioxin, categorized  
 49 dioxin, and 1987 dioxin. The same patterns with dioxin, particularly categorized dioxin and 1987 dioxin,  
 50 were observed for the analyses of the 1992, 1997, and 2002 follow-up examination data. The average  
 51 body mass index, however, was similar between Ranch Hands and Comparisons.

52 When the body fat measure or body mass index was categorized as obese (body mass index greater than  
 53 30 for the 2002 follow-up examination) or normal (less than 30), the same patterns were seen. Beginning  
 54 with the dioxin measurements in 1987, analyses showed increasing obesity with dioxin within Ranch  
 55 Hands. Similar patterns with dioxin, particularly categorized dioxin and 1987 dioxin, were observed for  
 56 the analyses of the 1992, 1997, and 2002 follow-up examination data. The percentage of obese  
 57 participants, however, was similar between Ranch Hands and Comparisons.

58 The association appears to be due to slower dioxin elimination pharmacokinetics in obese participants  
 59 relative to participants who were lean or not obese. In part, participants with the highest dioxin levels  
 60 retain dioxin due to their higher body fat content.

61 **11.3 SELF-PERCEPTION OF HEALTH**

62 During the health interview administered for all examinations, each AFHS participant was asked the  
 63 following: “Compared to other people your age, would you say your health is excellent, good, fair, or  
 64 poor?” This self-reported perception was analyzed as a measure of the general health status of each  
 65 participant, although it was recognized that the perception was susceptible to varying degrees of  
 66 conscious and subconscious bias (e.g., in 1992 and after, most participants were aware of their serum  
 67 dioxin levels). This variable was dichotomized as excellent or good and fair or poor for analyses.

68 At the 1982 baseline examination, more Ranch Hands perceived their health to be fair or poor than  
 69 Comparisons. This pattern was seen at the 1985, 1992, and 1997 follow-up examinations, with the largest  
 70 difference among enlisted groundcrew. Differences between Ranch Hands and Comparisons were not  
 71 observed at the 2002 follow-up examination.

72 Similar patterns were observed when examining the relation between self-perception of health and  
73 measures of dioxin. In 1987, 1992, and 1997, the percentage of participants perceiving their health as fair  
74 or poor increased with increased dioxin levels. An association between self-perception of health and  
75 measures of dioxin, however, was not observed at the 2002 follow-up examination.

#### 76 **11.4 RELATIVE AGE APPEARANCE AS ASSESSED BY A PHYSICIAN**

77 At each examination, a board-certified internist noted the appearance of the subject as younger than, older  
78 than, or the same as his stated age. This variable was dichotomized as older than stated age and same as  
79 or younger than stated age for analyses. Because the examining internist was kept blind to the  
80 participant's group membership, this assessment was less subject to bias than the self-perception of  
81 health.

82 Ranch Hands appeared younger relative to their age more often than Comparisons at the 1982 baseline  
83 examination. At the 1992 follow-up examination, the percentage of Ranch Hand officers who appeared  
84 older relative to his age decreased as 1987 dioxin levels increased.

#### 85 **11.5 CONCLUSION**

86 Body mass index was positively associated with 1987 dioxin, possibly reflecting the pharmacokinetics of  
87 dioxin elimination. More Ranch Hands perceived their health to be fair or poor than Comparisons and  
88 there was an increasing perception of fair or poor health with dioxin through the 1997 follow-up  
89 examination, but these differences were not observed for the 2002 follow-up examination.

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124 following exposure to herbicides: Final report. 2002 follow-up examination results. Air Force  
125 Research Laboratory, Brooks City-Base, TX.

## 12 HEMATOLOGY ASSESSMENT

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### 12.1 INTRODUCTION

Hematology is the study of the red blood cells, white blood cells, platelets, and plasma. These components perform important functions related to fighting infections, regulating temperature, transporting oxygen to other cells, and the balancing of body fluids. Scientific literature has not found any consistent relation between exposure to Agent Orange or dioxin and hematopoietic toxicity to date. The Air Force Health Study (AFHS) examined the basic components of the participants' blood at each of the six physical examinations (1-7).

A complete blood count was performed at the 1982, 1985, 1987, 1992, 1997, and 2002 AFHS examinations. Elements of the complete blood count that were analyzed were hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, and white blood cell (WBC) count. Analysis also was performed on mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume for the 1982, 1985, and 1987 examinations. In addition, associations between group or dioxin and erythrocyte sedimentation rate were examined for all six AFHS examinations.

Analysis of a differential WBC count was performed for the 1992, 1997, and 2002 follow-up examinations, with the differential results reported as absolute counts. The absolute WBC counts of segmented neutrophils, neutrophilic bands, lymphocytes, monocytes, eosinophils, and basophils were analyzed. Lymphocytes included both reactive and nonreactive lymphocytes. RBC morphology was constructed from a number of laboratory findings, many of which were minor abnormalities, measured at these three AFHS examinations.

In addition, associations between group or dioxin and prothrombin time were investigated for the 1987, 1992, 1997, and 2002 follow-up examinations, and fibrinogen measurements were collected and analyzed for the 2002 follow-up examination.

The following journal article on the relation of indices of hematologic function and their relations to dioxin and herbicides was written by AFHS staff and their colleagues:

- Relation of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) level to hematological examination results in veterans of Operation Ranch Hand (8).

This article is discussed later in this chapter.

#### 12.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

38 The results discussed below that were discovered as part of further analysis based on a statistical  
 39 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
 40 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
 41 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
 42 baseline examination. Older participants were defined as those born before 1942.

43 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 44 Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 45 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 46 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 47 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 48 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at  
 49 most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this  
 50 stratification based on the participant's tour of duty is given in Chapter 2.

51 The following chart lists the variables that were analyzed for the hematology assessment and at which  
 52 physical examination they were analyzed. The variables appearing in bold type are discussed  
 53 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Absolute Basophils</b>					X	X	X
Absolute Eosinophils					X	X	X
Absolute Lymphocytes					X	X	X
Absolute Monocytes					X	X	X
Absolute Neutrophils (bands)					X	X	X
Absolute Neutrophils (segs)					X	X	X
<b>Erythrocyte Sedimentation Rate</b>	X	X	X	X	X	X	X
Fibrinogen							X
<b>Hematocrit</b>	X	X	X	X	X	X	X
<b>Hemoglobin</b>	X	X	X	X	X	X	X
<b>Mean Corpuscular Hemoglobin</b>	X	X	X	X			
<b>Mean Corpuscular Hemoglobin Concentration</b>	X	X	X	X			
<b>Mean Corpuscular Volume</b>	X	X	X	X			
<b>Platelet Count</b>	X	X	X	X	X	X	X
<b>RBC Count</b>	X	X	X	X	X	X	X
<b>RBC Morphology</b>					X	X	X
<b>WBC Count</b>	X	X	X	X	X	X	X

54 **12.2 HEMATOCRIT**

55 Ranch Hands with later tours of duty showed increased hematocrit values at the 1987 follow-up  
 56 examination as 1987 dioxin increased.

57 **12.3 HEMOGLOBIN**

58 Analysis of 1987 follow-up examination data found that hemoglobin values for Ranch Hands with later  
59 tours of duty increased with increasing 1987 dioxin.

60 **12.4 MEAN CORPUSCULAR HEMOGLOBIN**

61 At the 1982 baseline examination, Ranch Hands had a higher average mean corpuscular hemoglobin  
62 value than did Comparisons.

63 **12.5 MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION**

64 At the 1987 follow-up examination, Ranch Hands in the background and low dioxin categories had a  
65 higher average mean corpuscular hemoglobin concentration than Comparisons.

66 **12.6 MEAN CORPUSCULAR VOLUME**

67 Ranch Hands had a greater mean corpuscular volume than Comparisons at the 1982 baseline examination.  
68 The 1987 follow-up examination found that among the heaviest lifetime smokers (>10 pack-years), the  
69 prevalence of mean corpuscular volume abnormalities increased with increasing initial dioxin levels. In  
70 addition, at the 1987 follow-up examination, Ranch Hands in the low dioxin category had a greater  
71 prevalence of abnormally high mean corpuscular volume levels than Comparisons.

72 **12.7 PLATELET COUNT**

73 For heavy smokers at the 1985 follow-up examination, Ranch Hands had a greater average platelet count  
74 than Comparisons.

75 Analysis performed for the 1987 follow-up examination showed that Ranch Hands had a greater average  
76 platelet count and a greater occurrence of abnormally high platelet counts than Comparisons. The  
77 differences were primarily in younger Ranch Hands and for Ranch Hands in the high dioxin category.

78 Ranch Hands had a greater average platelet count at the 1992 follow-up examination than Comparisons,  
79 with the difference in the platelet count averages occurring among enlisted participants rather than  
80 officers. In addition, Ranch Hands in the high dioxin category had a greater average platelet count and a  
81 greater prevalence of abnormally high platelet counts than Comparisons. The 1992 follow-up  
82 examination also found that the occurrence of abnormally high platelet counts increased with increasing  
83 1987 dioxin levels.

84 The 1997 follow-up examination found the average platelet count was lower among Ranch Hands officers  
85 than Comparison officers and greater among Ranch Hand enlisted personnel than Comparison enlisted  
86 personnel. Ranch Hand officers also had a higher prevalence of abnormally low platelet counts than  
87 Comparison officers. Ranch Hands in the high dioxin category had a greater average platelet count than  
88 Comparisons.

89 Ranch Hand enlisted flyers had a greater average platelet count than Comparison enlisted flyers at the  
90 2002 follow-up examination.

91 **12.8 RBC COUNT**

92 Analyses of RBC count performed for the 1987 follow-up examination found among older participants  
93 with earlier tours of duty, RBC counts decreased with increasing 1987 dioxin levels. Among younger  
94 participants with earlier tours of duty, however, RBC counts increased with increasing 1987 dioxin levels.  
95 In addition, for Ranch Hands with earlier tours of duty, the prevalence of abnormally low RBC counts  
96 increased with increasing 1987 dioxin levels.

97 The 1992 follow-up examination found that among the heaviest smoking officers (more than 20 cigarettes  
98 per day), Ranch Hands had a greater average RBC count than Comparisons. This difference was due  
99 primarily to heavy Ranch Hand smokers in the background dioxin category.

100 **12.9 WBC COUNT**

101 Younger Black officer and enlisted flyer Ranch Hands in the 1985 follow-up examination had lower  
102 average WBC counts than their Comparison counterparts. Younger non-Black heavy-smoking Ranch  
103 Hands had a greater average WBC count than younger non-Black heavy-smoking Comparisons.

104 A positive association was seen between initial dioxin and WBC count in the analysis of 1987 follow-up  
105 examination data. Ranch Hands in the high dioxin category also had a greater average WBC count than  
106 Comparisons. In addition, WBC counts increased with increasing 1987 dioxin levels. Among younger  
107 participants with earlier tours of duty, WBC counts also increased with increasing 1987 dioxin levels.

108 At the 1992 follow-up examination, Ranch Hands had lower average WBC counts than Comparisons  
109 among Black participants and among Black officers. Among Black participants and among officers,  
110 WBC counts increased with increasing initial dioxin levels. Similarly, WBC counts increased with  
111 increasing 1987 dioxin levels among Black participants.

112 WBC counts decreased with increasing 1987 dioxin levels based on the evaluation of 2002 follow-up  
113 examination data.

114 **12.10 ABSOLUTE BASOPHILS**

115 At the 1992 follow-up examination, absolute basophil counts increased with increasing levels of 1987  
116 dioxin among Black Ranch Hands.

117 **12.11 ABSOLUTE NEUTROPHILS**

118 Absolute neutrophil counts increased among Black Ranch Hand participants and among officers with  
119 increasing initial dioxin levels at the 1992 follow-up examination. In addition, the 1992 follow-up  
120 examination analysis detected increased absolute neutrophil counts as 1987 dioxin levels increased among  
121 Black Ranch Hands.

122 At the 1997 follow-up examination, Ranch Hands in the low and high dioxin categories combined had a  
123 higher average absolute neutrophil count than Comparisons.

124 **12.12 RBC MORPHOLOGY**

125 The 1992 follow-up examination revealed an increase in the occurrence of abnormal RBC morphology  
126 results as 1987 dioxin levels increased.

127 Ranch Hand enlisted groundcrew at the 2002 follow-up examination had a greater prevalence of RBC  
128 morphology abnormalities than Comparison enlisted groundcrew. In addition, Ranch Hands in the high  
129 dioxin category had a greater occurrence of RBC morphology abnormalities than Comparisons.

130 **12.13 ERYTHROCYTE SEDIMENTATION RATE**

131 Ranch Hands at the 1985 follow-up examination had a greater prevalence of erythrocyte sedimentation  
132 rate elevations than Comparisons.

133 The 1987 follow-up examination analyses found that Ranch Hands in the high dioxin category had a  
134 greater average erythrocyte sedimentation rate than Comparisons. This result was observed when all  
135 Ranch Hands were examined, as well as when the analysis was restricted to older Ranch Hands and  
136 Comparisons. Younger Ranch Hands in the low dioxin category had a greater average erythrocyte  
137 sedimentation rate than younger Comparisons. Similarly, Ranch Hands had a greater percentage of  
138 erythrocyte sedimentation rate elevations than Comparisons; this pattern also was seen when Ranch  
139 Hands were categorized with both low dioxin levels and high dioxin levels. Erythrocyte sedimentation  
140 rates and the prevalence of erythrocyte sedimentation rate elevations increased in Ranch Hands as initial  
141 dioxin levels increased and as 1987 dioxin levels increased.

142 Erythrocyte sedimentation rates at the 1992 and 1997 follow-up examinations increased with increasing  
143 1987 dioxin levels. The percentage of erythrocyte sedimentation rate elevations observed at the 1992  
144 follow-up examination increased with increasing 1987 dioxin levels.

145 Ranch Hands in the low and high dioxin categories combined had a greater average erythrocyte  
146 sedimentation rate than Comparisons at the 2002 follow-up examination.

147 **12.14 RELATION OF SERUM 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) LEVEL TO**  
148 **HEMATOLOGICAL EXAMINATION RESULTS IN VETERANS OF OPERATION RANCH HAND**

149 A journal article published in 2001 (8) provided results of a study of indices of hematologic function at  
150 the 1982, 1985, 1987, and 1992 AFHS examinations and their relations to dioxin and herbicides. No  
151 consistent relations between dioxin and RBC count, hemoglobin, hematocrit, WBC count, and  
152 erythrocyte sedimentation rate were found. Mean corpuscular volume and platelet count generally  
153 increased with increasing dioxin levels at each of these four AFHS examinations. The elevation in  
154 average levels of mean corpuscular volume and platelet count for Ranch Hands in the high dioxin  
155 category was minimal, however, and suggested that the findings, if causal, have little clinical significance.

156 **12.15 CONCLUSION**

157 These hematology results point to a relation between platelet count and erythrocyte sedimentation rate  
158 and exposure to herbicides and dioxin, but the biologic significance of these findings is uncertain.  
159 Increased platelet counts, in addition to the elevated erythrocyte sedimentation rates, may indicate the  
160 presence of a chronic inflammatory response to dioxin.

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## 13 IMMUNOLOGY ASSESSMENT

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### 13.1 INTRODUCTION

Overt damage to organs of the immune system and depressed immunologic function has been noted in a variety of animals exposed to dioxin. As the fields of immunology and immunotoxicology have grown in the past 25 years, a significant spectrum of subtle immunotoxic effects has also been described in animals, but for many possible reasons comparable adverse effects have not been recorded consistently in exposed humans.

Data from the physical examination (skin test measurements at the 1985 and 1987 follow-up examinations, as described below) and the immunology laboratory were used to assess the immunological function for the 1982, 1985, 1987, 1992, 1997, and 2002 Air Force Health Study (AFHS) examinations (1-7).

Absolute lymphocytes indicated the density of lymphocytes in the blood and were analyzed at all six of the AFHS physical examinations. Lymphocytes recognize and destroy bacteria, fungi, viruses, and other foreign bodies.

Responses to stimulation by pokeweed mitogen (PWM) were analyzed for the 1985 follow-up examination. The PWM study measured the functional capability of T cells to become activated by mitogen and undergo proliferations.

Cell function responses to stimulation by phytohemagglutinin (PHA), mixed lymphocyte culture (MLC), and two natural killer cell assays were analyzed for the 1985 and 1987 follow-up examinations. The PHA studies measure the functional capability of T-cells to become activated by mitogen and undergo proliferation. The MLC studies measured the reactivity of T cells to foreign histocompatibility class II antigens. The natural killer cells studies measured natural killer cell activity without Interleukin-2 (NKCA) and with Interleukin-2 (NKCI).

For the 1987 and 1992 follow-up examinations, a composite skin test was constructed based on the responses to four separate antigens – *Candida albicans*, mumps, Trichophyton, and staph-phage lysate. The antigens were injected intradermally and a positive response to any of the four indicated intact cell-mediated immunity. The skin test was considered abnormal if none of the four antigen responses was positive and normal if one or more of the antigen responses was positive.

Immunoglobulins measure the ability of a specific B-cell subgroup to secrete a specific antibody class of molecules. The antibodies typically rise in response to infections or immunizations with bacteria, fungi, and viruses. Analyses were performed on immunoglobulins IgA, IgG, and IgM for 1987, 1992, 1997, and 2002 follow-up examinations.

For the 1992 examination, B cell clones as detected by serum protein electrophoresis and other antibodies were studied, but no associations with group or dioxin were found.

Lupus panel tests were performed for the 1992, 1997, and 2002 follow-up examinations. These tests detected the most frequent autoantibodies found in humans. Autoantibodies are markers for autoimmune diseases, and the lupus panel is considered a screening assay for a wide spectrum of autoimmune

38 disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). Occasionally, autoantibodies are  
39 detected in asymptomatic persons; this is alternatively explained as evidence for incipient autoimmune  
40 disease or a finding of unknown meaning. The lupus panel, based on the manual indirect fluorescent  
41 antibody method, comprises the following individual tests on serum that follow:

- 42 • Antinuclear antibody (ANA) performed on HEp-2 cells
- 43 • Thyroid microsomal antibody
- 44 • Mouse stomach kidney (MSK) section stain for the following specific autoantibodies:
  - 45 - Anti-smooth muscle
  - 46 - Anti-mitochondrial
  - 47 - Anti-parietal cell
- 48 • Rheumatoid factor.

49 All the autoantibodies derive from abnormalities of the B-cell portion, the part of the immune system that  
50 produces immunoglobulins.

51 Cell surface marker measurements were carried out on a random sample of approximately 40 percent of  
52 the participants because of the complexity of the assay and the expense of the tests. Quantification of the  
53 different cell populations was carried out with the use of reagent mouse monoclonal antibodies. CD4+  
54 cells (helper T cells), CD8+ cells (suppressor cells), and CD20+ cells (B cells) were analyzed for all six  
55 AFHS examinations. The cell surface marker measurements of CD2+ cells, CD3+ cells, CD5+ cells,  
56 CD14+ cells, CD16+56+ cells, CD25+ cells, and human leukocyte antigen-DR (HLA-DR) cells were  
57 analyzed at one or more of the AFHS examinations. Analysis of double-labeled cells (cells that express  
58 two markers) were done for CD3+ with CD25+, CD5+ with CD20+, CD4+ with CD8+, and CD3- with  
59 CD16+56+ at the 1992 follow-up examination, and CD3+CD4+ at the 1997 and 2002 follow-up  
60 examinations.

61 The following journal article on the relation of immune response of AFHS participants at the 1992  
62 follow-up examination to dioxin exposure was written by AFHS staff and their colleagues:

- 63 • Serum dioxin and immunologic response in veterans of Operation Ranch Hand (8).

