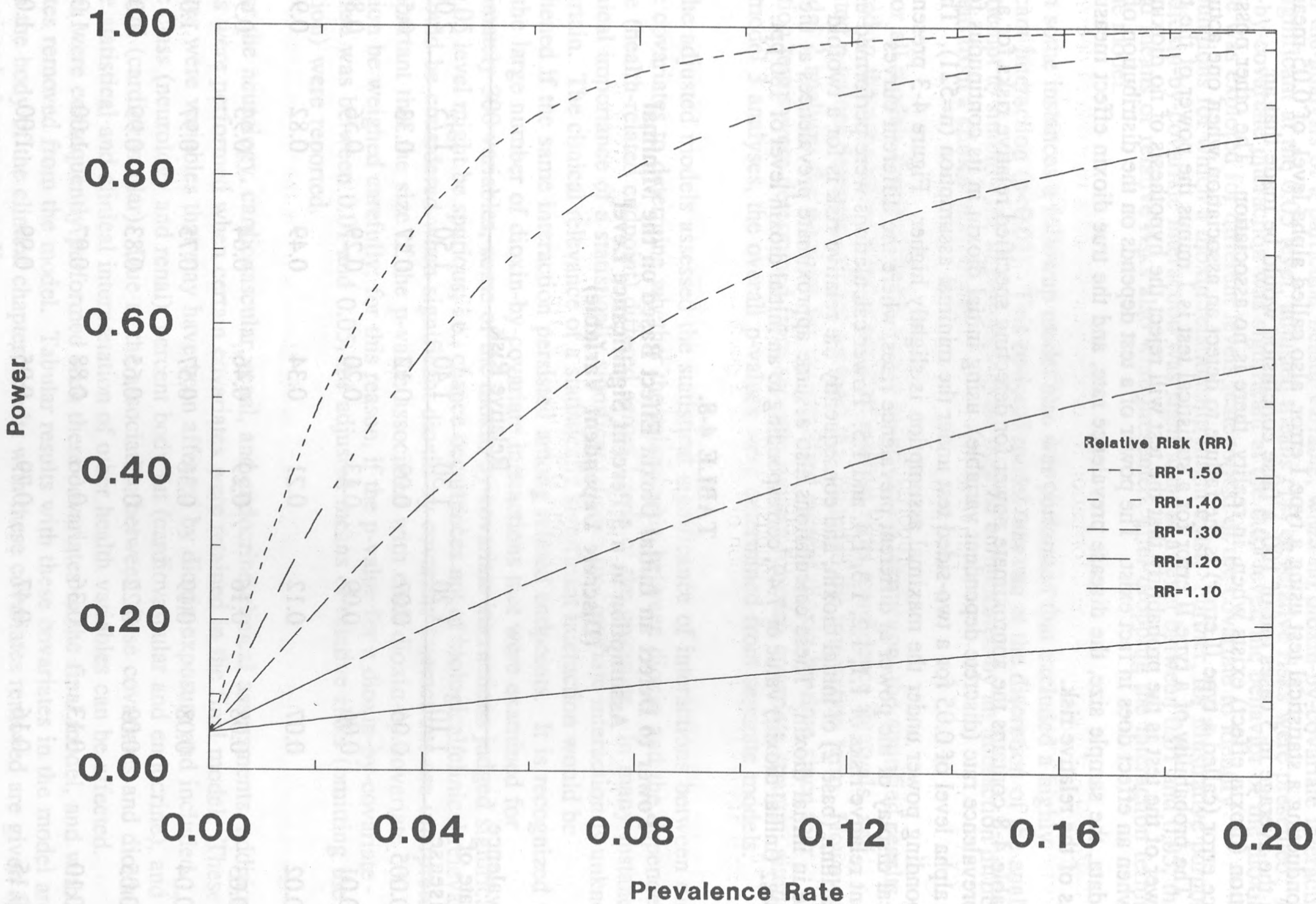

FIGURE 4-3. Power to Detect an Initial Dioxin Effect (Discrete Dependent Variable)

As an example, using age-adjusted incidence rates for all U.S. males (based on data from the Surveillance Epidemiology and End Results program of the National Cancer Institute), prevalence rates for all cancers, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma (STS) were estimated as 0.07, 0.002, and 0.001, respectively. Thus, Table 4-8 shows at least a power of 0.80 to detect a relative risk of 1.5 or greater given an estimated prevalence of 0.07 for all cancers. For the estimated prevalences of NHL and STS, the power to detect a relative risk of 2.0 would be less than 0.50.

Table 4-9 provides the same information for continuous variables in terms of coefficients of variation (100 times the standard deviation of the dependent variable divided by the mean of the dependent variable) and the proportion mean change. The proportion mean change in this table is defined as the change in the expected value (mean) of the dependent variable for a twofold increase in initial dioxin relative to the dependent variable mean. These mean changes are evaluated at the mean $\log_2$ (initial dioxin) value of 7.49, corresponding to an initial dioxin level of 180 ppt. The proportion mean change corresponds mathematically to the slope of the initial dioxin variable divided by the dependent variable mean, assuming no transformation of the dependent variable. An analogous quantity can be derived based on transformed statistics. Figure 4-4 shows a graphical display of the power at a given proportion mean change, where the different curves represent coefficients of variation of 5, 10, 25, 50, and 75. In this study, continuously distributed laboratory results were subject to a laboratory-error coefficient of variation of less than 3 percent.

TABLE 4-9.

Power to Detect an Initial Dioxin Effect Based on the Minimal Assumption at a 5 Percent Significance Level (Continuous Dependent Variable)

	Coefficient of Variation (σ/μ)				
Mean Change	5	10	25	50	75
0.005	0.78	0.28	0.09	0.06	0.05
0.01	1.00	0.78	0.20	0.09	0.07
0.02	1.00	1.00	0.59	0.20	0.11
0.03	1.00	1.00	0.91	0.38	0.20
0.04	1.00	1.00	0.99	0.59	0.31
0.05	1.00	1.00	1.00	0.78	0.45
0.10	1.00	1.00	1.00	1.00	0.96