64 In this article, delayed-type hypersensitivity skin test responses were studied. Lymphocyte  
65 measurements, including total lymphocyte counts; T cell (CD3+, CD4+, CD5+, and CD8+), B cell  
66 (CD20+), and natural killer cell (CD16+ and CD56+) subsets; and expression of the activation antigen  
67 CD25+ on CD3+ T cells, also were analyzed. Concentrations of immunoglobulins IgA, IgG, and IgM;  
68 the presence of monoclonal immunoglobulins (M proteins); and a broad range of autoantibodies  
69 (rheumatoid factor, ANA, smooth muscle autoantibody, mitochondrial autoantibody, parietal cell  
70 autoantibody, and thyroid microsomal autoantibodies) were examined. Overall, the authors found no  
71 evidence of a consistent relation between dioxin exposure category and immune system alteration.

72 In 2002, the Institute of Medicine found that the evidence determining whether an association exists  
73 between Agent Orange and other herbicides used in Vietnam and immune suppression or autoimmunity  
74 was inadequate or insufficient (9). This conclusion remained unchanged in the 2004 *Veterans and Agent*  
75 *Orange* update (10).

76 **13.1.1 Chapter Structure**

77 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
 78 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
 79 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
 80 results that appeared consistently across examinations or have biological meaning are emphasized,  
 81 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
 82 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
 83 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
 84 the parameter and either group or dioxin are not discussed.

85 The results discussed below that were discovered as part of further analysis based on a statistical  
 86 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
 87 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
 88 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
 89 baseline examination. Older participants were defined as those born before 1942.

90 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 91 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 92 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 93 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 94 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 95 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at  
 96 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
 97 stratification based on the participant’s tour of duty is given in Chapter 2.

98 The following chart lists the variables that were analyzed for the immunology assessment and at which  
 99 physical examination they were analyzed. The variables appearing in bold type are discussed  
 100 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Absolute Lymphocytes</b>	X		X	X	X	X	X
<b>CD14+ Cells (Monocytes)</b>		X	X	X	X		
<b>CD16+56+ Cells (Natural Killer Cells)</b>					X	X	X
<b>CD2+ Cells (Total T Cells)</b>	X	X	X	X			
<b>CD20+ Cells (B Cells)</b>	X	X	X	X	X	X	X
<b>CD25+ Cells (Activation Marker for Lymphocytes)</b>			X	X	X		
<b>CD3+ Cells (Total T Cells)</b>	X				X	X	X
<b>CD4+ Cells (Helper T Cells)</b>	X	X	X	X	X	X	X
<b>CD4+–CD8+ Ratio</b>	X	X	X	X	X		
<b>CD5+ Cells (T-cell Marker)</b>					X		
<b>CD8+ Cells (Suppressor Cells)</b>	X	X	X	X	X	X	X
<b>Composite Skin Test Diagnosis</b>			X	X	X		
<b>Double Labeled Cells: CD3- with CD16+56+</b>					X		
<b>Double Labeled Cells: CD3+ with CD25+</b>					X		
<b>Double Labeled Cells: CD3+CD4+Cells (Helper T Cells)</b>						X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Double Labeled Cells: CD4+ with CD8+					X		
Double Labeled Cells: CD5+ with CD20+					X		
HLA-DR Cells		X	X	X			
IgA			X	X	X	X	X
IgG			X	X	X	X	X
IgM			X	X	X	X	X
Lupus Panel: ANA Test					X	X	X
Lupus Panel: ANA Thyroid Microsomal Antibody					X	X	X
Lupus Panel: B-Cell Clones Detected by Serum Protein Electrophoresis					X		
Lupus Panel: MSK Anti-Mitochondrial Antibody					X	X	X
Lupus Panel: MSK Anti-Parietal Antibody					X	X	X
Lupus Panel: MSK Anti-Smooth Muscle Antibody					X	X	X
Lupus Panel: Other Antibodies					X		
Lupus Panel: Rheumatoid Factor					X	X	X
Lupus Panel: Summary Index					X		
MLC: Net Response			X	X			
MLC: Unstimulated Response			X	X			
NKCA 50/1: Net Response			X	X			
NKCA 50/1: Percent Release			X	X			
NKCI 50/1: Net Response			X	X			
NKCI 50/1: Percent Release			X	X			
PHA: Maximum Net Response			X	X			
PHA: Net Response			X	X			
PHA: Unstimulated Response			X	X			

101 **13.2 COMPOSITE SKIN TEST DIAGNOSIS**

102 Analysis of 1987 follow-up examination data showed that among all participants and among the heaviest  
103 lifetime cigarette smokers, Ranch Hands had a greater prevalence of composite skin test abnormalities  
104 than Comparisons.

105 Analyses of data from the 1992 follow-up examination found that a greater percentage of Ranch Hands in  
106 the background dioxin category than Comparisons had an abnormal composite skin test diagnosis.

107 **13.3 CD2+ CELLS (TOTAL T CELLS)**

108 The 1985 follow-up examination found that Black Ranch Hands had a lower average CD2+ cell count  
109 than Black Comparisons.

110 Among participants who drank more than one drink per day, CD2+ cell counts at the 1987 follow-up  
111 examination decreased with increasing levels of initial dioxin. In addition, younger Ranch Hands in the

112 background dioxin category who were moderate lifetime drinkers (no more than 40 drink-years) had a  
113 lower average CD2+ cell count than younger Comparisons who were moderate lifetime drinkers.

#### 114 **13.4 CD3+ CELLS (TOTAL T CELLS)**

115 Among officers at the 1992 follow-up examination, Ranch Hands in the high dioxin category had a  
116 greater average CD3+ cell count than Comparisons.

117 Analysis of data collected for the 1997 follow-up examination showed that CD3+ cell counts in Ranch  
118 Hands increased with increasing 1987 dioxin levels.

#### 119 **13.5 CD4+ CELLS (HELPER T CELLS)**

120 Among Ranch Hands who were moderate lifetime drinkers (no more than 40 drink-years) with later tours  
121 of duty who participated in the 1987 follow-up examination, CD4+ cell counts decreased as 1987 dioxin  
122 levels increased.

123 Analysis of CD4+ cells for the 1992 follow-up examination found that Ranch Hand officers in the high  
124 dioxin category had a greater average CD4+ cell count than Comparison officers.

125 CD4+ cell counts in Ranch Hands at the 1997 follow-up examination increased with increasing 1987  
126 dioxin levels.

#### 127 **13.6 CD5+ CELLS (T-CELL MARKER)**

128 Analysis of CD5+ cells for the 1992 follow-up examination showed Ranch Hand officers in the high  
129 dioxin category had a greater average CD5+ cell count than Comparison officers.

#### 130 **13.7 CD8+ CELLS (SUPPRESSOR CELLS)**

131 Among the heaviest drinkers (current and lifetime) as of the 1987 follow-up examination, CD8+ cell  
132 counts decreased with increasing levels of initial dioxin.

133 Among officers, CD8+ cell counts increased at the 1992 follow-up examination with initial dioxin levels.  
134 In addition, the categorized dioxin analysis showed that among officers, Ranch Hands in the high dioxin  
135 category had a greater average CD8+ cell count than Comparisons. Ranch Hand enlisted flyers in the  
136 high dioxin category had a lower mean CD8+ cell count than Comparison enlisted flyers. Ranch Hand  
137 enlisted groundcrew in the background dioxin category had a greater average CD8+ cell count than  
138 Comparison enlisted groundcrew.

#### 139 **13.8 CD4+—CD8+ RATIO**

140 The 1992 follow-up examination analysis of the ratio of CD4+ cells to CD8+ cells found that among  
141 participants with moderate physical activity, Ranch Hands had a greater average ratio than Comparisons.

142 **13.9 CD14+ CELLS (MONOCYTES)**

143 Analysis of CD14+ cells at the 1985 follow-up examination showed that among enlisted groundcrew who  
144 were currently drinking the most (more than four drinks per day), Ranch Hands had a greater average  
145 CD14+ cell count than Comparisons.

146 Among the heaviest lifetime smokers at the time of the 1987 follow-up examination (more than 10 pack-  
147 years) with earlier tours of duty, CD14+ cell counts increased with increasing 1987 dioxin levels.

148 The 1992 follow-up examination analysis of CD14+ cells found Ranch Hand enlisted flyers had a lower  
149 average CD14+ cell count than Comparison enlisted flyers. In addition, older Ranch Hands in the low  
150 dioxin category had lower average CD14+ cell counts than older Comparisons.

151 **13.10 CD16+56+ CELLS (NATURAL KILLER CELLS)**

152 At the 1987 follow-up examination, Ranch Hand officers showed an increase in CD16+56+ counts with  
153 increasing initial dioxin levels. In addition, among officers and lifetime nondrinkers, Ranch Hands in the  
154 high dioxin category had a greater average CD16+56+ cell count than Comparisons. A lower average  
155 CD16+56+ cell count was seen among Ranch Hands in the low dioxin category who were moderate  
156 drinkers (no more than 40 drink-years) or who were moderately active than among Comparisons. Ranch  
157 Hand enlisted flyers in the high dioxin category and Ranch Hand officers in the low dioxin category had  
158 lower average CD16+56+ cell counts than Comparison enlisted flyers and Comparison officers,  
159 respectively.

160 Among enlisted flyers at the 1997 follow-up examination, Ranch Hands had a lower average CD16+56+  
161 cell count than Comparisons. Similarly, Ranch Hands in the high dioxin category had a lower average  
162 CD16+56+ cell count than Comparisons.

163 **13.11 CD20+ CELLS (B CELLS)**

164 The 1985 follow-up examination of CD20+ cells revealed that among Non-Black participants who never  
165 smoked, Ranch Hands had a lower average CD20+ cell count than Comparisons.

166 Among older Ranch Hands who participated in the 1987 follow-up examination, CD20+ cell counts  
167 increased as initial dioxin levels increased. Also, among older participants, Ranch Hands in the  
168 background dioxin category, as well as Ranch Hands in the high dioxin category, had greater average  
169 CD20+ cell counts than Comparisons. Analysis of 1987 follow-up examination data also showed that  
170 among Ranch Hands with earlier tours of duty, CD20+ cell counts increased with increasing 1987 dioxin  
171 levels.

172 The analysis of CD20+ cells at the 1992 follow-up examination found that Ranch Hands in the  
173 background dioxin category had greater average CD20+ cell counts than Comparisons.

174 An increase in CD20+ cells counts in Ranch Hands was seen at the 2002 follow-up examination as initial  
175 dioxin levels increased.

176 **13.12 CD25+ CELLS (ACTIVATION MARKER FOR LYMPHOCYTES)**

177 Among Ranch Hands who were current cigarette smokers, lighter lifetime smokers and drinkers, and  
178 participated in the 1987 follow-up examination, CD25+ cell counts increased with increasing initial  
179 dioxin levels. CD25+ cell counts decreased with increasing 1987 dioxin levels for Ranch Hands with  
180 later tours of duty.

181 The analysis of CD25+ cells at the 1992 follow-up examination showed that among enlisted flyers, Ranch  
182 Hands had a lower average CD25+ cell count than Comparisons. Ranch Hand enlisted flyers in the low  
183 and high dioxin categories combined also had a lower average CD25+ cell count than Comparison  
184 enlisted flyer. Ranch Hand officers in the high dioxin category had a greater average CD25+ cell count  
185 than Comparison officers. In addition, among participants who did not drink, Ranch Hands in the high  
186 dioxin category had greater average CD25+ cell counts than Comparisons.

187 **13.13 HUMAN LEUKOCYTE ANTIGEN (HLA)-DR CELLS**

188 Among younger Ranch Hands who participated in the 1987 follow-up examination, HLA-DR counts  
189 decreased as initial dioxin levels increased. Among older participants, and, in particular, among older  
190 participants who currently drank no more than one drink per day, HLA-DR counts increased with  
191 increasing initial dioxin levels. In addition, among older participants, Ranch Hands in the high dioxin  
192 category had a greater average HLA-DR count than Comparisons.

193 **13.14 DOUBLE-LABELED CELLS**

194 **13.14.1 CD3- with CD16+56+**

195 Analysis for the 1992 follow-up examination found that the number of cells that expressed both CD3- and  
196 CD16+56+ markers decreased with increasing 1987 dioxin levels.

197 **13.14.2 CD3+ with CD25+**

198 Among enlisted flyers at the 1992 follow-up examination, Ranch Hands (in particular, Ranch Hands in  
199 the low and high dioxin categories combined) had a lower average CD3+ with CD25+ cell count than  
200 Comparisons. Among lifetime nondrinkers and among officers, Ranch Hands who were in the high  
201 dioxin category had a higher average CD3+ with CD25+ cell count than Comparisons.

202 **13.14.3 CD4+ with CD8+**

203 Among Blacks and officers at the 1992 follow-up examination, Ranch Hands in the background dioxin  
204 category had a lower average CD4+ with CD8+ cell count than their Comparison counterparts. In  
205 addition, older Ranch Hands in the low dioxin category had a lower average CD4+ with CD8+ cell count  
206 than older Comparisons. Ranch Hand enlisted groundcrew in the background dioxin category had a  
207 higher average CD4+ with CD8+ cell count than Comparison enlisted groundcrew.

208 **13.14.4 CD5+ with CD20+**

209 Analysis of 1992 follow-up examination data showed that the number of cells that express both CD5+  
210 and CD20+ markers increased with increasing 1987 dioxin levels.

211 **13.14.5 CD3+CD4+ Cells (Helper T Cells)**

212 The analysis for the 1997 follow-up examination revealed an increase in CD3+CD4+ cell counts in Ranch  
213 Hands as 1987 dioxin levels increased.

214 **13.15 ABSOLUTE LYMPHOCYTES**

215 Among Ranch Hands who drank more than one drink per day and participated in the 1987 follow-up  
216 examination, absolute lymphocytes decreased as initial dioxin levels increased. Among younger  
217 participants who were moderate lifetime drinkers (less than 40 drink-years at the time of the  
218 examination), Ranch Hands in the background dioxin category had a lower average absolute lymphocyte  
219 count than Comparisons. In addition, younger Ranch Hands in the high dioxin category who were  
220 lifetime nondrinkers had a lower average absolute lymphocyte count than their Comparison counterparts.

221 The 1992 follow-up examination found that among moderately active Ranch Hands, absolute  
222 lymphocytes increased with increasing initial dioxin levels.

223 **13.16 MAXIMUM PHYTOHEMAGGLUTININ (PHA) NET RESPONSE**

224 The 1987 follow-up examination analysis found that Ranch Hands with later tours of duty had increased  
225 maximum PHA net response values as 1987 dioxin levels increased.

226 **13.17 PHA NET RESPONSE**

227 Among heavy drinkers who participated in the 1987 follow-up examination, Ranch Hands had a lower  
228 average PHA net response value than Comparisons. Ranch Hands in the background dioxin category  
229 who were heavy drinkers had a greater average PHA net response than their Comparison counterparts.  
230 PHA net response values among Ranch Hands who were the heaviest lifetime drinkers with later tours of  
231 duty increased with increasing 1987 dioxin levels. PHA net response values increased with increasing  
232 initial dioxin among the heaviest lifetime drinkers and decreased with increasing initial dioxin among  
233 nondrinkers.

234 **13.18 UNSTIMULATED MIXED LYMPHOCYTE CULTURE (MLC) RESPONSE**

235 Analysis of data from the 1987 follow-up examination showed that Ranch Hands in the high dioxin  
236 category had a greater average unstimulated MLC response than Comparisons. In addition, among Ranch  
237 Hands who were lifetime nonsmokers and had earlier tours of duty, unstimulated MLC values increased  
238 as 1987 dioxin levels increased.

239 **13.19 NATURAL KILLER CELL ASSAY (NKCA) 50/1 PERCENT RELEASE**

240 Analysis of data from the 1987 follow-up examination found that Black Ranch Hands had a greater  
241 average NKCA 50/1 percent release than Black Comparisons.

242 **13.20 NATURAL KILLER CELL ASSAY WITH INTERLEUKIN-2 (NKCI) 50/1 PERCENT RELEASE**  
243 **AND NET RESPONSE**

244 Black Ranch Hands in the 1987 follow-up examination had a greater average NKCI percent release than  
245 Black Comparisons. Among non-Black participants who were the heaviest drinkers, Ranch Hands in the  
246 low dioxin category had a greater average NKCI percent release than Comparisons. In addition, among  
247 non-Black participants with later tours of duty and among Black participants with earlier tours of duty,  
248 NKCI percent release values increased with increasing levels of 1987 dioxin.

249 The same results were seen for NKCI 50/1 net response at the 1987 follow-up examination.

250 **13.21 IgA**

251 Among Ranch Hands with earlier tours of duty who used to smoke but quit and participated in the 1987  
252 follow-up examination, IgA values increased with increasing 1987 dioxin levels. Ranch Hands in the  
253 background dioxin category had a lower average IgA value than Comparisons.

254 IgA values in Ranch Hands at both the 1987 and 1997 follow-up examinations increased with increasing  
255 initial dioxin levels.

256 Among Black participants at the 1992 follow-up examination, Ranch Hands in the low dioxin category  
257 had a greater average IgA value than Comparisons.

258 **13.22 IgG**

259 At the 1987 follow-up examination, Ranch Hands in the background dioxin category had a lower average  
260 IgG value than Comparisons. At the 1992 follow-up examination, Ranch Hand officers in the high dioxin  
261 category had a lower average IgG value than Comparison officers.

262 **13.23 IgM**

263 Among Ranch Hands who were moderate current drinkers (between one and four drinks per day) and  
264 participated in the 1987 follow-up examination, IgM values decreased with increasing initial dioxin  
265 levels. Analysis for the 1987 follow-up examination also found that, among Ranch Hands with later tours  
266 of duty, IgM values decreased with increasing 1987 dioxin levels.

267 Based on data from the 1992 follow-up examination, Black Ranch Hands had a lower average IgM value  
268 than Black Comparisons. Similarly, among sedentary participants (in particular, sedentary enlisted  
269 flyers), Ranch Hands had a lower average IgM value than their Comparison counterparts. Very active  
270 Ranch Hands (primarily in the low dioxin category), however, had a greater average IgM value than  
271 Comparisons.

272 Ranch Hand enlisted flyers at the 2002 follow-up examination had a lower average IgM value than  
273 Comparison enlisted flyers.

274 **13.24 LUPUS PANEL**

275 **13.24.1 Antinuclear Antibody (ANA) Test**

276 At the 2002 follow-up examination, the presence of ANA increased with increasing initial dioxin levels.

277 **13.24.2 ANA Thyroid Microsomal Antibody**

278 Among heaviest lifetime drinkers (more than 40 drink-years at the time of the examination) and among all  
279 minimal current drinkers (no more than one drink per day), a greater percentage of Ranch Hands than  
280 Comparisons had thyroid microsomal antibodies present at the 1992 follow-up examination.

281 Among participants who were currently smoking cigarettes at the time of the 1992 follow-up  
282 examination, a greater percentage of Ranch Hands in each of the background, low, and high dioxin  
283 categories than Comparisons had thyroid microsomal antibodies present. Among former smokers and the  
284 heaviest lifetime drinkers, Ranch Hands in the low dioxin category and in the high dioxin category each  
285 had a greater prevalence of thyroid microsomal antibodies present than Comparisons. Among minimal  
286 current drinkers, a greater percentage of Ranch Hands in the low dioxin category than Comparisons had  
287 thyroid microsomal antibodies present.

288 **13.24.3 Mouse Stomach Kidney (MSK) Anti-smooth Muscle Antibody**

289 The 2002 follow-up examination found that Ranch Hand officers had a greater presence of anti-smooth  
290 muscle antibodies than Comparison officers. In addition, a greater percentage of Ranch Hands in the  
291 background dioxin category had anti-smooth muscle antibodies present than Comparisons.

292 **13.24.4 Rheumatoid Factor**

293 Among Ranch Hand enlisted groundcrew who participated in the 1992 follow-up examination, the  
294 occurrence of a positive rheumatoid factor increased with initial dioxin levels. In addition, among Ranch  
295 Hands in the background dioxin category, enlisted groundcrew and moderately physically active  
296 participants had a greater presence of positive rheumatoid factor results than their Comparison  
297 counterparts.