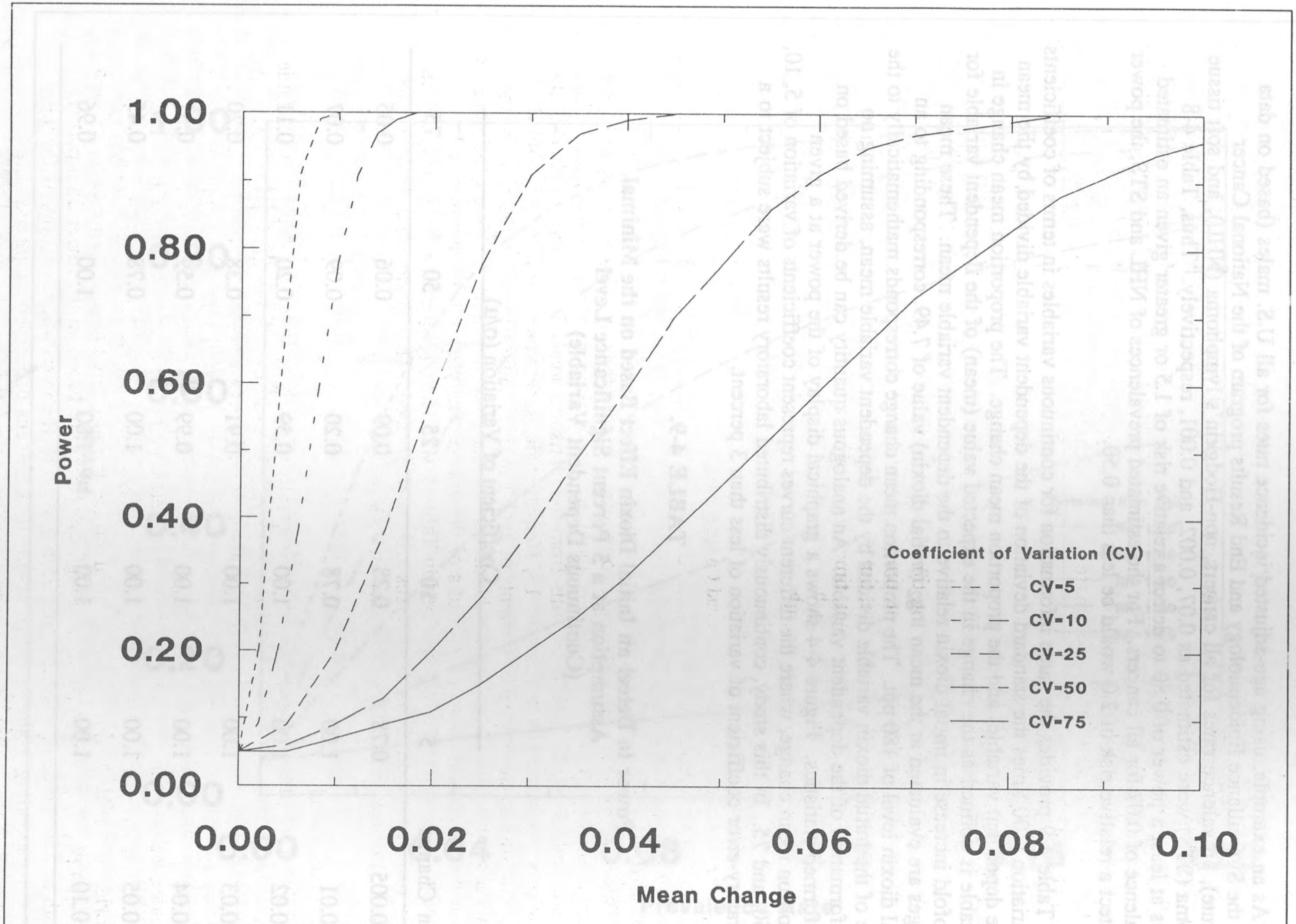

FIGURE 4-4. Power to Detect an Initial Dioxin Effect (Continuous Dependent Variable)

TABLE 4-10.

Location of Table Results from Different Analysis Models

Subpanel in Table	Dioxin Estimate	Type of Analysis	Assumption
a	initial[a]	unadjusted	minimal
b	initial[a]	unadjusted	maximal
c	initial[a]	adjusted	minimal
d	initial[a]	adjusted	maximal
e	current, time[a]	unadjusted	minimal
f	current, time[a]	unadjusted	maximal
g	current, time[a]	adjusted	minimal
h	current, time[a]	adjusted	maximal
i	current[b]	unadjusted	--
j	current[b]	adjusted	--

[a]Ranch Hands only.
[b]Categorized current dioxin, Ranch Hands and Comparisons.

EXPLANATION OF TABLES

This section introduces the reader to the contents of the tables that are used to report the results of the analyses for continuous and discrete dependent variables (two levels and more than two levels). Selected results from the statistical analysis methods applied in the hematology assessment (see Chapter 13, Hematologic Assessment) will be referenced throughout this discussion. The contents of each summary table depend on the form of the health status endpoint (i.e., whether the dependent variable under analysis is a continuous or discrete variable). Generally, the results of the various analyses will be summarized in subpanels within each table as specified in Table 4-10. The subpanel specifications may be slightly different when adjusted analyses are not performed. This section also provides an explanation of the information contained in these tables.

Continuous Variables

Table 13-3 presents an example of the results of analysis when the dependent variable is continuous. Subpanels (a) and (b) report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association between the dependent variable and initial dioxin without adjusting for covariate information. Immediately below the specified assumption, the aggregate sample size (n) and the coefficient of determination (R^2) associated with the simple linear regression of the continuous dependent variable on $\log_2$ (initial dioxin) are presented. Sample sizes also are presented for low, medium, and high categories of initial dioxin. The numerical values defining these categories are specified in a table footnote. The low, medium, and high categories are based on the lower 25th percent, the 25th to 75th percent, and the upper 25th percent of the initial dioxin estimates for the cohort corresponding to the specified assumption. Means of the dependent variable (transformed to the original units, if necessary) are calculated from the data and are presented for the low, medium, and high initial dioxin categories. Based on the simple linear regression analysis, the estimated slope and its associated standard error are reported for each assumption. If the dependent variable was transformed for the regression analysis, the means, slope, and standard error are footnoted and the transformation is identified in the footnote. The p-value associated with testing whether the estimated slope is equal to zero also is presented under both assumptions.

Based on analyses that incorporate covariate and interaction information, subpanels (c) and (d) report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association between the dependent variable and initial dioxin. Immediately below the specified assumption, the aggregate sample size (n) and the multiple coefficient of determination (R^2) are presented for a multiple linear regression of the continuous dependent variable on $\log_2$ (initial dioxin) including covariate and interaction effect terms in the adjusted model. Similar to the unadjusted analyses, sample sizes are also presented for low, medium, and high categories of initial dioxin. The numerical values defining these categories are specified in a table footnote. Sample sizes for corresponding panels of unadjusted and adjusted analyses may differ because of missing covariate information. Adjusted means of the dependent variable (transformed to the original units, if necessary) also are presented. The adjusted means are presented for the low, medium, and high initial dioxin categories. Based on the multiple linear regression analysis, the adjusted slope for the $\log_2$ (initial dioxin) term and its associated standard error are reported for each assumption. If the dependent variable was transformed for the regression analysis, the adjusted means, adjusted slope, and standard error are footnoted and the transformation is identified in the footnote. The p-value for testing whether the adjusted slope is equal to zero also is presented under both assumptions.