298 A greater percentage of Ranch Hand officers at the 2002 follow-up examination had a positive  
299 rheumatoid factor than Comparison officers. In addition, Ranch Hands in the low dioxin category had a  
300 higher prevalence of positive rheumatoid factor results than Comparisons.

301 **13.25 CONCLUSION**

302 Consistent with previous AFHS physical examinations, IgA increased with increasing initial dioxin at the  
303 1997 follow-up examination, but was not increased in enlisted groundcrew or the high dioxin category.  
304 The IgA results were small in magnitude and their clinical significance was unknown.

305 In the lupus panel, a positive association was found between initial dioxin level and the presence of the  
306 ANA at the 2002 follow-up examination, but the association did not appear to support a dose-response  
307 relation. There was an increasing prevalence of a positive ANA in Ranch Hands with increasing initial  
308 dioxin levels. When looking at the individual autoantibodies, however, there were no consistent findings  
309 to support the presence of ANA.

310 The indices of immune responses analyzed in the AFHS examination provided a comprehensive  
311 reflection of in vivo and in vitro immune function in the study population. No biologically meaningful  
312 indicators reflecting a relation between the body burden of dioxin or the initial exposure and immune  
313 function were found.

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## 14 NEOPLASIA ASSESSMENT

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### 14.1 INTRODUCTION

Many types of cancer are thought to be related to chlorophenols, phenoxy herbicides, and dioxin. Although exposure to herbicides has been determined to be carcinogenic in animal studies, the exposure required for malignant transformation of normal cells and the types of tumors produced are species-dependent. Therefore, while animal studies provide conclusive evidence on the carcinogenic potential of dioxin, the determination of causality in humans remains to be established.

Many studies have assessed the carcinogenic potential of dioxin in humans. While the cumulative data from these studies have not been entirely consistent, associations between dioxin exposure in humans and an increased risk of developing cancers of the skin, lung, bladder, kidney, connective tissue, and lymphatic system have been reported.

During the health interview at the 1982, 1985, 1987, 1992, 1997, and 2002 Air Force Health Study (AFHS) examinations, each study participant was asked a series of questions on the occurrence of cancer. Medical records review was accomplished to confirm reported neoplasms and identify any unreported neoplasms. The data were combined to form a complete lifetime neoplasia history for each participant. These data were the basis of the majority of the analysis for the neoplasia assessment (1-7). The neoplasia assessment itself was based on the occurrence of neoplasms (both benign and malignant) after service in Southeast Asia (SEA).

Some possible neoplasms were discovered by the physicians at the physical examination. Contingent upon participant authorization, suspicious skin lesions were biopsied and the pathology determined; no other invasive procedures were used to detect systemic neoplasms.

For chest x-ray findings needing follow-up at the 2002 physical examination, the AFHS staff made every effort to contact and encourage participants to see their primary physicians. The participants were then recontacted to determine whether a final diagnosis was available, and, if so, results were included in the analysis.

In the AFHS examination reports, skin neoplasms were analyzed by behavior. In particular, analysis was conducted on skin neoplasms according to the following four behaviors:

- All skin neoplasms
- Malignant skin neoplasms
- Benign skin neoplasms
- Skin neoplasms of uncertain behavior or unspecified nature.

Analysis of malignant skin neoplasms was conducted for all sites combined and by the following cell types:

- Basal cell carcinoma

- 35 • Squamous cell carcinoma
- 36 • Sun exposure-related neoplasm (basal cell carcinoma, squamous cell carcinoma, melanoma,  
37 and malignant epithelial neoplasms not otherwise specified)
- 38 • Nonmelanoma (basal cell carcinoma, squamous cell carcinoma, and malignant epithelial  
39 neoplasms not otherwise specified)
- 40 • Melanoma.

41 Systemic neoplasms were analyzed by behavior. In particular, analysis was conducted on systemic  
42 neoplasms according to the following four behaviors:

- 43 • All systemic neoplasms
- 44 • Malignant systemic neoplasms
- 45 • Benign systemic neoplasms
- 46 • Systemic neoplasms of uncertain behavior or unspecified nature.

47 Analysis of malignant systemic neoplasms also was conducted based on the site of the neoplasms. The  
48 various sites examined are described later in this chapter.

49 In addition, analysis was performed on all skin and systemic neoplasms, regardless of behavior or site,  
50 and all malignant neoplasms, which was a combination of malignant skin and malignant systemic  
51 neoplasms.

52 The prostate-specific antigen (PSA) test was developed to detect prostate enlargement and prostate  
53 cancer. Each participant had a PSA test as a standard part of the laboratory assay.

54 The following journal articles on skin and systemic cancer were written by AFHS staff and their  
55 colleagues:

- 56 • Serum dioxin and cancer in veterans of Operation Ranch Hand (8)
- 57 • Cancer in US Air Force veterans of the Vietnam War (9)
- 58 • Did TCDD exposure or service in Southeast Asia increase the risk of cancer in Air Force  
59 Vietnam veterans who did not spray Agent Orange? (10).

60 The Institute of Medicine (IOM), as reported first in their 1994 publication, *Veterans and Agent Orange*  
61 (11), concluded that there is “sufficient” evidence to establish an association, although not a causal  
62 relation, between dioxin exposure and the occurrence of soft tissue sarcoma, non-Hodgkin’s lymphoma,  
63 and Hodgkin’s disease (11-16). In the 2002 *Veterans and Agent Orange* update, the epidemiologic  
64 evidence was considered to be sufficient concerning chronic lymphocytic leukemia based primarily on  
65 studies of agricultural workers (15). The evidence for an association with respiratory cancers, prostate  
66 cancer, and multiple myeloma was considered “limited/suggestive” (11-16).

67 **14.1.1 Chapter Structure**

68 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
 69 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
 70 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
 71 results that appeared consistently across examinations or have biological meaning are emphasized,  
 72 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
 73 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
 74 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
 75 the parameter and either group or dioxin are not discussed.

76 The results discussed below that were discovered as part of further analysis based on a statistical  
 77 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
 78 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
 79 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
 80 baseline examination. Older participants were defined as those born before 1942.

81 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 82 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 83 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 84 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 85 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 86 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at  
 87 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
 88 stratification based on the participant’s tour of duty is given in Chapter 2.

89 The following chart lists the variables that were analyzed for the neoplasia assessment and at which  
 90 physical examination they were analyzed. The variables appearing in bold type are discussed  
 91 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<i>Skin Neoplasms</i>							
<b>All</b>		X	X	X	X	X	X
<b>Malignant</b>		X	X	X	X	X	X
<b>Basal Cell Carcinoma</b>	X	X	X	X	X	X	X
Fibrosarcoma	X						
Melanoma	X	X	X	X	X	X	X
<b>Nonmelanoma</b>					X	X	X
Squamous Cell Carcinoma	X	X	X	X	X	X	X
<b>Sun Exposure-Related</b>		X	X	X			
<b>Benign</b>		X	X	X	X	X	X
<b>Uncertain Behavior or Unspecified Nature</b>		X	X	X	X	X	X
<i>Systemic Neoplasms</i>							
<b>All</b>		X	X	X	X	X	X
All Stomach							X
<b>Malignant</b>		X	X	X	X	X	X
Bone and Articular Cartilage	X						X
Brain			X	X	X	X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Bronchus and Lung</b>	X	X	X	X	X	X	X
<b>Carcinoma In Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and Other Male Genitals, and Bladder and Other and Nonspecified Urinary)</b>			X	X	X	X	X
<b>Colon and Rectum</b>		X	X	X	X	X	X
Connective and Other Soft Tissues		X			X	X	X
Digestive Organ, Peritoneum, and Esophagus	X	X			X	X	X
<b>Eye, Ear, Face, Head, and Neck</b>		X	X	X	X	X	X
Hodgkin's Disease	X	X	X	X	X	X	X
Ill-Defined Sites		X	X	X	X	X	X
<b>Urinary System</b>		X	X	X	X	X	X
Kidney and Ureter							X
Leukemia		X	X	X	X		X
Lip, Oral Cavity, Pharynx, and Larynx	X	X	X	X	X	X	X
<b>Liver</b>						X	X
Lymphoreticular Sarcoma							X
Multiple Myeloma					X		X
Non-Hodgkin's Lymphoma		X			X	X	X
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	X		X	X	X	X	X
<b>Penis and Other Male Genital Organs</b>	X						X
<b>Prostate</b>		X	X	X	X	X	X
Soft Tissue Sarcoma		X					
Stomach							X
Testicles		X	X	X	X	X	X
Thymus, Heart, and Mediastinum			X	X	X	X	X
Thyroid Gland		X	X	X	X	X	X
<b>Benign</b>		X	X	X	X	X	X
<b>Uncertain Behavior or Unspecified Nature</b>		X	X	X	X	X	X
<i>Skin and Systemic Neoplasms</i>							
<b>All</b>		X	X	X	X	X	X
<b>Malignant</b>						X	X
<b>PSA</b>					X	X	X

92

93 **14.2 SKIN NEOPLASMS**

94 **14.2.1 All Skin Neoplasms**

95 When the 1992 follow-up examination data were analyzed, the prevalence of any type of skin neoplasm  
96 was higher for Ranch Hands in the low dioxin category than Comparisons.

97 In the analysis of the 1997 follow-up examination data, the prevalence of any type of skin neoplasm was  
98 higher in Ranch Hands than Comparisons among all participants, among officers, and among enlisted  
99 flyers. Ranch Hands in the background and low dioxin categories also had a higher prevalence of any  
100 type of skin neoplasm than Comparisons.

101 The analysis of the 2002 follow-up examination data showed that among all participants, Ranch Hands  
102 had a higher prevalence of any type of skin neoplasm than Comparisons. Ranch Hands in the low dioxin  
103 category also had a higher prevalence of any type of skin neoplasm than Comparisons.

#### 104 **14.2.2 Malignant Skin Neoplasms**

105 The analysis of the 1982 baseline examination data showed that Ranch Hands had a higher prevalence of  
106 a malignant skin neoplasm than Comparisons.

107 The 1992 follow-up examination data analysis showed that, among participants who did not report  
108 exposure to industrial chemicals, Ranch Hands in the low dioxin category had a higher prevalence of a  
109 malignant skin neoplasm than Comparisons.

110 A higher percentage of Ranch Hands in the low dioxin category than Comparisons had a malignant skin  
111 neoplasm in the 2002 follow-up examination data analysis.

##### 112 *14.2.2.1 Basal Cell Carcinoma*

113 In 1985, the analysis of the follow-up examination data showed a higher prevalence of basal cell  
114 carcinoma among Ranch Hand enlisted flyers than Comparison enlisted flyers.

115 The analysis of the 1987 follow-up examination data showed a higher percentage of Ranch Hands with  
116 basal cell carcinoma than Comparisons.

117 Data from the 1987 follow-up examination also showed that Ranch Hands in the background and low  
118 dioxin categories had a higher prevalence of basal cell carcinoma at multiple sites than Comparisons. The  
119 prevalence of basal cell carcinoma on sites that were not specified increased with increasing initial dioxin  
120 among Ranch Hand enlisted flyers. In addition, Ranch Hands in the low dioxin category had a higher  
121 prevalence than Comparisons of basal cell carcinoma on sites that were not specified. Among enlisted  
122 flyers, however, Ranch Hands in the high dioxin category had a higher prevalence of basal cell carcinoma  
123 on sites that were not specified than Comparisons.

124 The analysis of the 1992 follow-up examination data showed that the prevalence of basal cell carcinoma  
125 on the trunk increased with increasing 1987 dioxin levels among Ranch Hand participants who did not  
126 report exposure to insecticides (a covariate in the analysis).

127 The 1997 follow-up examination data analysis showed a higher prevalence of basal cell carcinoma in  
128 Ranch Hand enlisted flyers than Comparison enlisted flyers. In addition, Ranch Hands in the low dioxin  
129 category had a higher prevalence of basal cell carcinoma than Comparisons. The prevalence of basal cell  
130 carcinoma on the trunk for Ranch Hands also increased with increasing 1987 dioxin levels.

131 The 2002 follow-up examination data analysis showed that among all participants and among officers,  
132 Ranch Hands had a higher prevalence of basal cell carcinoma than Comparisons. Ranch Hands in the low  
133 dioxin category also had a higher prevalence of basal cell carcinoma than Comparisons.

134 *14.2.2.2 Nonmelanoma*

135 The 1997 follow-up examination data analysis showed that Ranch Hand enlisted flyers had a higher  
136 prevalence of a nonmelanoma malignant skin neoplasm than Comparison enlisted flyers.

137 Ranch Hands had a higher prevalence of a nonmelanoma malignant skin neoplasm than Comparisons in  
138 the analysis of the 2002 follow-up examination data; this difference was seen primarily in officers. In  
139 addition, a greater percentage of Ranch Hands in the low dioxin category had a nonmelanoma malignant  
140 skin neoplasm than Comparisons.

141 *14.2.2.3 Sun Exposure-related Malignant Skin Neoplasm*

142 The analysis of the 1987 follow-up examination data showed that Ranch Hands had a higher prevalence  
143 of a sun exposure-related malignant skin neoplasm than Comparisons. Ranch Hands in the low dioxin  
144 category had a higher prevalence of a sun exposure-related malignant skin neoplasm than Comparisons on  
145 sites that were not specified. Among enlisted flyers, Ranch Hands in the high dioxin category also had a  
146 greater prevalence of a sun exposure-related malignant skin neoplasm than Comparisons on sites that  
147 were not specified. In addition, the prevalence of Ranch Hand enlisted flyers with a sun exposure-related  
148 malignant skin neoplasm on sites that were not specified increased with increasing initial dioxin.

149 **14.2.2 Benign Skin Neoplasms**

150 The analysis of the 1997 follow-up examination data showed that the prevalence of a benign skin  
151 neoplasm was higher in Ranch Hands than in Comparisons among officers. Ranch Hands in the  
152 background dioxin category also had a greater prevalence of a benign skin neoplasm than Comparisons.

153 **14.2.3 Skin Neoplasms of Uncertain Behavior or Unspecified Nature**

154 The 2002 follow-up examination data analysis showed that the prevalence of a skin neoplasm of uncertain  
155 behavior or unspecified nature was greater for Ranch Hands in the low dioxin category than for  
156 Comparisons.

157 **14.3 SYSTEMIC NEOPLASMS**

158 Statistical power is an issue in a study with a population the size of the AFHS. A study with a population  
159 of the approximately 2,000 veterans who completed physical examinations lacks power to determine  
160 increases in relative risks for rare events (such as soft tissue sarcoma and other systemic neoplasms)  
161 because such events are unlikely to occur in large numbers in a group this small. While certain  
162 occupational toxins have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic  
163 angiosarcoma for vinyl chloride) that is virtually nonexistent in the absence of the causative agent, other  
164 toxins merely increase the risk of nondiagnostic pathology. For example, the AFHS would likely not  
165 discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology.

166 **14.3.1 All Systemic Neoplasms**

167 The 1987 follow-up examination data analysis showed that the prevalence of any type of systemic  
168 neoplasm in Ranch Hands increased with increasing initial dioxin. The prevalence of any type of  
169 systemic neoplasm in Ranch Hands with later tours also increased with increasing 1987 dioxin.

170 **14.3.2 Malignant Systemic Neoplasms**

171 The 1985 follow-up examination data analysis showed that Ranch Hand enlisted flyers had a higher  
172 prevalence of a malignant systemic neoplasm than Comparison enlisted flyers.

173 Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm than  
174 Comparisons in the analysis of the 1987 follow-up examination data.

175 The analysis of the 1992 follow-up examination data showed that the prevalence of a malignant systemic  
176 neoplasm increased with increasing 1987 dioxin levels among Ranch Hands who did not report exposure  
177 to degreasing chemicals.

178 Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm than  
179 Comparisons in the analysis of the 1997 follow-up examination data.

180 The 2002 follow-up examination data analysis showed Ranch Hand officers had a higher prevalence of a  
181 malignant systemic neoplasm than Comparison officers. In addition, a higher percentage of Ranch Hands  
182 in the low dioxin category had a malignant systemic neoplasm than Comparisons.

183 *14.3.2.1 Bronchus and Lung*

184 The analyses of the 1997 and 2002 follow-up examination data showed that Ranch Hands in the low  
185 dioxin category had a higher prevalence of a malignant systemic neoplasm of the bronchus and lung than  
186 Comparisons.

187 *14.3.2.2 Colon and Rectum*

188 The 1992 and 2002 follow-up examination data analyses showed that the prevalence of a malignant  
189 systemic neoplasm of the colon and rectum was higher among Ranch Hands in the low dioxin category  
190 than among Comparisons. The analysis of the 2002 follow-up examination data also showed that the  
191 prevalence of a malignant systemic neoplasm of the colon and rectum was higher for Ranch Hand officers  
192 than Comparison officers.

193 *14.3.2.3 Eye, Ear, Face, Head, and Neck*

194 The 1992 follow-up examination data analysis showed that Ranch Hands in the low dioxin category had a  
195 higher prevalence of a malignant systemic neoplasm of the eye, ear, face, head, or neck than Comparisons  
196 among moderate lifetime cigarette smokers (more than 0 pack-years but no more than 10 pack-years) and  
197 among participants who did not report exposure to degreasing chemicals.

198 *14.3.2.4 Liver*

199 The analysis of the 1997 follow-up examination data showed that the prevalence of a malignant systemic  
200 neoplasm of the liver among Ranch Hands increased with increasing 1987 dioxin levels.

201 *14.3.2.5 Malignant Systemic Neoplasms of the Penis and Other Male Genital Organs*

202 The 2002 follow-up examination data analysis showed that the prevalence of a malignant systemic  
203 neoplasm of the penis and other male genital organs increased with increasing 1987 dioxin levels.

204 *14.3.2.6 Prostate*

205 When the 1992 follow-up examination data were analyzed, the findings showed that the prevalence of a  
206 malignant systemic neoplasm of the prostate increased with increasing 1987 dioxin levels among Ranch  
207 Hand participants who did not report exposure to degreasing chemicals.

208 The 2002 follow-up examination data analysis showed that Ranch Hands in the low dioxin category had a  
209 higher prevalence of a malignant systemic neoplasm of the prostate than Comparisons.

210 *14.3.2.7 Urinary System*

211 The analyses of 1987 and 1997 follow-up examination data showed that Ranch Hands in the low dioxin  
212 category had a higher prevalence of a malignant systemic neoplasm of the urinary system than  
213 Comparisons.

214 The analysis of the 2002 follow-up examination data showed that Ranch Hands had a higher prevalence  
215 of a malignant systemic neoplasm of the urinary system than Comparisons, primarily among officers.  
216 The prevalence of a malignant systemic neoplasm of the urinary system among Ranch Hands increased  
217 with increasing initial dioxin. In addition, Ranch Hands in the low dioxin category had a higher  
218 prevalence of a malignant systemic neoplasm of the urinary system than Comparisons.

219 *14.3.2.8 Carcinoma in Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and Other Male*  
220 *Genitals, and Bladder and Other and Nonspecified Urinary)*

221 The analysis of the 2002 follow-up examination data showed that a higher percentage of Ranch Hands in  
222 the low dioxin category had a carcinoma in situ than Comparisons.

223 **14.3.3 Benign Systemic Neoplasms**

224 The prevalence of a benign systemic neoplasm in Ranch Hands increased with increasing initial and 1987  
225 dioxin levels in the analysis of the 1997 follow-up examination data.

226 **14.3.4 Systemic Neoplasms of Uncertain Behavior or Unspecified Nature**

227 The analysis of the 1992 follow-up examination data showed that the prevalence of a systemic neoplasm  
228 of uncertain behavior or unspecified nature increased with increasing 1987 dioxin among Ranch Hands  
229 who reported exposure to asbestos.

230 **14.4 SKIN AND SYSTEMIC NEOPLASMS**

231 **14.4.1 All Skin and Systemic Neoplasms**

232 The analysis of the 1992 follow-up examination data showed that the prevalence of any type of skin or  
233 systemic neoplasm increased with increasing 1987 dioxin levels among Ranch Hand participants with  
234 hazel or green eyes.

235 In the analysis of the 2002 follow-up examination data, a higher percentage of Ranch Hands in the low  
236 dioxin category had an occurrence of any type of skin or systemic neoplasm than Comparisons.

237 **14.4.2 Malignant Skin and Systemic Neoplasms**

238 Both the 1997 and the 2002 follow-up examination data analyses showed that Ranch Hands in the low  
239 dioxin category had a higher prevalence of a malignant skin or systemic neoplasm than Comparisons.

240 **14.5 PROSTATE-SPECIFIC ANTIGEN (PSA)**

241 The analysis of the 1992 follow-up examination data showed that the prevalence of abnormally high PSA  
242 levels increased with increasing 1987 dioxin among Ranch Hand participants who did not report exposure  
243 to degreasing chemicals.

244 **14.6 AFHS JOURNAL ARTICLES ON CANCER**

245 **14.6.1 Serum Dioxin and Cancer in Veterans of Operation Ranch Hand**

246 A 1999 *American Journal of Epidemiology* article (8) described results of an analysis of cancers for all  
247 AFHS veterans who attended at least one of the 1982, 1985, 1987, or 1992 examinations and who had a  
248 dioxin measurement. All cancers verified as of July 1997 were included. Analysis of cancer prevalence  
249 and latency analyses were conducted for all cancers, skin cancers, and cancer at all sites other than the  
250 skin. Subgroups of skin cancers and cancer at all sites other than the skin were also analyzed. An  
251 inherent limitation of the AFHS is that low statistical power existed to detect an effect for specific or rare  
252 cancers.

253 There was no evidence of dose-response pattern or of latency effect for all cancers or for skin cancers.  
254 The risk of cancer at sites other than the skin was not increased for Ranch Hands in the high dioxin  
255 category, but an increased risk for Ranch Hands in the low dioxin category who had ended their service in  
256 SEA within the past 20 years was observed. Kidney or bladder cancer was increased for Ranch Hands in  
257 the low dioxin category. Ranch Hands in the low dioxin category, but not in the high dioxin category,  
258 had an earlier time to onset of cancer of any type. These results were inconsistent with a NIOSH study of  
259 workers at 12 plants in the United States that produced chemicals contaminated with dioxin (17) and  
260 suggest that the increased risk may not have been caused by dioxin exposure. Overall, there was no  
261 consistent evidence of a dose-response relation and no significant increase in cancer risk in the high  
262 dioxin category, the subgroup of greatest interest based on average dioxin levels.

263 **14.6.2 Cancer in US Air Force Veterans of the Vietnam War**

264 An analysis of cancers for all AFHS veterans who attended at least one of the 1982, 1985, 1987, 1992, or  
265 1997 examinations was conducted and the results were reported in a 2004 journal article (9). The effects  
266 of time spent in SEA, the calendar period of service, and the percentage of SEA service spent in Vietnam  
267 were explored relative to cancer in AFHS participants. The conditions included cancers verified as of  
268 December 1999. Cancer morbidity was classified by anatomical site using the Surveillance,  
269 Epidemiology, and End Results (SEER) section of the National Cancer Institute (NCI) classification  
270 system. The SEER categories included all anatomical sites except basal cell and squamous cell  
271 carcinoma. Cancer incidence and mortality were considered separately. External contrasts against U.S.  
272 national cancer rates and internal analyses by dioxin category were conducted. To maximize available  
273 data, all AFHS veterans who attended at least one of the 1982, 1985, 1987, 1992, or 1997 examinations  
274 were used for external analysis, whereas the internal measurements used the subset of the participants  
275 from the external analyses who additionally had a dioxin measurement.

276 External contrasts found that the incidences of melanoma and prostate cancer were increased among  
277 white Ranch Hand veterans; the same pattern was found when the analysis was restricted to white Ranch  
278 Hand participants whose tour of duty occurred between 1966 and 1970, the period of heaviest Agent  
279 Orange spraying. The incidence of prostate cancer also was increased among white Comparison veterans;  
280 the same pattern was found when the analysis was restricted to Comparison participants whose tour of  
281 duty occurred between 1966 and 1970. No significant increases in cancer mortality were found relative to  
282 national rates.

283 Two internal analyses were conducted to address concerns that Comparisons who spent time in Vietnam  
284 may have developed cancer. The first analysis was restricted to participants who spent at most 2 years in  
285 SEA and the second analysis to Ranch Hands who spent 100 percent of their SEA tours in Vietnam and to  
286 Comparisons who spent 0 percent of their SEA tours in Vietnam. Categorization by time spent in SEA  
287 approximated categorization by the percentage of SEA service spent in Vietnam. Stratification by the  
288 percentage of SEA service spent in Vietnam provided a clearer dichotomy on the Vietnam experience at  
289 the expense of a reduction in sample size. Among veterans who spent at most 2 years in SEA, the risk of  
290 cancer at any site, of prostate cancer, and of melanoma was increased in the high dioxin category.  
291 Among Ranch Hands who spent 100 percent of their SEA tours of duty in Vietnam, the risk of cancer at  
292 any site was increased in the low and high dioxin categories relative to Comparisons who spent 0 percent  
293 of their SEA tours of duty in Vietnam.

#### 294 **14.6.3 Did TCDD Exposure or Service in Southeast Asia Increase the Risk of Cancer in Air Force** 295 **Vietnam Veterans Who Did Not Spray Agent Orange?**

296 The effects of time spent in SEA and dioxin level were explored relative to cancer in AFHS Comparison  
297 participants and reported in a 2005 journal article by Pavuk et al. (10). Cancer morbidity was classified  
298 by anatomical site using the SEER classifications. The SEER categories included all anatomical sites  
299 except basal cell and squamous cell carcinoma. The analysis was based on Comparisons who had a  
300 dioxin measurement and attended at least one of the six AFHS examinations in 1982, 1985, 1987, 1992,  
301 1997, and 2002. An increased risk of all-sites cancer and trends of increased risks of all SEER sites  
302 cancer and melanoma with dioxin were found in AFHS Comparison participants. These veterans had  
303 background dioxin levels and were not occupationally exposed to Agent Orange or other herbicides. The  
304 results suggested that dioxin acts as an initiator or a promoter of carcinogenesis at low levels or may be a  
305 surrogate for other unmeasured risk factors associated with an increased risk of cancer. The results  
306 indicated an interrelationship between all-sites cancer, dioxin, and service in SEA, and further suggested  
307 that a combination of factors related to time spent in SEA were probably involved. Service in SEA was  
308 itself a risk factor for prostate cancer in these AFHS Comparison participants, independent of dioxin  
309 exposure. The authors of the journal article noted that interpretation of these results should be made  
310 cautiously, as sample sizes for most individual cancer sites were small and detailed locations of individual  
311 tours of duty in SEA were not yet available.

## 312 **14.7 CONCLUSION**

313 The associations between herbicide exposure or dioxin levels and the likelihood of developing cancer  
314 were seen primarily for Ranch Hand officers and Ranch Hands in the low dioxin category. No  
315 associations were observed for enlisted groundcrew, the military occupational category that had the  
316 highest median level of exposure to dioxin in Ranch Hands. Other risk and operational factors discussed  
317 in published articles did not show consistent associations in Ranch Hands but did show some associations  
318 in the Comparisons. The AFHS is limited in its ability to detect increases in risks of rare diseases because  
319 of the small size of the Ranch Hand population.

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## 15 NEUROLOGY ASSESSMENT

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### 15.1 INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and dioxin. Animal research and studies of humans exposed to high levels of dioxin imply that the peripheral nervous system is a target organ for acute dioxin toxicity. The recognized acute neurotoxicity of these chemicals and the prevalence of neurological complaints among veterans are primary factors in the decision to place a major emphasis on the neurological evaluation of participants in the Air Force Health Study (AFHS).

Analyses were performed to assess the neurological function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). The neurology assessment was based on extensive physical examination data on cranial nerve function, peripheral nerve status, and central nervous system (CNS) coordination processes. This information was supplemented by verified histories of neurological diseases.

The questionnaire captured data on the occurrence of neurological disorders. Medical records reviews were conducted to confirm reported neurological conditions and to identify any unreported conditions for each participant. Neurological diseases and disorders were classified into four categories: hereditary and degenerative diseases, inflammatory diseases, peripheral disorders, and other neurological disorders.

The physical examination included various indicators of cranial nerve function, peripheral nerve status, and CNS coordination processes. The evaluation of cranial nerve function was based on the following 15 variables: balance, facial sensation, smell, visual fields, light reaction, ocular movement, corneal reflex, jaw clench, smile, palpebral fissure, gag reflex, speech, tongue position relative to midline, palate and uvula movement, and shoulder shrug. All of these variables were scored as normal or abnormal, except for jaw clench and palate and uvula movement, which were scored as symmetric or deviated. For variables with left and right determinations, the two results were combined to produce a single normal or abnormal result, where normal indicated that both responses were normal, and abnormal indicated that at least one of the responses was abnormal. Abnormal speech conditions included aphasia, dysarthria, agnosia, and other speech abnormalities. Associations between dioxin or herbicides and balance, facial sensation, smell, and visual fields were found and are discussed later in this chapter.

A cranial nerve index was created by combining responses for the 15 cranial nerve determinations. This index was classified as abnormal if at least one of the determinations was abnormal, and was classified as normal if all of the cranial nerve parameters were normal. Analyses in 1985, 1987, and 1992 investigated the effects of neck range of motion in conjunction with the cranial nerve index. The examining neurologist asked each participant to move his head to the left, right, and to tilt his head forward and backward. This test assessed the musculoskeletal and vertebral column function. This neck range of motion variable was coded as abnormal if there was a decreased range of motion forward or backward or to the left or right.

Peripheral nerve status was assessed by light touch (cotton sticks), visual inspection of muscle mass (and palpation, if indicated), light pinprick, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. Pinprick and light touch were considered normal if the reaction was normal on both legs. A variable to judge muscle status was constructed using data on bulk; tone of upper and lower

41 extremities; and the strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip  
42 flexors. Bulk was classified as either normal or abnormal. Tone was classified as abnormal if there was  
43 either a decreased or increased response on either the left side, right side, or both sides. The strength of  
44 distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors was considered abnormal  
45 if either the left or right side or both sides were decreased. Composite muscle status was classified as  
46 normal if all of the components were normal on both the left and right sides and abnormal if at least one  
47 of the components was abnormal on either or both sides.

48 The patellar, Achilles, and biceps reflexes were divided into three categories: “absent,” “sluggish,” and  
49 “active or very active.” The categories of “active” and “very active” were combined because of the  
50 sparse number of participants with very active reflexes. Two contrasts that preserved the ordinal structure  
51 of the data were examined: “sluggish or absent” versus “active or very active” (i.e., less than active  
52 versus active), and “absent” versus “sluggish, active, or very active” (i.e., reflexes absent versus not  
53 absent). When the assessments of the reflex were different between the left and right body side, the more  
54 severe condition was assigned. For example, if the left Achilles reflex was sluggish and the right Achilles  
55 reflex was absent, the composite Achilles reflex variable was designated as absent.

56 Indices to assess signs and degree of polyneuropathy also were constructed from the neurologist’s  
57 assessment of the following seven parameters and a vibrotactile threshold measurement:

- 58 • Ankle and toe flexors
- 59 • Balance
- 60 • Achilles reflexes
- 61 • Light touch
- 62 • Pinprick
- 63 • Ankle vibration
- 64 • Position of great toe.

65 The evaluation of CNS coordination processes was based on the analyses of Romberg sign, coordination,  
66 gait, tremor, and a CNS index. For these variables, multiple determinations, which included left and  
67 right, as well as upper and lower responses, were combined to form a single result. A result was  
68 classified as normal if all determinations were normal and abnormal if at least one determination was  
69 abnormal. Tremor was examined for the left and right upper and lower extremities. Abnormal tremors  
70 included resting, essential, intention, and other tremors. Coordination was a composite index defined as  
71 normal if the Romberg sign, finger-nose-finger and heel-knee-shin coordination processes, rapidly  
72 alternating movements of pronation and supination of hands, and rapid patting were normal. The  
73 Romberg sign variable was equivalent to the “balance” variable analyzed as part of the cranial nerve  
74 function assessment. The gait variable was based on the examining physician’s assessment of the  
75 participant’s gait. An abnormal gait included conditions such as broad-based, small-stepped, ataxic, or  
76 other irregular gait patterns. A CNS index was constructed and based on a composite variable of tremor,  
77 coordination, and gait. This index was coded as normal if all three of the components were normal and  
78 abnormal if otherwise.

79 The following journal article on polyneuropathy in AFHS veterans was written by AFHS staff and their  
80 colleagues:

- 81 • Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand (8).

82 This article is discussed later in this chapter.

83 In the 1996 Institute of Medicine (IOM) *Veterans and Agent Orange* update (9), the committee concluded  
84 that there is “limited/suggestive” evidence of an association between exposure to certain herbicides used  
85 in Vietnam and the development of an acute or subacute transient peripheral neuropathy. This conclusion  
86 remained unaltered in the 2002 and 2004 IOM *Veterans and Agent Orange* update (10, 11). The evidence  
87 regarding the association between exposure to dioxin and disorders involving persistent peripheral  
88 neuropathy, or motor or coordination deficits, was considered inadequate or insufficient (10, 11).

89 In the 1994 *Veterans and Agent Orange* report (12), the IOM concluded that there was inadequate or  
90 insufficient evidence to determine whether an association existed between dioxin and motor coordination  
91 problems. This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (11).

92 A persisting concern exists about the role of herbicides and pesticides in the pathogenesis of Parkinson’s  
93 disease. The relation between pesticide exposure and Parkinson’s disease was evaluated in the 1996,  
94 1998, 2000, 2002, and 2004 *Veterans and Agent Orange* update (9-11, 13-14). Some indication of an  
95 association between Parkinson’s disease and herbicides and pesticides was seen based on a review of 30  
96 epidemiologic studies, most of which were case-control studies focusing on occupational exposure. An  
97 association of Parkinson’s disease with exposure to dioxin, however, was not reported in any of these  
98 studies. Therefore, the 2002 IOM committee considered the evidence for an association of Parkinson’s  
99 disease with exposure to dioxin to be inadequate or insufficient (10), and this conclusion was unchanged  
100 in the 2004 *Veterans and Agent Orange* update (11).

### 101 **15.1.1 Chapter Structure**

102 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
103 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
104 demographic factors. Statistically significant results ( $p$ -value of 0.05 or less) are emphasized. Significant  
105 results that appeared consistently across examinations or have biological meaning are emphasized,  
106 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
107 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
108 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
109 the parameter and either group or dioxin are not discussed.

110 The results discussed below that were discovered as part of further analysis based on a statistical  
111 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
112 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
113 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
114 baseline examination. Older participants were defined as those born before 1942.

115 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
116 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
117 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
118 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
119 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
120 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at  
121 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
122 stratification based on the participant’s tour of duty is given in Chapter 2.

123 The following chart lists the variables that were analyzed for the neurology assessment and at which  
 124 physical examination they were analyzed. The variables appearing in bold type are discussed  
 125 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Achilles Reflex</b>	X	X	X	X	X	X	X
Babinski Reflex	X	X	X	X	X	X	X
<b>Balance/Romberg Sign</b>	X	X	X	X	X	X	X
Biceps Reflex	X	X	X	X	X	X	X
<b>CNS Index</b>		X	X	X	X	X	X
Conduction Velocity – Distal Ulnar	X						
Conduction Velocity – Peroneal	X						
Conduction Velocity – Proximal Ulnar	X						
<b>Confirmed Polyneuropathy Index</b>						X	
<b>Coordination</b>	X	X	X	X	X	X	X
Corneal Reflex	X	X	X	X	X	X	X
<b>Cranial Nerve Index</b>		X	X	X	X	X	X
Disorders of the Ear	X	X	X				
Disorders of the Eye	X	X	X	X			
<b>Facial Sensation</b>	X	X	X	X	X	X	X
Gag Reflex	X	X	X	X	X	X	X
<b>Gait</b>	X	X	X	X	X	X	X
Hearing Loss				X			
<b>Hereditary and Degenerative Neurological Disease</b>	X	X	X	X	X	X	X
<b>Inflammatory Neurological Disease</b>	X	X	X	X	X	X	X
Jaw Clench	X	X	X	X	X	X	X
Light Reaction	X	X	X	X	X	X	X
Light Touch	X	X	X	X	X	X	X
<b>Multiple Polyneuropathy Index</b>						X	
<b>Muscle Status</b>	X	X	X	X	X	X	X
<b>Neck Range of Motion</b>	X	X	X	X	X	X	
Ocular Movement	X	X	X	X	X	X	X
<b>Other Neurological Disorders</b>		X	X	X	X	X	X
Otitis				X			
Palate and Uvula Movement	X	X	X	X	X	X	X
Palpebral Fissure	X	X	X	X	X	X	X
<b>Patellar Reflex</b>	X	X	X	X	X	X	X
<b>Peripheral Disorders</b>	X	X	X	X	X	X	X
<b>Pinprick</b>	X	X	X	X	X	X	X
<b>Polyneuropathy Prevalence Indicator</b>						X	X
<b>Polyneuropathy Severity Index</b>						X	
Possible Peripheral Neuropathy							X
Probable Peripheral Neuropathy							X
Shoulder Shrug							X
<b>Smell</b>	X	X	X	X	X	X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Smile	X	X	X	X	X	X	X
Speech	X	X	X	X	X	X	X
Tongue Position Relative to Midline	X	X	X	X	X	X	X
<b>Tremor</b>	X	X	X	X	X	X	X
Tympanic Membrane Disorder				X			
Vibration	X	X	X	X			
<b>Vibrotactile Threshold Measurement of Great Toes</b>					X		
<b>Visual Fields</b>	X	X	X	X	X	X	X

126 **15.2 HEREDITARY AND DEGENERATIVE NEUROLOGICAL DISEASE**

127 Based on data collected at the 2002 follow-up examination, more Ranch Hand officers than Comparison  
128 officers had hereditary and degenerative disorders after service in Southeast Asia (SEA).

129 **15.3 INFLAMMATORY NEUROLOGICAL DISEASE**

130 Based on data collected at the 1997 follow-up examination, more Ranch Hands than Comparisons had  
131 inflammatory diseases after service in SEA. The prevalence of inflammatory diseases also was increased  
132 in the background, low, and high dioxin categories. The increase in Ranch Hands was due to seven  
133 Ranch Hands and one Comparison who have had an inflammatory disease since service in SEA. Further  
134 review of these diseases revealed that three of the seven Ranch Hands had meningitis caused by bacterial  
135 infection. The Comparison had encephalitis of unknown cause. This review suggested that this finding  
136 was unrelated to herbicide or dioxin exposure. At the 2002 follow-up examination, nine Ranch Hands  
137 and seven Comparisons were verified to have had an inflammatory disease since service in SEA, but no  
138 differences between the two groups were detected.

139 **15.4 PERIPHERAL DISORDERS**

140 At the 1992 follow-up examination, among moderate lifetime drinkers (>0-40 drink-years), the  
141 prevalence of peripheral disorders after service in SEA increased with increasing levels of 1987 dioxin.  
142 The same relation between peripheral disorders and 1987 dioxin was seen in 1997 for all Ranch Hands.

143 **15.5 OTHER NEUROLOGICAL DISORDERS**

144 The majority of other neurological disorders were unspecified encephalopathies, but conditions such as  
145 multiple sclerosis and other demyelinating diseases of the CNS, hemiplegia, other paralytic syndromes,  
146 epilepsy, migraine, catalepsy or narcolepsy, other conditions of the brain, and other unspecified disorders  
147 of the CNS were included.

148 Based on data collected at the 1987 follow-up examination, as 1987 dioxin increased in Ranch Hands  
149 with later tours of duty, the prevalence of other neurological disorders after service in SEA increased.  
150 This pattern also was seen between initial dioxin and other neurological disorders after service in SEA.