Covariates with p-values less than or equal to 0.15 and interactions with p-values or equal to 0.05 retained in the multiple regression model after implementing the modeling strategy are presented under covariate remarks, along with the associated p-values. If the multiple regression model contains a significant initial dioxin-by-covariate interaction with an associated p-value less than or equal to 0.01, then the adjusted means, adjusted slope, standard error, and p-value generally are not reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained in the model are, however, reported under covariate remarks. For some clinical assessments, an analyst may exercise discretion and report the adjusted means, adjusted slope, standard error, and a p-value from a model that excludes the interaction having a p-value less than 0.01. When these discretionary followup analyses are performed, the results are reported along with three asterisks (***) and are explained by a table footnote. If the multiple regression model contains a significant initial dioxin-by-covariate interaction with an associated p-value between 0.01 and 0.05, then the adjusted means, adjusted slope, standard error, and p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case (i.e., $p \leq 0.01$ or $0.01 < p \leq 0.05$), stratified analyses are undertaken and the results are reported in an associated appendix for each individual clinical area.

Subpanels (e) and (f) of Table 13-3, for example, report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association of the dependent variable with current dioxin and time since tour without adjusting for covariate information.

Multiple regression techniques are used to generate the statistics provided in both panels. In the multiple regression model, current dioxin is included as a continuous variable and time since tour as a discrete variable. The interaction of current dioxin and time since tour also is included. For these models, time since tour is dichotomized and separate statistics are presented on the association between the dependent variable and current dioxin within each time stratum. For each subpanel, the aggregate sample size (n) and the coefficient of determination (R^2) are presented, under each specified assumption, for the multiple linear regression model. For presentation purposes, current dioxin and time since tour both are categorized. The numerical values defining the current dioxin categories are specified in a table footnote. The low, medium, and high categories are based on the lower 25th percent, the 25th to 75th percent, and the upper 25th percent of the current dioxin estimates for the cohort corresponding to the specified assumption. The value of 18.6 years for time since tour corresponds to approximately the median value of time since tour in the Ranch Hand cohort. The means of the dependent variable (transformed to the original units, if necessary) are calculated from the data and are presented, along with sample size, for the combinations of trichotomized current dioxin and dichotomized time since tour. The first p-value within each subpanel evaluates the interaction term of the multiple regression using current dioxin in continuous form and time since tour in discrete form. The p-value for the interaction term provides a test of the equality of the slopes for the two time strata. For each time stratum, a simple linear regression model of the dependent variable on current dioxin ($\log_2$ scale) provides an estimated slope, associated standard error, and p-value for testing the significance of the slope. If the dependent variable was transformed for regression analysis, the means, slope, and standard error are footnoted and the transformation identified in the footnote.

Incorporating covariate and current dioxin-by-time-by-covariate interaction information into the analysis, subpanels (g) and (h) report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association of the dependent variable with current dioxin, time since tour, and the current dioxin-by-time interaction. Multiple linear regression techniques are used to generate the statistics provided. In the overall multiple regression model, current dioxin is included as a continuous variable and time since tour as a discrete variable. The interaction of current dioxin and time since tour also is included. The test of the interaction of current dioxin and time since tour (i.e., the first p-value in each subpanel) determines whether the adjusted slopes of the two time strata differ significantly.

Immediately below the specified assumption, the aggregate sample size (n) and the multiple coefficient of determination (R^2) are presented for the multiple linear regression of the continuous dependent variable on current dioxin ($\log_2$ scale), time since tour, the current dioxin-by-time interaction, covariates, and other interactions retained in the model. For each time stratum ($\leq$18.6 years or >18.6 years), separate statistics relating the dependent variable to current dioxin ($\log_2$ scale) are presented. In particular, based on the multiple linear regression analysis, the adjusted slope for the current dioxin term ($\log_2$ scale), its associated standard error, and a p-value for testing the significance of the slope are reported.

Sample sizes also are presented for combinations of low, medium, and high categories of current dioxin and dichotomized time since tour. The numerical values defining these categories are specified in a table footnote. Sample sizes for corresponding panels of unadjusted and adjusted analyses may differ because of missing covariate information.