151 **15.6 CRANIAL NERVE FUNCTION**

152 **15.6.1 Balance/Romberg Sign**

153 The prevalence of an abnormal balance determination in Ranch Hands at the 2002 follow-up examination  
154 increased as initial dioxin increased.

155 **15.6.2 Facial Sensation**

156 More Ranch Hands in the low dioxin category had an abnormal facial sensation at the 2002 follow-up  
157 examination than Comparisons.

158 **15.6.3 Smell**

159 Among participants who did not report exposure to insecticides, more Ranch Hand participants in the low  
160 dioxin category had an abnormal sense of smell at the 1992 follow-up examination than Comparisons.

161 **15.6.4 Visual Fields**

162 Among Ranch Hands who participated in the 1997 follow-up examination, the prevalence of abnormal  
163 visual fields increased as initial dioxin levels increased. At the 2002 follow-up examination, more Ranch  
164 Hands than Comparisons had abnormal visual fields. In particular, the increase appeared to be for Ranch  
165 Hands with background dioxin levels relative to Comparisons.

166 **15.6.5 Neck Range of Motion**

167 The prevalence of a neck range of motion abnormality at the 1987 follow-up examination increased for  
168 Ranch Hand diabetics (2-hour postprandial glucose  $\geq 200$  mg/dL or previously diagnosed as diabetic by a  
169 physician) as initial dioxin increased. Ranch Hands with earlier tours of duty showed an increase in neck  
170 range of motion abnormalities as 1987 dioxin levels increased.

171 The prevalence of a neck range of motion abnormality was increased for Ranch Hands at the 1997 follow-  
172 up examination. This pattern was seen when all participants were analyzed and when analyses were  
173 restricted to enlisted flyers. The increase also was observed in the low and high Ranch Hand dioxin  
174 categories relative to Comparisons.

175 **15.6.6 Cranial Nerve Index**

176 The results for the cranial nerve index at the 1987 follow-up examination were similar to neck range of  
177 motion. Neck range of motion abnormalities were included in the definition of the cranial nerve index for  
178 analysis at this examination and were the primary source of abnormalities for this index.

179 Analysis of 1987 follow-up examination data also was done without including neck range of motion in  
180 the definition of the cranial nerve index. Ranch Hands who did not report exposure to insecticides had  
181 more abnormalities on the index without including neck range of motion than Comparisons who did not  
182 report exposure to insecticides. When categorizing Ranch Hands according to dioxin levels, these  
183 differences between Ranch Hands and Comparisons were seen primarily in the low Ranch Hand dioxin  
184 category.

185 Analyses without including neck range of motion in the definition of the cranial nerve index also were  
186 performed for the 1992 follow-up examination. The prevalence of an abnormal index in Ranch Hands

187 with normal glucose levels (2-hour postprandial glucose < 140 mg/dL) increased as initial dioxin levels  
188 increased. In addition, Ranch Hand enlisted groundcrew had a higher prevalence of abnormalities than  
189 Comparison enlisted groundcrew; this increase in Ranch Hands was seen in the background and high  
190 dioxin categories.

191 Analysis for the cranial nerve index was done for the 2002 follow-up examination without considering  
192 neck range of motion. Ranch Hands showed a higher prevalence of an abnormal index than Comparisons,  
193 as did Ranch Hands in the background and low dioxin categories.

## 194 **15.7 PERIPHERAL NERVE STATUS**

### 195 **15.7.1 Muscle Status**

196 More Ranch Hand enlisted groundcrew than Comparison enlisted groundcrew had an abnormal muscle  
197 status at the 1997 follow-up examination.

### 198 **15.7.2 Pinprick**

199 Pinprick was considered normal if the reaction was normal on both feet and abnormal if the reaction was  
200 abnormal on either foot. At the 1987 follow-up examination for Ranch Hands with earlier tours of duty,  
201 the prevalence of an abnormal reaction to pinprick increased as 1987 dioxin increased. For Ranch Hands  
202 who were considered diabetic (2-hour postprandial glucose  $\geq$  200 mg/dL or previously diagnosed as  
203 diabetic by a physician), the prevalence of an abnormal reaction to pinprick at the 1992 follow-up  
204 examination increased as 1987 dioxin increased. At the 2002 follow-up examination, Ranch Hands in the  
205 high dioxin category had an increased abnormal reaction to pinprick.

### 206 **15.7.3 Achilles Reflex**

207 The classification of the status of the Achilles reflex was divided into three categories: absent, sluggish,  
208 and active or very active. The categories of active and very active were combined because of the sparse  
209 number of participants with very active Achilles reflexes. When the assessments of the Achilles reflex  
210 were different between the left and right body side, the more severe condition was assigned.

211 A greater prevalence of Ranch Hand nondrinkers in the high dioxin category had an absent Achilles  
212 reflex at the 1992 follow-up examination than Comparison nondrinkers. At the 2002 follow-up  
213 examination, Ranch Hand officers had an absent or sluggish Achilles reflex more often than Comparison  
214 officers.

### 215 **15.7.4 Patellar Reflex**

216 The classification of the status of the patellar reflex was divided into three categories: absent, sluggish,  
217 and active or very active. The categories of active and very active were combined because of the sparse  
218 number of participants with very active patellar reflexes. When the assessments of the patellar reflex  
219 were different between the left and right body side, the more severe condition was assigned.

220 The prevalence of Ranch Hands with an absent patellar reflex at the 1997 follow-up examination  
221 increased as initial dioxin levels increased. The percentage of participants with an absent patellar reflex  
222 at the 2002 follow-up examination was increased in Ranch Hands in the high dioxin category. As 1987  
223 dioxin increased, the prevalence of Ranch Hands with an absent patellar reflex at both the 1992 and 2002  
224 follow-up examinations increased.

225 **15.8 POLYNEUROPATHY**

226 For the 1997 follow-up examination, three indices to assess polyneuropathy were based on a severity  
227 index. These indices assessed bilateral abnormalities and were considered abnormal only if both the left  
228 and right determinations were abnormal. These indices were based on the following seven conditions or  
229 sets of conditions:

- 230 • Both left and right ankle and toe flexors were abnormal (no=0, yes=1)
- 231 • The Romberg sign (equilibratory) was abnormal (no=0, yes=1)
- 232 • Both left and right Achilles reflexes were absent (no=0, yes=1)
- 233 • Reaction to a light touch was abnormal on both the left and right feet (no=0, yes=1)
- 234 • Reaction to a pinprick was abnormal on both the left and right feet (no=0, yes=1)
- 235 • Both left and right ankle vibrations were abnormal (no=0, yes=1)
- 236 • The position of both the left and right great toe was abnormal (no=0, yes=1).

237 A polyneuropathy severity index, which ranged from 0 to 7, was constructed as the sum of the above  
238 seven scores. The polyneuropathy severity index was classified as mild (index = 0, 1, or 2), moderate  
239 (index = 3 or 4), or severe (index = 5, 6, or 7). A second index, termed a polyneuropathy prevalence  
240 indicator, was coded as abnormal if the polyneuropathy severity index was at least 1 and normal if the  
241 polyneuropathy severity index was 0. A third index, termed a multiple polyneuropathy index, was coded  
242 as “abnormal” if the polyneuropathy severity index was at least 2 and “normal” if the polyneuropathy  
243 severity index was 0 or 1.

244 In addition, a confirmed polyneuropathy index was constructed as follows:

245 If at least two of the following three conditions held,

- 246 • Both left and right Achilles reflexes were absent
- 247 • Reaction to a pinprick was abnormal on both the left and right feet
- 248 • Both left and right ankle vibrations were abnormal

249 and the minimum of the left and right toe averages (in log microns) was greater than 4.02, the confirmed  
250 polyneuropathy index was coded as abnormal. If the minimum vibrotactile measurement was less than or  
251 equal to 4.02, or no more than one of the above conditions was present, the confirmed polyneuropathy  
252 index was coded as normal. The value of 4.02 was determined by taking the minimum value of the left  
253 and right great toe average for each participant and using the 90<sup>th</sup> percentile of the minimum values for  
254 Comparisons.

255 Associations between these indices and dioxin that were found based on the 1997 follow-up examination  
256 data are described below.

257 **15.8.1 Vibrotactile Threshold Measurement of the Great Toes**

258 A vibrotactile measurement was performed as part of a collaborative effort with the National Institute of  
259 Dental and Craniofacial Research at the 1992 and 1997 follow-up examinations. A Vibratron II<sup>®</sup> device  
260 was used to measure vibrotactile threshold on both the left and right great toes. The Vibratron II<sup>®</sup>  
261 provided a noninvasive means of measuring the sensitivity to vibration of a participant’s feet. The left  
262 and right great toes were analyzed separately. For each great toe, the average (in log microns) of four of

263 seven trials was determined. The four trials were those remaining after eliminating the results of the first  
264 of the seven trials and the high and low readings of the other six results following a method-of-limits  
265 protocol (15).

266 Among Ranch Hands exposed to heavy metals, the vibrotactile threshold level of the left and right great  
267 toes at the 1992 follow-up examination increased as initial dioxin increased. For Ranch Hands whose  
268 glucose levels were considered impaired ( $140 \text{ mg/dL} \leq 2\text{-hour postprandial glucose} < 200 \text{ mg/dL}$ ), the  
269 vibrotactile threshold level of the left great toe increased as initial dioxin increased. Ranch Hands in the  
270 background dioxin category who were heavy drinkers (>40 lifetime drink-years) had a greater average  
271 vibrotactile threshold measurement of the right great toe than Comparisons who were heavy drinkers.  
272 Ranch Hands in the high dioxin category who were nondrinkers had a greater average vibrotactile  
273 threshold measurement of the right great toe than Comparisons who were nondrinkers. For Ranch Hands  
274 who worked with heavy metals, the vibrotactile threshold level of the right great toe increased as 1987  
275 dioxin levels increased. For Ranch Hands who worked with vibrating power equipment or tools, the  
276 vibrotactile threshold level of the left great toe increased as 1987 dioxin levels increased.

### 277 **15.8.2 Polyneuropathy Severity Index**

278 The prevalence of a moderate polyneuropathy severity index at the 1997 follow-up examination was  
279 increased for Ranch Hands. Among Ranch Hands, the prevalence of a moderate polyneuropathy severity  
280 index at this examination increased with increasing initial dioxin and 1987 dioxin, and was increased for  
281 Ranch Hands in the high dioxin category.

### 282 **15.8.3 Polyneuropathy Prevalence Indicator**

283 The prevalence of an abnormal polyneuropathy prevalence indicator at the 1997 follow-up examination  
284 increased with increasing initial dioxin in Ranch Hands.

### 285 **15.8.4 Multiple Polyneuropathy Index**

286 The prevalence of an abnormal multiple polyneuropathy index at the 1997 follow-up examination  
287 increased with increasing initial dioxin in Ranch Hands. Ranch Hands in the high dioxin category also  
288 had an increased prevalence of polyneuropathy based on this index.

### 289 **15.8.5 Confirmed Polyneuropathy Index**

290 The prevalence of confirmed polyneuropathy, according to this index, at the 1997 follow-up examination  
291 increased with increasing initial dioxin in Ranch Hands. Ranch Hands in the high dioxin category also  
292 had an increased prevalence of confirmed polyneuropathy using this index.

### 293 **15.8.6 Serum Dioxin and Peripheral Neuropathy in Veterans of Operation Ranch Hand**

294 In a 2001 journal article, Michalek and colleagues (8) performed additional analysis on the study of  
295 polyneuropathy in AFHS veterans. Four indices to assess polyneuropathy were used:

- 296 • Any symmetrical peripheral abnormality
- 297 • Possible symmetric peripheral neuropathy
- 298 • Probable symmetric peripheral neuropathy
- 299 • Diagnosed peripheral neuropathy.

300 Any symmetrical peripheral abnormality was equivalent to the polyneuropathy prevalence indicator  
301 defined in Section 15.8 and described in Section 15.8.3. Diagnosed peripheral neuropathy was equivalent  
302 to the confirmed polyneuropathy index defined in Section 15.8 and described in Section 15.8.5. Possible  
303 symmetric peripheral neuropathy and probable symmetric peripheral neuropathy dealt with three  
304 outcomes first described in Section 15.8; that is,

- 305 • Both left and right Achilles reflexes were absent
- 306 • Reaction to a pinprick was abnormal on both the left and right feet
- 307 • Both left and right ankle vibrations were abnormal.

308 Possible symmetric peripheral neuropathy was defined to be present if at least one of the above three  
309 conditions held. Probable symmetric peripheral neuropathy was defined as present if at least two of the  
310 above three conditions held.

311 Data from the 1982, 1985, 1987, 1992, and 1997 examinations were analyzed using the categorized  
312 dioxin model described in Section 2.4.2. This model categorized Ranch Hands and Comparisons  
313 according to their estimated initial and 1987 dioxin levels into four categories: Comparisons, background  
314 Ranch Hands (1987 dioxin levels at or below 10 ppt), low Ranch Hands (1987 dioxin level greater than  
315 10 ppt, initial dioxin level  $\leq$  94 ppt), and high Ranch Hands (1987 dioxin level greater than 10 ppt, initial  
316 dioxin level  $>$  94 ppt).

317 The analysis of diagnosed peripheral neuropathy was restricted to data from the 1992 follow-up  
318 examination and the 1997 follow-up examination because vibrotactile threshold data were collected only  
319 at these examinations. Nerve conduction velocities, measured at the 1982 baseline examination, also  
320 were analyzed, but no associations with dioxin were found. The analysis of bilateral vibrotactile  
321 abnormalities also showed no relations with dioxin.

322 A consistent increased risk of all indices of peripheral neuropathy among Ranch Hand veterans in the  
323 high dioxin category at the 1997 follow-up examination was found. An increased risk of diagnosed  
324 peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, in Ranch Hand  
325 veterans in the high dioxin category at the 1992 follow-up examination also was seen. Restricting the  
326 analysis to the enlisted veterans did not alter these results. The authors stressed that cautious  
327 interpretation of these results was appropriate until the relationship between pre-clinical diabetes mellitus  
328 and peripheral neuropathy had been further evaluated.

329 The first three indicators of polyneuropathy described above—any symmetrical peripheral abnormality,  
330 possible symmetric peripheral neuropathy, and probable symmetric peripheral neuropathy—were  
331 evaluated for participants who attended the 2002 physical examination (7). No associations between  
332 dioxin and these indicators were observed.

## 333 **15.9 CENTRAL NERVOUS SYSTEM (CNS) COORDINATION PROCESSES**

### 334 **15.9.1 Coordination**

335 Coordination was a composite index defined as normal if the Romberg sign, finger-nose-finger and heel-  
336 knee-shin coordination processes, rapidly alternating movements of pronation and supination of hands,  
337 and rapid patting were normal. Ranch Hands had a higher prevalence of a coordination abnormality at  
338 the 1987 follow-up examination than Comparisons. Further analysis on subsets of these participants  
339 showed that the increase was in Ranch Hand enlisted groundcrew who did report exposure to insecticides.

340 Ranch Hands in the high dioxin category had a higher prevalence of a coordination abnormality than  
341 Comparisons. In particular, the increase was most pronounced in older Ranch Hands and Comparisons.  
342 As 1987 dioxin in Ranch Hands with later tours of duty increased, the prevalence of a coordination  
343 abnormality at the 1987 follow-up examination increased. The prevalence of an abnormal coordination at  
344 the 2002 follow-up examination increased as initial dioxin increased.

### 345 **15.9.2 Gait**

346 The gait variable was based on the examining physician's assessment of the participant's gait. An  
347 abnormal gait included conditions such as broad-based, small-stepped, ataxic, or other irregular gait  
348 patterns. The prevalence of an abnormal gait at the 1992 follow-up examination among older Ranch  
349 Hands increased as initial dioxin increased.

### 350 **15.9.3 Tremor**

351 Tremor was examined for the left and right upper and lower extremities. Abnormal tremors included  
352 resting, essential, intention, and other tremors. As 1987 dioxin in older Ranch Hands with later tours of  
353 duty increased, the prevalence of an abnormal tremor at the 1987 follow-up examination increased.

### 354 **15.9.4 CNS Index**

355 A CNS index was constructed and based on a composite variable of tremor, coordination, and gait. This  
356 index was coded as normal if all three of the components were normal and abnormal if otherwise. Ranch  
357 Hands had more abnormalities of the CNS index at the 1985 follow-up examination than Comparisons.  
358 At the 1987 follow-up examination, the prevalence of an abnormal CNS index in Ranch Hands increased  
359 as initial dioxin increased, primarily among older Ranch Hands. As 1987 dioxin in Ranch Hands with  
360 later tours of duty increased, the prevalence of a CNS index abnormality at the 1987 follow-up  
361 examination increased.

## 362 **15.10 CONCLUSION**

363 Increased risk of peripheral neuropathy has been somewhat indicated in those personnel with the highest  
364 levels of dioxin. Some indication for an association with probable peripheral neuropathy was found in  
365 the 1985, 1992, and 1997 follow-up examinations. Although a dose-response pattern was somewhat  
366 inconsistent in those years, the highest risk was observed in the group with the highest dioxin levels, most  
367 notably in the 1997 follow-up examination.

368 In a 2001 journal article, Michalek and colleagues (8) performed additional analysis on the study of  
369 polyneuropathy in AFHS veterans. A consistent increased risk of all indices of peripheral neuropathy  
370 among Ranch Hand veterans in the high dioxin category at the 1997 follow-up examination was found.  
371 An increased risk of diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of  
372 the great toes, in Ranch Hand veterans in the high dioxin category at the 1992 follow-up examination also  
373 was seen. The authors stressed that cautious interpretation of these results was appropriate until the  
374 relationship between pre-clinical diabetes mellitus and peripheral neuropathy had been further evaluated.

375 In the 2002 follow-up examination, Ranch Hands in the high dioxin category had an increased risk for an  
376 abnormal pinprick examination and an absent patellar reflex. The risk of an absent patellar reflex  
377 increased as the 1987 dioxin level increased. The composite indices for assessing neuropathy, however,  
378 were weak and did not show the same associations that were present in the analysis of 1997 follow-up  
379 examination data.

380 Based on the results of the analysis of pinprick, balance, and the patellar reflex in the 2002 follow-up  
381 examination, there was some limited support of an association between dioxin levels and neurological  
382 disease related to the peripheral nerves. No consistent associations or clinical evidence, however, to  
383 support a relation between dioxin and cranial nerve function or other CNS processes appeared.

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## 16 PSYCHOLOGY ASSESSMENT

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### 16.1 INTRODUCTION

A wide array of psychological abnormalities or impairments has been attributed or alleged to occur following exposure to chlorophenols, phenoxy herbicides, and dioxin. Many Southeast Asia (SEA) veterans have expressed concern that exposure to herbicides has caused psychological and behavioral problems, as reflected by the Veterans Health Administration's Agent Orange Registry (1). Emotional illnesses or psychological abnormalities, however, are not recognized in the scientific community as primary clinical endpoints following exposure to chlorophenols, phenoxy herbicides, and dioxin. "Neurobehavioral effects" occasionally ascribed to such exposures have been, in fact, predominantly neurological symptoms for which causation is not disputed. Higher central nervous system functioning, in terms of cognitive skills and reactivity, may be temporarily or permanently impaired depending on the exposure and the ability to measure accurately the psychological changes.

Analyses were performed to assess the psychological function of Air Force Health Study (AFHS) participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (2-9). The psychology assessment was based on the Cornell Index and the Minnesota Multiphasic Personality Inventory (MMPI) in 1982 and the Cornell Medical Index (CMI) and the MMPI in 1985. Data from the Millon Clinical Multiaxial Inventory (MCMI) were analyzed for the 1987 follow-up examination report. The Symptom Checklist-90-Revised (SCL-90-R) was used at the 1987, 1992, 1997, and 2002 follow-up examinations. Central nervous system functional testing was accomplished using a modified Halstead-Reitan Battery in 1982 and 1985. Intelligence was measured by the Wechsler Adult Intelligence Scale in 1982 and reading skills were tested by the reading subtest of the Wide Range Achievement Test in 1982. Memory was tested by the Wechsler Memory Scale-Version 1 at the 1982 baseline examination and the Wechsler Memory Scale-Revised at the 2002 follow-up examination. Short descriptions of the Cornell Index, the CMI, the MCMI, the MMPI, and the SCL-90-R are provided in subsequent sections of this chapter.

The questionnaire captured data on the occurrence of mental or emotional disorders at each of the six AFHS examinations. Medical record reviews confirmed reported conditions and identified any unreported conditions for each participant. As a result, psychological disorders were classified into five categories: psychoses, alcohol dependence, drug dependence, anxiety, and other neuroses. In addition to this verified history of psychological disorders, self-reported responses to questions assessing anger, anxiety, fatigue, and isolation were analyzed for the 1982 baseline examination. Responses to a series of questions on 12 types of sleep problems were analyzed for the 1987 follow-up examination.

In addition to the eight reports (2-9), two journal articles were published based on the psychological data collected at the AFHS examinations. One article,

- Serum dioxin and psychological functioning in U.S. Air Force veterans of the Vietnam War (10),

related dioxin levels to data collected from the MMPI in 1982 and 1985 and from the MCMI in 1987 and 1992.

38 The other article,

- 39 • Serum dioxin and cognitive functioning in veterans of Operation Ranch Hand (11),  
40 related dioxin to cognitive function measures from the Halstead-Reitan Battery, the Wechsler Adult  
41 Intelligence Scale, and the Wechsler Memory Scale.

42 In the Institute of Medicine (IOM) 2004 *Veterans and Agent Orange* update (12), the committee  
43 concluded that there is “inadequate or insufficient” evidence of an association between exposure to  
44 certain herbicides used in Vietnam and cognitive or neuropsychiatric disorders.

### 45 **16.1.1 Chapter Structure**

46 This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where  
47 possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and  
48 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
49 results that appeared consistently across examinations or have biological meaning are emphasized,  
50 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
51 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
52 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
53 the parameter and either group or dioxin are not discussed.

54 The results discussed below that were discovered as part of further analysis based on a statistical  
55 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
56 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
57 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
58 baseline examination. Older participants were defined as those born before 1942.

59 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
60 Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987  
61 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
62 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
63 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
64 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at  
65 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
66 stratification based on the participant’s tour of duty is given in Chapter 2.

67 The following chart lists the variables that were analyzed for the psychology assessment and at which  
68 physical examination they were analyzed. The variables appearing in bold type are discussed  
69 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>Alcohol Dependence</b>	X	X	X	X	X	X	X
Anxiety	X	X	X	X	X	X	X
<b>Cornell Index (Overall and 10 Scales):</b>	X						
<b>Cornell Medical Index (3 Scores)</b>		X					
Drug Dependence			X	X	X	X	X
Halstead-Reitan Battery Impairment Index	X	X					

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>MCMI (20 Scales)</b>			X	X			
<b>MMPI (14 Scales)</b>	X	X					
<b>Other Neuroses</b>	X	X	X	X	X	X	X
Psychoses	X	X	X	X	X	X	X
<b>Questionnaire Indices (Anger, Anxiety, Depression [Severity], Erosion, Fatigue, Isolation)</b>	X						
<b>SCL-90-R (12 Scales)</b>			X	X	X	X	X
<i>Sleep Disorders:</i>							
Abnormal Movement/Activity During the Night			X	X			
<b>Average Sleep Each Night</b>			X	X			
<b>Frightening Dreams</b>			X	X			
Great or Disabling Fatigue During the Day			X	X			
Insomnia			X	X			
Involuntarily Falling Asleep During the Day			X	X			
Overall Sleep Disorder Index			X	X			
Sleep Problems Requiring Medication			X	X			
Sleepwalking			X	X			
Snore Loudly in All Sleeping Positions			X	X			
Talking in Sleep			X	X			
Trouble Falling Asleep			X	X			
Waking Up During the Night			X	X			
Waking Up Too Early and Can't Go Back to Sleep			X	X			
Waking Up Unrefreshed			X	X			
Wechsler Adult Intelligence Scale (Verbal, Performance, and Full Scale)	X						
WMS-R Memory Tests (5 Scores)							X

70 **16.2 ALCOHOL DEPENDENCE**

71 As of the 1992 follow-up examination, married enlisted groundcrew Ranch Hands showed a higher  
72 prevalence of alcohol dependence after service in SEA than married enlisted groundcrew Comparisons.

73 **16.3 OTHER NEUROSES**

74 At the health interview during the six AFHS examinations, each participant was asked whether he had a  
75 mental or emotional disorder since the date of his last interview. The category of disorders named “other  
76 neuroses” included the following conditions:

- 77 • Neurotic disorders, comprising hysteria, phobic disorders, obsessive-compulsive disorders,  
78 neurotic depression, neurasthenia, hypochondriasis, other neurotic disorders, and unspecified  
79 neurotic disorders
- 80 • Personality disorders

- 81 • Sexual deviations and disorders
- 82 • Nondependent abuse of drugs
- 83 • Physiological malfunction arising from mental factors
- 84 • Special symptoms or syndromes not elsewhere classified
- 85 • Acute reaction to stress
- 86 • Adjustment reaction
- 87 • Depressive disorder not elsewhere classified.

88 Based on data at the 1987 follow-up examination, Ranch Hands in the low dioxin category exhibited a  
89 higher prevalence of other neuroses than Comparisons after service in SEA.

90 Among enlisted groundcrew personnel, participants with at most a high school education, and participants  
91 in higher income households, Ranch Hands showed a higher prevalence of other neuroses at the 1992  
92 follow-up examination than Comparisons after service in SEA. Among participants with at most a high  
93 school education, Ranch Hands in the background and low dioxin categories also showed a higher  
94 prevalence of other neuroses than Comparisons after service in SEA. Among participants in higher  
95 income households, Ranch Hands in the high dioxin category showed a greater prevalence of other  
96 neuroses than Comparisons after service in SEA.

97 Based on data collected at the 1997 follow-up examination, Ranch Hand enlisted groundcrew had a  
98 higher prevalence of other neuroses than Comparison enlisted groundcrew after service in SEA. Ranch  
99 Hands in the low dioxin category also exhibited a higher prevalence of other neuroses than Comparisons  
100 after service in SEA. Based on data collected at the 1997 follow-up examination, further analysis of other  
101 neuroses by the individual categories provided above showed no predominance of any one category (8).

#### 102 **16.4 ANGER, ANXIETY, FATIGUE, AND ISOLATION**

103 Questionnaire response from the 1982 baseline examination concerning anger, anxiety, fatigue, and  
104 isolation showed higher levels of these parameters for Ranch Hands than Comparisons in participants  
105 with at most a high school education, but not in participants with a college education.

#### 106 **16.5 SLEEP PROBLEMS**

107 Each participant was asked a series of questions on whether he had a current or past problem with 12  
108 different sleep disorders (13). Associations between frightening dreams and average sleep each night and  
109 dioxin were observed at the 1987 follow-up examination and are discussed below.

110 Based on data collected at the 1987 follow-up examination, Ranch Hands in the high dioxin category had  
111 a greater prevalence of past or present problems with frightening dreams. In addition, as 1987 dioxin  
112 increased for Ranch Hands with later tours of duty, the prevalence of past or present problems with  
113 frightening dreams increased.

114 Based on information reported by participants at the 1987 follow-up examination, the average number of  
115 hours of sleep each night decreased as 1987 dioxin increased among Black participants with earlier tours  
116 of duty.

117 **16.6 CORNELL INDEX**

118 The Cornell Index (14) was a subjective 10- to 15-minute self-administered inventory of neuropsychiatric  
119 symptoms and complaints given only at the 1982 baseline examination. Among those participants with at  
120 most a high school education, Ranch Hands had a greater (adverse effect) average total Cornell index  
121 score than Comparisons.

122 **16.7 CORNELL MEDICAL INDEX (CMI)**

123 The CMI (15) was a self-administered instrument used only at the 1985 follow-up examination to collect  
124 a substantial amount of medical and psychiatric data. The 195 questions of the CMI were partitioned into  
125 18 sections (A-R), with the number of questions within a section ranging from 6 to 23. Three scores were  
126 derived from the CMI: the total CMI score, an A-H area subscore, and an M-R subscore. The A-H  
127 subscore was a measure of the scatter of complaints, indicating a diffuse medical problem, although other  
128 interpretations were possible. The M-R subscore, which deals with mood and feeling patterns, was a  
129 useful indicator of emotional ill health. The total CMI score was the number of affirmative responses on  
130 the entire CMI questionnaire.

131 Ranch Hands had a higher (adverse effect) average A-H area subscore than Comparisons. Among those  
132 participants with at most a high school education, Ranch Hands had a higher average total CMI score than  
133 Comparisons.

134 **16.8 MILLON CLINICAL MULTIAXIAL INVENTORY (MCMI)**

135 The MCMI (16), a self-administered test comprising 175 items and divided into 20 scales, was used only  
136 at the 1987 AFHS follow-up examination. Each of its 20 scales was constructed as an operational  
137 measure of a syndrome derived from a theory of personality and psychopathology. The MCMI was not  
138 designed to be a general personality instrument to be used for “normal” populations or for purposes other  
139 than diagnostic screening or clinical assessment. The 20 scales were organized into three broad  
140 categories to reflect distinctions between basic personality patterns, pathological personality disorders,  
141 and clinical symptom syndromes. Many of these scales were directly or indirectly correlated. Higher  
142 MCMI scores represented an adverse effect. All results provided in Sections 16.8.1 through 16.8.17 are  
143 based on data reported from the 1987 follow-up examination.

144 Eight scales from the MCMI focused on everyday ways of functioning that characterized participants  
145 even when they were not suffering acute symptom states. These eight scales are antisocial (aggressive),  
146 avoidant, compulsive (conforming), dependent (submissive), histrionic (gregarious), narcissistic, passive-  
147 aggressive (negativistic), and schizoid (asocial), all of which are discussed in Sections 16.8.1 through  
148 16.8.8.

149 Three MCMI scales described patients who clearly evidence chronic or periodically severe pathology in  
150 the overall structure of personality. These scales are borderline (cycloid), paranoid, and schizotypal  
151 (schizoid), all of which are discussed in Sections 16.8.9 through 16.8.11.

152 Nine scales from the MCMI measured reactive disorders, often precipitated by external events, that are of  
153 substantially briefer duration than the personality disorders. Six scales—alcohol abuse, anxiety, drug  
154 abuse, dysthymic, hypomanic, and somatoform—represented disorders of moderate severity. Except for  
155 drug abuse, where no adverse effects to Ranch Hands were found, the other five scales are discussed  
156 below in Sections 16.8.12 through 16.8.16. The other three scales—psychotic delusions, psychotic  
157 depression, and psychotic thinking—reflected disorders of marked severity. The psychotic depression

158 score is discussed below in Section 16.8.17. No adverse effects to Ranch Hands were found for psychotic  
159 delusions and psychotic thinking.

160 A summary of a journal article published in 2003 (10) that relates the MCMI results to dioxin levels is  
161 provided in Section 16.8.18.

### 162 **16.8.1 Antisocial**

163 Ranch Hands in the background dioxin category who were heavy drinkers (more than four drinks per day)  
164 had a higher average MCMI antisocial score than Comparisons who were heavy drinkers. In addition,  
165 Ranch Hands in the low dioxin category who were light drinkers (no more than one drink per day) had a  
166 higher average MCMI antisocial score than Comparisons who were light drinkers.

### 167 **16.8.2 Avoidant**

168 The MCMI avoidant score increased as initial dioxin increased. This relation between the MCMI  
169 avoidant score and initial dioxin was present when all Ranch Hands were examined and when analysis  
170 was restricted to college-educated Ranch Hands. In addition to the relation with initial dioxin, an  
171 association between the MCMI avoidant score and 1987 dioxin levels was observed in Ranch Hands with  
172 earlier tours of duty.

### 173 **16.8.3 Compulsive**

174 For participants who were heavy drinkers, Ranch Hands had a higher average MCMI compulsive score  
175 than Comparisons.

### 176 **16.8.4 Dependent**

177 The MCMI dependent score in Ranch Hands increased as initial dioxin increased and as 1987 dioxin  
178 levels increased in Ranch Hands with earlier tours of duty.

### 179 **16.8.5 Histrionic**

180 The MCMI histrionic score increased as initial dioxin increased in Black Ranch Hands with later tours of  
181 duty.

### 182 **16.8.6 Narcissistic**

183 Ranch Hands had a higher average MCMI narcissistic score than Comparisons.

### 184 **16.8.7 Passive-aggressive**

185 Among participants with at most a high school education, Ranch Hands had a higher average MCMI  
186 passive-aggressive score than Comparisons. Younger Ranch Hands in the background dioxin category  
187 also had a higher average MCMI passive-aggressive score than younger Comparisons.

### 188 **16.8.8 Schizoid**

189 Among nondrinkers and moderate drinkers (no more than 40 lifetime drink-years), the MCMI schizoid  
190 score in Ranch Hands with earlier tours of duty increased as 1987 dioxin increased. The MCMI schizoid  
191 score also increased as initial dioxin in Ranch Hands increased.

192 **16.8.9 Borderline**

193 The MCMI borderline score increased as initial dioxin increased in college-educated Ranch Hands.

194 **16.8.10 Paranoid**

195 Ranch Hands had a higher average MCMI paranoid score than Comparisons.

196 **16.8.11 Schizotypal**

197 The MCMI schizotypal score increased as initial dioxin in Ranch Hands increased and as 1987 dioxin  
198 increased in Ranch Hands with earlier tours of duty.

199 **16.8.12 Alcohol Abuse**

200 The average MCMI alcohol abuse score for Black Ranch Hands in the background and high dioxin  
201 categories was higher than the average MCMI alcohol abuse score for Black Comparisons.

202 **16.8.13 Anxiety**

203 Black Ranch Hands had a higher average MCMI anxiety score than Black Comparisons. Black Ranch  
204 Hands in the background dioxin category also had a higher average MCMI anxiety score than Black  
205 Comparisons. An association between the MCMI anxiety score and initial dioxin was observed in  
206 non-Black Ranch Hands. As initial dioxin increased, the MCMI anxiety score increased for non-Black  
207 Ranch Hands.

208 **16.8.14 Dysthymia**

209 The MCMI dysthymia score in non-Black Ranch Hands increased as initial dioxin increased.

210 **16.8.15 Hypomania**

211 The MCMI hypomania score in Black Ranch Hands increased as initial dioxin increased. The average  
212 MCMI hypomania score also was increased in Black Ranch Hands in the high dioxin category relative to  
213 Black Comparisons.

214 **16.8.16 Somatoform**

215 The MCMI somatoform score increased as 1987 dioxin levels in Ranch Hands with later tours of duty  
216 increased and as initial dioxin in Ranch Hands increased.

217 **16.8.17 Psychotic Depression**

218 The MCMI psychotic depression score increased as initial dioxin in Ranch Hands increased and as 1987  
219 dioxin levels in Ranch Hands with earlier tours of duty increased.

220 **16.8.18 Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam**  
221 **War: MCMI**

222 A 2003 journal article related dioxin levels to data collected for the MCMI at the 1987 and 1992 follow-  
223 up examinations (10). Only Ranch Hands in the background dioxin category were more likely to have

224 elevated MCMI scale scores based on data from the 1992 follow-up examination. These elevations were  
225 primarily in the basic personality patterns. Ranch Hand veterans in the low and the high dioxin categories  
226 were similar to Comparisons in analysis of both the 1987 and 1992 follow-up examination data.

## 227 **16.9 MINNESOTA MULTIPHASIC PERSONALITY INVENTORY (MMPI)**

228 The MMPI is a self-administered test that was used at the 1982 and 1985 AFHS examinations. It  
229 comprises 566 questions on various aspects of behavior and personality (17). The results of the MMPI  
230 are numerical scores for 14 scales. The scales are anxiety (psychasthenia), consistency, defensiveness,  
231 denial, depression, hypochondria, hysteria, mania/hypomania, masculinity/femininity, paranoia,  
232 psychopathic/deviate, schizophrenia, social introversion, and validity. Differences between Ranch Hands  
233 and Comparisons at the 1982 and 1985 examinations are discussed in Sections 16.9.1 through 16.9.8. A  
234 summary of a journal article published in 2003 (10) that relates the MMPI results to dioxin levels is  
235 provided in Section 16.9.9.

### 236 **16.9.1 Depression**

237 Ranch Hands had a greater prevalence of high scores on the MMPI depression scale than Comparisons at  
238 the 1982 baseline examination.

### 239 **16.9.2 Hypochondria**

240 Ranch Hands had a greater prevalence of high scores on the MMPI hypochondria scale than Comparisons  
241 at the 1982 baseline examination.

### 242 **16.9.3 Hysteria**

243 Ranch Hands had a greater prevalence of high scores on the MMPI hysteria scale than Comparisons at the  
244 1982 baseline examination.

### 245 **16.9.4 Mania/Hypomania**

246 Among participants with at most a high school education, Ranch Hands had a higher average MMPI  
247 mania/hypomania score than Comparisons at the 1982 baseline examination.

### 248 **16.9.5 Masculinity/Femininity**

249 Among participants with at most a high school education, Ranch Hands had a higher average MMPI  
250 masculinity/femininity score than Comparisons at the 1982 baseline examination.

### 251 **16.9.6 Paranoia**

252 Older Ranch Hands had a greater prevalence of abnormal scores on the MMPI paranoia scale than older  
253 Comparisons at the 1985 follow-up examination.

### 254 **16.9.7 Schizophrenia**

255 Ranch Hands with at most a high school education had a greater prevalence of abnormal scores on the  
256 MMPI schizophrenia scale at the 1985 follow-up examination than Comparisons with at most a high  
257 school education.

258 **16.9.8 Social Introversion**

259 Among participants with at most a high school education, Ranch Hands had a higher average MMPI  
260 social introversion score at the 1982 baseline examination than Comparisons. Ranch Hands had a greater  
261 prevalence of abnormal scores on the MMPI social introversion scale at the 1985 follow-up examination  
262 than Comparisons.

263 **16.9.9 Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam**  
264 **War: MMPI**

265 A 2003 journal article related dioxin levels to data collected for the MMPI at the 1982 and 1985  
266 examinations (10). Few associations between dioxin levels and clinical elevations on the MMPI were  
267 seen based on data collected at the 1982 baseline examination. The direction and patterns of the  
268 associations were inconsistent. Ranch Hand veterans with higher dioxin levels showed some difficulties  
269 in anxiety, somatization, depression, and a denial of psychological factors. Ranch Hand veterans with  
270 background levels also showed indications of emotional distress, primarily in emotional numbing and  
271 lability; a guarded, suspicious, and withdrawn style of relating to others; and unusual thoughts or  
272 behaviors.

273 No positive associations between dioxin level and clinical elevations on the MMPI scales were observed  
274 based on data collected at the 1985 follow-up examination. No association between dioxin and post-  
275 traumatic stress disorder, as measured from questions on the MMPI, was observed at either the 1982 or  
276 1985 AFHS examinations.

277 **16.10 SYMPTOM CHECKLIST-90-REVISED (SCL-90-R)**

278 Twelve variables were derived from the SCL-90-R, which comprises nine primary symptom categories  
279 and three global indices of distress. A short description of each of the primary symptom categories and  
280 global indices of distress, which was taken from the SCL-90-R reference manual (18), is given before the  
281 description of the results in each of the sections that follow. The function of the three global measures of  
282 the SCL-90-R—the global severity index, the positive symptom distress index, and the positive symptom  
283 total—was to communicate in a single score the level or depth of the individual’s psychopathology. The  
284 SCL-90-R was a self-administered test taken by participants at the 1987, 1992, 1997, and 2002 follow-up  
285 examinations.

286 No associations showing an adverse effect to Ranch Hands or a positive association with dioxin were  
287 found for the primary symptom categories of interpersonal sensitivity and phobic anxiety and for the  
288 global indices of the positive symptom distress index and the positive symptom total. The primary  
289 symptom categories of anxiety, depression, hostility, obsessive-compulsive behavior, paranoid ideation,  
290 psychoticism, somatization, and the global severity index are discussed below.

291 **16.10.1 Anxiety**

292 The SCL-90-R anxiety dimension is a set of signs and symptoms that are associated clinically with high  
293 levels of manifest anxiety. General signs such as nervousness, tension, and trembling are included in the  
294 definition, as are panic attacks and feelings of terror. Cognitive components involving feelings of  
295 apprehension and dread, and some of the somatic correlates of anxiety, also are included as dimensional  
296 components. The symptoms comprising the anxiety dimension are experiencing nervousness or shakiness  
297 inside, trembling, being suddenly scared for no reason, feeling fearful, experiencing heart pounding or

298 racing, feeling tense and keyed up, having spells of terror and panic, feeling so restless you couldn't sit  
299 still, feeling that something bad is going to happen, and experiencing frightening thoughts and images.

300 Based on data from the 1987 follow-up examination, the prevalence of high SCL-90-R anxiety scores  
301 increased as 1987 dioxin increased in Ranch Hands with earlier tours of duty. This positive association  
302 between SCL-90-R anxiety and 1987 dioxin also was seen at the 1992 follow-up examination for  
303 participants who drank, on average, at most one drink per day.

#### 304 **16.10.2 Depression**

305 The symptoms of the depression dimension reflect a broad range of the manifestations of clinical  
306 depression. Symptoms of dysphoric mood and affect are represented, as are signs of withdrawal of life  
307 interest, lack of motivation, and loss of vital energy. In addition, feelings of hopelessness, thoughts of  
308 suicide, and other cognitive and somatic correlates of depression are included. The symptoms comprising  
309 the depression dimension are losing sexual interest or pleasure, feeling low in energy or a slowing down,  
310 thinking of ending your life, crying easily, feeling trapped or caught, blaming yourself for things, feeling  
311 lonely, feeling blue, worrying too much about things, feeling no interest in things, feeling hopeless about  
312 the future, feeling everything is an effort, and feeling worthless.

313 For moderate lifetime Ranch Hand drinkers (between 0 and 40 lifetime drink-years), the prevalence of  
314 high SCL-90-R depression scores at the 1992 follow-up examination increased as initial dioxin increased.  
315 Among Ranch Hands in higher income households and Black Ranch Hands, the prevalence of high SCL-  
316 90-R depression scores also increased as 1987 dioxin increased.

#### 317 **16.10.3 Hostility**

318 The hostility dimension reflects thoughts, feelings, or actions that are characteristic expressions of anger.  
319 The items comprising the hostility dimension were selected to measure the three modes of manifestation  
320 (i.e., thoughts, feelings, actions) and reflect qualities such as aggression, irritability, rage, and resentment.  
321 The dimension's symptoms are feeling easily annoyed or irritated; having uncontrollable temper  
322 outbursts; having urges to beat, injure, or harm someone; having urges to break or smash things; getting  
323 into frequent arguments; and shouting or throwing things.

324 At the 1992 follow-up examination, for enlisted groundcrew who had at most a high school education,  
325 Ranch Hands had a greater prevalence of high SCL-90-R hostility scores than Comparisons.

#### 326 **16.10.4 Obsessive-compulsive Behavior**

327 The obsessive-compulsive dimension reflects symptoms that are highly identified with the standard  
328 clinical syndrome of the same name. This measure focuses on thoughts, impulses, and actions that are  
329 experienced as unremitting and irresistible by the individual and inconsistent with the individual's own  
330 beliefs about what is desirable or reasonable. Behaviors and experiences of a more general cognitive  
331 performance attenuation also are included in this measure. The symptoms comprising the obsessive-  
332 compulsive dimension are experiencing repeated unpleasant thoughts that won't leave the mind, having  
333 trouble remembering things, worrying about sloppiness or carelessness, feeling blocked in getting things  
334 done, having to do things very slowly to ensure correctness, having to check and double-check what is  
335 done, having difficulty making decisions, having mind blanks, having trouble concentrating, and having  
336 to repeat the same actions (e.g., touching, counting, washing).

337 Ranch Hands had a greater prevalence of high SCL-90-R obsessive-compulsive scores than Comparisons  
338 at the 1992 follow-up examination. In relation to dioxin levels, this difference was seen for Ranch Hands  
339 in the background dioxin category. An interaction between current alcohol use, household income, and  
340 1987 dioxin also was observed in the analysis of SCL-90-R obsessive-compulsive scores.

#### 341 **16.10.5 Paranoid Ideation**

342 The present dimension represents paranoid behavior fundamentally as a disordered mode of thinking.  
343 The cardinal characteristics of projective thought, hostility, suspiciousness, grandiosity, centrality, fear of  
344 loss of autonomy, and delusions are viewed as primary reflections of this disorder; item selection was  
345 oriented toward representing this conceptualization. The symptoms comprising the paranoid ideation  
346 dimension are feeling others are to blame for most of your troubles, feeling that most people cannot be  
347 trusted, feeling that you are watched or talked about by others, having ideas and beliefs that others do not  
348 share, not receiving proper credit from others for your achievements, and feeling that people will take  
349 advantage of you if you let them.

350 At the 1992 follow-up examination, for non-Black enlisted personnel, Ranch Hands had a greater  
351 prevalence of high SCL-90-R paranoid ideation scores than Comparisons. Ranch Hands in the  
352 background dioxin category also had a greater prevalence of high SCL-90-R paranoid ideation scores  
353 than Comparisons.

#### 354 **16.10.6 Psychoticism**

355 The psychoticism scale was developed in a fashion to represent the construct as a continuous dimension  
356 of human experience. Items indicative of a withdrawn, isolated, schizoid lifestyle were included, as were  
357 Schneiderian first-rank symptoms of schizophrenia, such as hallucinations and thought broadcasting. The  
358 symptoms comprising the psychoticism dimension are having the idea that someone else can control your  
359 thoughts, hearing voices that other people do not hear, believing that other people are aware of your  
360 private thoughts, having thoughts that are not your own, feeling lonely even when you are with people,  
361 having thoughts about sex that are continuously bothersome, believing that you should be punished for  
362 your sins, thinking that something serious is wrong with your body, never feeling close to another person,  
363 and thinking that something is wrong with your mind.

364 Among moderate and heavy current drinkers (greater than one drink per day, on average), Ranch Hands  
365 in the background dioxin category had a greater prevalence of high SCL-90-R psychoticism scores than  
366 Comparisons at the 1992 follow-up examination.

#### 367 **16.10.7 Somatization**

368 The somatization dimension reflects distress arising from perceptions of bodily dysfunction. Complaints  
369 focusing on cardiovascular, gastrointestinal, respiratory, and other systems with strong autonomic  
370 mediation are included. Headaches, pain, and discomfort of the gross musculature and additional somatic  
371 equivalents of anxiety are components of the definition. These symptoms and signs have all been  
372 demonstrated to have high prevalence in disorders demonstrated to have a functional etiology, although  
373 all may be reflections of true physical disease. The symptoms comprising the somatization dimension are  
374 headaches, faintness or dizziness, pains in heart or chest, pains in lower back, nausea or upset stomach,  
375 soreness of muscles, trouble getting breath, hot or cold spells, numbness or tingling in parts of body, lump  
376 in throat, weakness in parts of body, and heavy feelings in arms or legs.

377 Ranch Hands with at most a high school education had a greater prevalence of high SCL-90-R  
378 somatization scores than Comparisons with at most a high school education at the 1987 follow-up  
379 examination.

380 At the 1992 follow-up examination, more Ranch Hands than Comparisons had high SCL-90-R  
381 somatization scores. In particular, the increase appeared to be for Ranch Hands with background dioxin  
382 levels relative to Comparisons. Among Ranch Hands with a college education, the prevalence of high  
383 SCL-90-R somatization scores at the 1992 follow-up examination increased as 1987 dioxin increased.

#### 384 **16.10.8 Global Severity Index**

385 The global severity index represents the best single indicator of the current level or depth of the disorder  
386 and should be used in most instances in which a single summary measure is required. The global severity  
387 index combines information on numbers of symptoms and intensity of perceived distress.

388 Among non-Black Ranch Hands with earlier tours of duty at the 1987 follow-up examination, the  
389 prevalence of high SCL-90-R global severity index scores increased as 1987 dioxin increased.

390 Ranch Hands had a higher prevalence of high SCL-90-R global severity index scores than Comparisons at  
391 the 1992 follow-up examination. Among Ranch Hands who drank less than one alcoholic drink per day,  
392 the prevalence of high SCL-90-R global severity index scores at the 1992 follow-up examination  
393 increased with both initial and 1987 dioxin. In addition, among Ranch Hands in higher income  
394 households, the prevalence of high SCL-90-R global severity index scores at the 1992 follow-up  
395 examination increased as 1987 dioxin increased.

#### 396 **16.11 SERUM DIOXIN AND COGNITIVE FUNCTIONING IN VETERANS OF OPERATION RANCH** 397 **HAND**

398 The Halstead–Reitan Battery (19), the Wechsler Adult Intelligence Scale-Revised (20), the Wechsler  
399 Memory Scale (21), and the Wide Range Achievement Test (22) were used to assess cognitive  
400 functioning among Air Force veterans at the 1982 baseline examination. Measures of cognitive  
401 functioning from these tests were examined for associations with dioxin levels that were measured in  
402 1987 and 1992. The results of these analyses are documented in a 2001 journal article (11) and are  
403 summarized below.

404 The results of this study suggested that, although there are not global decrements in cognitive functioning  
405 associated with dioxin exposure among Vietnam veterans, there may be specific decrements involving  
406 verbal and tactual memory functioning. Based on the Wechsler Memory Scale administered at the 1982  
407 baseline examination, there were decrements in tasks involving verbal memory functioning in Ranch  
408 Hands with the highest dioxin levels relative to Comparisons. The same pattern also was found in Ranch  
409 Hand enlisted personnel with reported skin exposure to herbicides, relative to enlisted Comparison  
410 personnel. The differences were relatively small, however, and of uncertain clinical meaning.

411 A revised version of the Wechsler Memory Scale (23) was administered at the 2002 follow-up  
412 examination. No differences in the memory scale between groups were found, and no associations  
413 between the memory scales and dioxin were observed.

414 Analysis of the Halstead impairment index as derived from the Halstead-Reitan Battery, which was a  
415 crude measure for categorizing brain damage, showed that Ranch Hand veterans with low dioxin  
416 exposure were more likely than Comparison veterans to be rated as severely impaired. The number of

417 veterans categorized as severely impaired, however, was small (n=64), and the average impairment score  
418 for Ranch Hand veterans was not different from Comparisons.

419 Ranch Hand veterans with low dioxin levels showed slower motor speed, as measured by the Halstead-  
420 Reitan finger-tapping test on both the dominant and the nondominant hand. Ranch Hand veterans with  
421 background dioxin levels showed decreased motor strength, as measured by the Halstead-Reitan grip  
422 strength test with the nondominant hand only. These results were of small and uncertain clinical  
423 meaning, with no clear dose-response pattern.

## 424 **16.12 CONCLUSION**

425 The 1982 baseline examination showed more differences between Ranch Hands and Comparisons  
426 (primarily those participants with at most a high school education) in subjective measurements rather than  
427 objective measurements. When multiple test instruments that measured similar variables were used, such  
428 as the SCL-90-R and the MCMI at the 1987 follow-up examination, there appeared to be a lack of  
429 consistency in the outcomes. Although differences between groups and associations with dioxin were  
430 seen in the psychological tests performed across the six examinations, no clear patterns were discernible.

431 Although differences between Ranch Hands with the highest dioxin levels and Comparisons were seen for  
432 tasks involving verbal memory functioning at the 1982 baseline examination, these differences were not  
433 observed at the 2002 follow-up examination.

434 Psychological disorders that were verified by medical records review and the SCL-90-R were analyzed  
435 for the follow-up examinations in 1987, 1992, 1997 and 2002. Except for other neuroses, based on data  
436 at the 1997 follow-up examination, no adverse effects to Ranch Hands or associations with dioxin were  
437 found. In summary, there does not appear to be any clear evidence of disorders or syndromes that can be  
438 associated with exposure to herbicides and dioxin.

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## 17 PULMONARY ASSESSMENT

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### 17.1 INTRODUCTION

Pulmonary dysfunction and overt pulmonary disease are not recognized clinical entities resulting from exposure to chlorophenols, phenoxy herbicides, or dioxin. Acute exposure to chlorophenols, phenoxy herbicides, and dioxin has caused the traditional acute symptoms of cough, nasal/lung irritation, shortness of breath, and occasionally, bronchitis. These acute effects and the high likelihood of inhalation exposure to herbicides among the operation Ranch Hand personnel in Vietnam prompted the evaluation of the pulmonary status of Air Force Health Study (AFHS) participants.

Analyses were performed to assess the pulmonary function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). In the self-administered family and personal history section, each study participant was asked whether he had ever experienced asthma, bronchitis, pleurisy, pneumonia, or tuberculosis. Medical records reviews were conducted to confirm reported pulmonary conditions and to identify any unreported conditions for each participant.

Part of the pulmonary assessment was based on the results of the physical examination of the thorax and lungs. A composite variable—thorax and lung abnormality—was constructed based on the presence or absence of asymmetrical expansion, hyperresonance, dullness, wheezes, rales, or chronic obstructive pulmonary disease, as well as the physician’s assessment of abnormality. The individual conditions of asymmetrical expansion, hyperresonance, dullness, wheezes, and rales also were analyzed for the reports describing the 1985 and 1987 follow-up examinations.

The assessment of the laboratory examination data included the interpretation of pulmonary abnormalities detected on a routine chest x-ray film. This variable was coded as normal or abnormal. The assessment also included the analysis of pulmonary physiological data collected during the physical examination employing standard spirometry techniques. Numerous indices were derived, including forced vital capacity (FVC)—a measurement of the amount of air in liters expelled from maximum inspiration to full expiration—and forced expiratory volume in 1 second (FEV<sub>1</sub>) in liters, an index derived from the FVC that quantifies the amount of air expelled in 1 second. The values used for these variables were the percentages of predicted values rather than the actual volume or flow rate. In addition, the ratio of observed FEV<sub>1</sub> to observed FVC was calculated as an index reflective of obstructive airway disease. For these indices, lower values indicated greater compromise in lung function. The FVC and the FEV<sub>1</sub> were based on the percent of predicted values, and the predicted values were adjusted for age and height. Loss of vital capacity and obstructive abnormality were classified by the examiner as none, mild, moderate, or severe.

The Institute of Medicine *Veterans and Agent Orange* reports, including the most recent 2004 update (8), consistently concluded that there is “inadequate or insufficient” evidence to determine the existence of an association between exposure to certain herbicides used in the Vietnam War and nonmalignant respiratory disorders.

#### 17.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and

40 demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant  
 41 results that appeared consistently across examinations or have biological meaning are emphasized,  
 42 particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated,  
 43 or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison  
 44 group, no mention is made in the chapter. In addition, the results of a nonsignificant association between  
 45 the parameter and either group or dioxin are not discussed.

46 The results discussed below that were discovered as part of further analysis based on a statistical  
 47 interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which  
 48 the results were found is identified in the description of the analysis. In addition, unless otherwise stated,  
 49 younger participants were those born in or after 1942, which corresponds to 40 years of age at the  
 50 baseline examination. Older participants were defined as those born before 1942.

51 For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the  
 52 Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987  
 53 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 54 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 55 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 56 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at  
 57 most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this  
 58 stratification based on the participant's tour of duty is given in Chapter 2.

59 The following chart lists the variables that were analyzed for the pulmonary assessment and at which  
 60 physical examination they were analyzed. The variables appearing in bold type are discussed  
 61 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Asymmetrical Expansion		X	X	X			
<b>Asthma</b>		X	X	X	X	X	X
<b>Bronchitis</b>		X	X	X	X	X	X
Dullness		X	X	X			
<b>FEV<sub>1</sub></b>	X		X	X	X	X	X
FEV <sub>2</sub>			X				
FEV <sub>3</sub>			X				
Forced Expiratory Flow Maximum			X	X			
<b>FVC</b>	X		X	X	X	X	X
<b>Hyperresonance</b>		X	X	X			
<b>Loss of Vital Capacity</b>			X	X	X	X	X
<b>Obstructive Abnormality</b>			X	X	X	X	X
<b>Pleurisy</b>		X	X	X			
<b>Pneumonia</b>		X	X	X	X	X	X
<b>Rales</b>		X	X	X			
<b>Ratio of Observed FEV<sub>1</sub> to Observed FVC</b>	X		X	X	X	X	X
<b>Thorax and Lung Abnormality</b>		X	X	X	X	X	X
Tuberculosis		X	X	X			
<b>Wheezes</b>		X	X	X			
<b>X-ray Interpretation</b>		X	X	X	X	X	X

62 **17.2 ASTHMA**

63 Ranch Hands in the background dioxin category had a higher prevalence of asthma after service in  
64 Southeast Asia (SEA) than Comparisons at the time of the 1987 follow-up examination.

65 **17.3 BRONCHITIS**

66 In the enlisted flyer cohort and the background dioxin category, Ranch Hands had a higher prevalence of  
67 bronchitis after service in SEA than Comparisons in the analysis of the 1992 follow-up examination data.

68 **17.4 PLEURISY**

69 The prevalence of pleurisy after service in SEA was increased among Ranch Hands with a moderate  
70 lifetime cigarette smoking history (more than 0 pack-years but no more than 10 pack-years) at the time of  
71 the 1985 follow-up examination.

72 **17.5 PNEUMONIA**

73 The prevalence of pneumonia after service in SEA was increased among Ranch Hand enlisted flyers at  
74 the 2002 physical examination. No other findings adverse to Ranch Hands or positive associations with  
75 dioxin were observed.

76 **17.6 THORAX AND LUNG ABNORMALITY**

77 The occurrence of thorax and lung abnormalities identified at the 1987 follow-up examination increased  
78 with dioxin (initial and 1987 levels). At the 1992 follow-up examination, Ranch Hands had a greater  
79 prevalence of thorax and lung abnormalities, primarily among enlisted flyers. Ranch Hands in the  
80 background dioxin category also had a greater prevalence of thorax and lung abnormalities than  
81 Comparisons at this examination.

82 **17.7 HYPERRESONANCE**

83 The prevalence of hyperresonance was elevated among Ranch Hand enlisted flyers at the 1987 follow-up  
84 examination. In addition, as 1987 dioxin levels increased in Ranch Hands with early tours of duty, the  
85 prevalence of hyperresonance in 1987 increased. No association between hyperresonance and group was  
86 found at the 1985 follow-up examination.

87 **17.8 RALES**

88 The prevalence of rales was increased for Ranch Hands in the high dioxin category at the 1987 follow-up  
89 examination.

90 **17.9 WHEEZES**

91 The prevalence of wheezes increased as initial dioxin increased for the serum dioxin analysis of the 1987  
92 follow-up report. Analysis in this report also showed the prevalence of wheezes increased as 1987 dioxin  
93 increased among older Ranch Hand participants with later tours of duty.

94 **17.10 X-RAY INTERPRETATION**

95 Ranch Hands in the background dioxin category had a higher prevalence of an abnormal chest x-ray  
96 interpretation than Comparisons in the analysis of the 1997 follow-up examination.

97 **17.11 FEV<sub>1</sub>**

98 For the analysis of data from the 1987 follow-up examination, the average FEV<sub>1</sub> was smaller (adverse  
99 effect) in older Ranch Hands than in older Comparisons. Among participants who had never smoked and  
100 former smokers, Ranch Hands in the high dioxin category had a smaller average FEV<sub>1</sub> than Comparisons.  
101 FEV<sub>1</sub> levels in 1987 decreased as initial and 1987 dioxin levels increased.

102 **17.12 FVC**

103 Similar interaction patterns to those seen for FEV<sub>1</sub> were observed with average FVC levels at the 1987  
104 follow-up examination. Among participants who had never smoked and former smokers, Ranch Hands in  
105 the high dioxin category had a smaller average FVC (adverse effect) than Comparisons. FVC levels in  
106 1987 decreased as initial and 1987 dioxin levels increased.

107 FVC, as measured at the 1992 follow-up examination, decreased as initial dioxin increased. Average  
108 FVC levels at the 2002 follow-up examination were smaller for Ranch Hands in the low dioxin category  
109 than for Comparisons.

110 **17.13 RATIO OF OBSERVED FEV<sub>1</sub> TO OBSERVED FVC**

111 Ranch Hands in the background dioxin category had a smaller average ratio of FEV<sub>1</sub> to FVC (adverse  
112 effect) than Comparisons at the 1987 follow-up examination. This pattern also was observed in older  
113 Ranch Hands at the 1992 follow-up examination.

114 **17.14 LOSS OF VITAL CAPACITY**

115 At the 1987 follow-up examination, more Ranch Hands with high levels of 1987 dioxin and later tours of  
116 duty had mild losses of vital capacity than did Ranch Hands with low levels of 1987 dioxin and later tours  
117 of duty. More Ranch Hands with high levels of 1987 dioxin had mild losses of vital capacity than did  
118 Comparisons. In addition, as initial dioxin increased, the risk of a mild loss of vital capacity increased.

119 At the 1992 follow-up examination, the occurrence of a mild loss of vital capacity in nonsmokers  
120 increased as 1987 dioxin increased.

121 **17.15 OBSTRUCTIVE ABNORMALITY**

122 The occurrence of a mild obstructive abnormality was increased for Ranch Hands in the background  
123 dioxin category at the 1987 follow-up examination. This same increase was observed at the 1992  
124 follow-up examination for Ranch Hand smokers who were heavy smokers. At the 1997 follow-up  
125 examination, the occurrence of a mild obstructive abnormality was increased for Ranch Hand officers.

126 **17.16 CONCLUSION**

127 Patterns that might be expected if there were dioxin or herbicide effects on the pulmonary function,  
128 namely consistent results across examinations, an adverse health effect for Ranch Hands or Ranch Hand  
129 enlisted groundcrew, and adverse effects to Ranch Hands in the high dioxin category, were not evident.  
130 Sporadic and isolated effects were present in many of the endpoints examined, but there was no consistent  
131 evidence to suggest that herbicide or dioxin exposure was associated with ill effects on respiratory health.

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## 18 RENAL ASSESSMENT

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### 18.1 INTRODUCTION

Renal (kidney) dysfunction and overt renal disease are not considered to be important clinical sequelae of exposure to phenoxy herbicides, chlorophenols, or 2,3,7,8-tetrachlorodibenzo-p-dioxin. Both 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), however, are excreted by the kidney as both metabolized and unmetabolized compounds. Therefore, it is consistent that acute renal dysfunction has been reported following acute, high-dose exposure to phenoxy herbicides and dioxin.

Analyses were performed to assess the renal function of Air Force Health Study (AFHS) participants at the 1982, 1985, 1987, 1992, and 2002 examinations (1-6). The renal assessment was based on laboratory data collected at the physical examination, as well as a verified lifetime history of kidney stones and kidney disease, as reported by the participant and subsequently verified by a medical records review.

In the self-administered family and personal history questionnaire, each AFHS participant was asked whether he had ever experienced kidney trouble or kidney stones in the past. A medical records review was accomplished to confirm reported problems with kidney function and to identify any unreported kidney problems. Predominate conditions for past kidney disease included kidney stones, unspecified disorders of the kidney and ureter, and nonspecific findings on the examination of the urine.

Renal variables were quantified by laboratory tests to assess nonspecific renal system function. Urinary protein and urine specific gravity were determined by accepted dipstick methods. Urinary occult blood and urinary white blood cell count were measured by high-powered microscopic examination. Serum creatinine, urinary creatinine, urinary microalbumin, and blood urea nitrogen also were collected and analyzed at selected physical examinations.

#### 18.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987

39 follow-up examination was calculated. The median difference between the date of the 1987 follow-up  
 40 examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health  
 41 variable and 1987 dioxin were investigated separately for participants whose difference was greater than  
 42 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at  
 43 most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this  
 44 stratification based on the participant’s tour of duty is given in Chapter 2.

45 The following chart lists the variables that were analyzed for the renal assessment and at which physical  
 46 examination they were analyzed. The variables appearing in bold type are discussed subsequently in the  
 47 chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<b>History of Kidney Stones</b>						Analysis not performed	X
Occurrence of Past Kidney Disease	X	X	X	X	X		X
Blood Urea Nitrogen	X	X	X	X			X
<b>Serum Creatinine</b>					X		X
Creatinine Clearance	X						X
Urinary Microalbumin to Urinary Creatinine Ratio							X
<b>Urine Specific Gravity</b>	X	X	X	X	X		X
<b>Urinary Occult Blood</b>	X	X	X	X	X		X
<b>Urinary White Blood Cells</b>	X	X	X	X	X		X
<b>Urinary Protein</b>	X	X	X		X		X
Kidney Stones from Kidney, Urethra, and Bladder X-ray Assessment					X		
Composite Renal Abnormalities (Blood Urea Nitrogen, Creatinine Clearance, Urinary Occult Blood, Urinary White Blood Cells, Urinary Protein)	X						

48 **18.2 HISTORY OF KIDNEY DISEASE**

49 Answers to the question “Have you ever had kidney disease?” at the 1982 baseline examination showed  
 50 that Ranch Hands self-reported more kidney disease than Comparisons. At subsequent examinations,  
 51 affirmative responses to this question were verified by a medical records review.

52 **18.3 SERUM CREATININE**

53 For participants whose glucose levels were considered impaired ( $140 \text{ mg/dL} \leq 2\text{-hour postprandial}$   
 54  $\text{glucose} < 200 \text{ mg/dL}$ ), more Ranch Hands had a higher average serum creatinine level at the 1992 follow-  
 55 up examination than Comparisons.

56 **18.4 URINARY OCCULT BLOOD**

57 Black Ranch Hands exhibited a greater percentage of abnormal levels of urinary occult blood (greater  
 58 than 2 cells per high-powered field) than Black Comparisons at the 1987 follow-up examination. The  
 59 percentage of abnormal levels of urinary occult blood also increased with increasing initial dioxin at the

60 1987 follow-up examination. At the 1992 follow-up examination, the prevalence of abnormal levels of  
61 urinary occult blood increased with categorized dioxin and 1987 dioxin.

### 62 **18.5 URINARY WHITE BLOOD CELLS**

63 Younger non-Black Ranch Hands exhibited a greater percentage of abnormal levels of urinary white  
64 blood cells (greater than 2 cells per high-powered field) than younger non-Black Comparisons at the 1985  
65 follow-up examination. At the 1992 follow-up examination, the prevalence of abnormal levels of urinary  
66 white blood cells was greater for Ranch Hand enlisted groundcrew than for Comparison enlisted  
67 groundcrew.

### 68 **18.6 URINARY PROTEIN**

69 For participants whose glucose levels were considered normal (2-hour postprandial glucose < 140  
70 mg/dL), more Ranch Hands had urinary protein present at the 1985 follow-up examination than did  
71 Comparisons.

72 For participants whose glucose levels were considered impaired ( $140 \text{ mg/dL} \leq$  2-hour postprandial  
73 glucose < 200 mg/dL), the percentage of Ranch Hands who had urinary protein present at the 1992  
74 follow-up examination increased as the level of 1987 dioxin increased.

### 75 **18.7 URINE SPECIFIC GRAVITY**

76 Average urine specific gravity levels were greater for non-Black Ranch Hand enlisted groundcrew than  
77 for non-Black Comparison enlisted groundcrew at the 1985 follow-up examination. Urine specific  
78 gravity levels among older participants increased as initial dioxin increased at the 1992 follow-up  
79 examination. Urine specific gravity levels at the 1992 follow-up examination also increased as 1987  
80 dioxin increased.

### 81 **18.8 CONCLUSION**

82 The AFHS evaluated renal disorders based on medical histories and standard laboratory measures.  
83 Throughout the AFHS, the findings of adverse effects or associations with dioxin that were observed  
84 appeared to be sporadic and inconsistent across examinations. Many of the relations that were found  
85 were present only in subpopulations with no biological basis. The results from the renal assessment  
86 indicated no association between any marker of kidney disease and either herbicides or dioxin. In  
87 particular, there was no evidence that exposure to herbicides or dioxin was associated with renal  
88 dysfunction, kidney stones, prevalence of proteinuria or albuminuria, or cells in the urine.

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## 19 CONCLUSION

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The objective of the Air Force Health Study (AFHS) was to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides, with specific emphasis on Agent Orange, a one-to-one mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This report is a discussion and a compilation of the findings from research related to the mortality, reproductive outcomes, and morbidity components of the AFHS.

Congress directed the Secretary of Veterans Affairs in Public Law 102-4 signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam War. In 1994, the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides published its first report, "Veterans and Agent Orange: Health effects of herbicides used in Vietnam." (1) This report classified evidence of an association between a health problem and exposure to herbicides as "sufficient," "limited/suggestive," or "inadequate/insufficient." The evidence regarding association was drawn from occupational, environmental, and veterans studies in which individuals were exposed to the herbicides used in Vietnam, to their components, or to their contaminants. Since this report, the IOM has published five *Veterans and Agent Orange* updates in 1996, 1998, 2000, 2002, and 2004 (2-6), which incorporated results from additional studies.

As a result of the committee's work, the Department of Veterans Affairs has presumed that any veteran who served in Vietnam between January 9, 1962, and May 7, 1975, and has one or more of the following conditions, has been exposed to Agent Orange, and, therefore, his condition is to be considered service-connected: acute and subacute transient peripheral neuropathy (must appear within 1 year of exposure and resolve within 2 years of date of onset); chloracne (must occur within 1 year of exposure); chronic lymphocytic leukemia; Hodgkin's disease; multiple myeloma; non-Hodgkin's lymphoma; porphyria cutanea tarda (must occur within 1 year of exposure); prostate cancer; respiratory cancers, including cancers of the lung, larynx, trachea, and bronchus; soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma); spina bifida (in children of Vietnam veterans born after the veteran's tour in Vietnam) (except spina bifida occulta); and type 2 diabetes.

In interpreting results from any epidemiological study, no single result should be evaluated in isolation or out of context. Rather, interpretations should be addressed in the context of the overall study design, the data collection procedures, the data analysis methods, dose-response effects, strength of association, temporal relation, biological plausibility, and internal and external consistency. This especially applies to the AFHS, a large-scale, prospective observational study in which thousands of measurements and diagnoses were compiled on each participant. Those measurements and diagnoses were subjected to extensive statistical analyses, testing thousands of individual hypotheses. Each positive result should be scrutinized relative to findings in other studies, and relative to the statistical methods used and the medical and biological 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 possibly incorrect assertion that there is no effect. In addition, no epidemiological study can establish that there is no effect; i.e., that dioxin is safe.

42 In December 1999, the Government Accounting Office (GAO) published the report *Actions Needed to*  
43 *Improve Communications of Air Force Ranch Hand Study Data and Results (7)*. This report described  
44 the actions needed to improve communications of AFHS data and results to the public. The GAO  
45 recommended that more information on the limitations of the AFHS should be communicated in press  
46 releases and executive summaries. Below are the strengths and limitations of the study, as determined by  
47 AFHS investigators:

48 Strengths:

- 49 • High level of Ranch Hand and Comparison participation
- 50 • Existence of a biomarker for exposure to dioxin and herbicides of interest
- 51 • Long follow-up period
- 52 • Six physical examinations over a 20-year period
- 53 • Medical record verification of most health conditions
- 54 • Rigorous quality control
- 55 • Independently appointment and administered advisory committee (Ranch Hand Advisory  
56 Committee)
- 57 • Periodic review by the National Academy of Sciences
- 58 • Two-tiered management structure based on separate but parallel program management and  
59 technical teams
- 60 • Adjustment for confounding factors

61 Limitations:

- 62 • Findings cannot be generalized to all Vietnam veterans
- 63 • Sample size not adequate to detect small to moderate increases in rare diseases
- 64 • Serum dioxin measured over 15 years after Agent Orange exposure
- 65 • Possible incomplete adjustment due to unknown confounding factors.

66 There was no meaningful elevation in risk for spontaneous abortion or stillbirth. There were some  
67 elevations in risk in some birth defect organ system categories that were not considered biologically  
68 meaningful. There was no indication of increased birth defect severity, delays in development, or  
69 hyperkinetic syndrome with paternal dioxin. No association was seen between paternal dioxin level and  
70 intrauterine growth retardation. The risk of infant death was increased among children of Ranch Hands  
71 whose fathers had the highest dioxin levels and among children whose fathers had background dioxin  
72 levels, but the pattern of results implied that the outcomes might not be related to paternal dioxin level.  
73 No consistent or meaningful associations between serum dioxin levels and testosterone, follicle-  
74 stimulating hormone, luteinizing hormone, testicular abnormalities, and testicular volume were observed.

75 As of 31 December 1999, 186 Ranch Hands and 2,330 Comparisons had died. The risk of death caused  
76 by cancer was not increased, but the risk of death caused by circulatory system diseases was increased in  
77 enlisted groundcrew. The cumulative all-cause mortality experience of Ranch Hands was not statistically  
78 greater than Comparisons, but this trend bears further monitoring to confirm the increased risk suggested  
79 by these results. To examine cancer mortality in a way that accounts for latency, the risk was evaluated  
80 among those subjects who survived at least 20 years after entry into follow-up. No differences were

81 found in this subset, as was also the case with cancer mortality within 20 years of service in Southeast  
82 Asia (SEA).

83 The prevalence of cardiovascular disease does not appear to be associated with dioxin exposure.  
84 Abnormal pulses appeared to be related to dioxin in earlier phases of the study, but not in the 2002  
85 follow-up examination. The increase in the number of deaths caused by the diseases of the circulatory  
86 system for Ranch Hand nonflying enlisted personnel, however, does point to the possibility of an  
87 association with dioxin.

88 No evidence of chloracne was found. An increased frequency of reported acne after service in SEA in  
89 Ranch Hand enlisted groundcrew was observed, but is of uncertain meaning because secondary lesions  
90 that were observed revealed no association with herbicide or dioxin exposure.

91 Results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent and potentially  
92 meaningful adverse relation between dioxin levels and diabetes. Although the existence of diabetes was  
93 comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the  
94 possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. A  
95 dioxin-related increase in severity, a decrease in the time from exposure to first diagnosis, and an increase  
96 in fasting glucose and hemoglobin A1c supported the dioxin relation with the occurrence of diabetes.  
97 Increased risks of diabetes and diabetic-related measurements were found with initial dioxin, in the high  
98 dioxin category, and with 1987 dioxin levels.

99 Sporadic associations between dioxin levels and thyroid or gonadal hormone abnormalities appeared  
100 unlikely to be clinically important.

101 Analysis of gastrointestinal data indicated that dioxin was associated with hepatic enzymes, such as  
102 alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase, and also with  
103 lipid-related health indices, such as cholesterol, high-density lipoprotein cholesterol, and triglycerides.  
104 Although hepatic enzymes showed an association with dioxin, there was no evidence of an increase in  
105 overt liver disease. These findings may represent a dioxin-mediated alteration of biochemical processes  
106 or a subtle relation between dioxin and lipid metabolism.

107 Body mass index was positively associated with 1987 dioxin, possibly reflecting the pharmacokinetics of  
108 dioxin elimination.

109 Increased platelet counts, in addition to the elevated erythrocyte sedimentation rates, may indicate the  
110 presence of a chronic inflammatory response to dioxin.

111 The significant associations between herbicide exposure or dioxin levels and the likelihood of developing  
112 cancer were seen primarily for Ranch Hand officers and Ranch Hands in the low dioxin category. Other  
113 risk and operational factors discussed in published articles did not show consistent associations in Ranch  
114 Hands, but did show some associations in the Comparisons. The AFHS is limited in its ability to detect  
115 increases in risks of rare diseases because of the small size of the Ranch Hand population. There was  
116 some limited support of an association between dioxin levels and neurological disease related to the  
117 peripheral nerves. No consistent associations or clinical evidence, however, appeared to support a  
118 relation between dioxin and cranial nerve function or other central nervous system processes.

119 Although differences between groups and associations with dioxin were seen in the psychological tests  
120 performed across the six examinations, no clear patterns were discernible. Differences between Ranch  
121 Hands with the highest dioxin levels and Comparisons were seen for tasks involving verbal memory

122 functioning at the 1982 baseline examination, but these differences were not observed at the 2002 follow-  
123 up examination. There does not appear to be any clear evidence of psychological disorders or syndromes  
124 that can be associated with exposure to herbicides and dioxin.

125 There was no evidence of dioxin or herbicide effects on the pulmonary function. Sporadic and isolated  
126 effects were present in many of the endpoints examined, but there was no consistent evidence to suggest  
127 that either herbicide or dioxin exposure was associated with ill effects on respiratory health.

128 Throughout the AFHS, the findings of adverse renal effects or associations between renal function and  
129 dioxin that were observed appeared to be sporadic and inconsistent across examinations. Many of the  
130 relations that were found were present only in subpopulations with no biological basis. The results from  
131 the renal assessment indicated no association between any marker of kidney disease and either herbicides  
132 or dioxin.

133 In conclusion, results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent  
134 and potentially meaningful adverse relation between dioxin levels and diabetes. Although the existence  
135 of diabetes was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism  
136 showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin  
137 production. In addition, the occurrence of and mortality from diabetes and 11 other conditions that were  
138 considered service-connected by the Department of Veterans Affairs because of exposure to herbicides  
139 are described in this report for the population of AFHS veterans.

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## APPENDIX: ABBREVIATIONS AND ACRONYMS

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2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
ADA	American Diabetes Association
AFHS	Air Force Health Study
ALT	alanine aminotransferase
ANA	antinuclear antibody
APP	active pedal plantarflexion
AST	aspartate aminotransferase
ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
CMI	Cornell Medical Index
CNS	central nervous system
ECG	electrocardiograph
FEV <sub>1</sub>	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GADA	glutamic acid decarboxylase antibodies
GAO	Government Accounting Office
GGT	gamma glutamyltransferase
HDL	high-density lipoprotein
HLA-DR	human leukocyte antigen-DR
ICD-9-CM	International Classification of Diseases, 9 <sup>th</sup> Revision, Clinical Modification
Ig	immunoglobulins
IOM	Institute of Medicine
KUB	kidney, urethra, and bladder
LDH	lactate dehydrogenase

LH	luteinizing hormone
MCM	Millon Clinical Multiaxial Inventory
MLC	mixed lymphocyte culture
MMPI	Minnesota Multiphasic Personality Inventory
MSK	mouse stomach kidney
NIOSH	National Institute for Occupational Safety and Health
NKCA	natural killer cell assay
NKCI	natural killer cell assay with Interleukin-2
NCI	National Cancer Institute
PCT	porphyria cutanea tarda
PHA	phytohemagglutinin
ppm	parts per million
ppt	parts per trillion
PSA	prostate-specific antigen
PWM	pokeweed mitogen
RBBB	right bundle branch block
RBC	red blood cell
RVN	Republic of Vietnam
SCL-90-R	Symptom Checklist-90-Revised
SEA	Southeast Asia
SEER	Surveillance, Epidemiology, and End Results
SHBG	sex hormone-binding globulin
T <sub>3</sub>	triiodothyronine
T <sub>4</sub>	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TNF $\alpha$	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
USAF	United States Air Force
WBC	white blood cell