Adjusted means of the dependent variable (transformed to the original units, if necessary) are presented. The adjusted means are presented for the combinations of trichotomized current dioxin and dichotomized time since tour. If the dependent variable was transformed for the regression analysis, the adjusted means, adjusted slope, and standard error are footnoted and the transformation is identified in the footnote.

Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple regression model after implementing the modeling strategy are presented under covariate remarks, along with the associated p-values. If the multiple regression model contains a significant current dioxin-by-time-by-covariate interaction term with an associated p-value less than or equal to 0.01, then the adjusted means, adjusted slope, standard error, and p-value generally are not reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained in the model are, however, reported under covariate remarks. For some clinical assessments, an analyst may exercise discretion and report adjusted means, adjusted slope, standard error, and a p-value from a model that excludes the interaction having a p-value less than 0.01. When these discretionary followup analyses are performed, the results are reported along with three asterisks (***) and are explained by a table footnote. If the multiple regression model contains a significant current dioxin-by-time-by-covariate interaction with an associated p-value between 0.01 and 0.05, then the adjusted means, adjusted slope, standard error, and p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case, interactions are investigated within strata of the covariate and reported in an associated appendix for each clinical area.

Subpanels (i) and (j) of Table 13-3, for example, show the results of unadjusted and adjusted analyses that compare the means of a continuous dependent variable for Ranch Hands with high, low, and unknown current dioxin levels and for Comparisons having background current dioxin levels. The note at the bottom of the table defines the four current dioxin categories. Sample sizes for each category and across the four categories are reported. The coefficient of determination (R^2) also is presented.

For the unadjusted analysis, dependent variable means are presented for each category. If the dependent variable was transformed for the analysis, the means of the transformed values are converted to the original scale and the column heading is footnoted. A test of the simultaneous equality of the four category means is evaluated by the first p-value cited. If the analysis was performed on a transformed scale, the p-value column is footnoted to indicate that the p-value is based on the difference of means on a transformed scale. For the individual contrasts of the three Ranch Hand categories versus Comparison background category, differences in means are reported on the original scale. If the analyses were performed on a transformed scale, 95 percent confidence intervals on the differences of means are not presented and the column is footnoted. A p-value also is reported to determine whether a difference in means for a specified contrast is significantly different from zero.

For an adjusted analysis, the table is modified to include adjusted means, differences in adjusted means (reported on the original scale), 95 percent confidence intervals on the differences in adjusted means (if the analysis was performed on the original scale), and any covariates and interactions retained in the adjusted model along with their associated p-values.

Discrete Variables

Discrete Variable With Two Categories

Table 13-4 presents an example of the results of analysis when the dependent variable is discrete and dichotomous in form. Subpanels (a) and (b) report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association between the dependent variable and initial dioxin without adjusting for covariate information. Immediately below the specified assumption, the aggregate sample size (n) associated with the simple logistic regression of the continuous dependent variable on $\log_2$ (initial dioxin) is presented. Sample sizes also are presented for low, medium, and high categories of initial dioxin. The numerical values defining these categories are specified in a table footnote. The low, medium, and high categories are based on the lower 25th percent, the 25th to 75th percent, and the upper 25th percent of the initial dioxin estimates for the cohort corresponding to the specified assumption. The percentage of Ranch Hands with the specified dichotomous characteristic (as cited in the column heading) is calculated from the data and presented for the low, medium, and high initial dioxin categories. Based on the simple logistic regression model, an estimated relative risk and its associated 95 percent confidence interval are reported for each assumption. The p-value associated with testing whether the relative risk is equal to one also is presented for both assumptions. The relative risk, confidence interval, and p-value are based on $\log_2$ (initial dioxin) in its continuous form.

Results may exhibit a significant ($p \leq 0.05$) p-value associated with testing whether the relative risk is equal to 1.00, while the corresponding 95 percent confidence interval on the relative risk contains the number 1.00. These results occur because the BMDP®-LR procedure uses a normal distribution in calculating an approximate 95 percent confidence interval and a chi-square distribution based on a likelihood radio statistic (9) in the determination of a p-value. Similarly, the results may exhibit a 95 percent confidence interval of a relative risk that does not contain the number 1.00, while the corresponding p-value is not significant ($p > 0.05$) for the reasons stated above.

Incorporating covariate and interaction information, subpanels (c) and (d) report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association between the discrete dependent variable and initial dioxin. Immediately below the specified assumption, the aggregate sample size (n) is presented for a multiple logistic regression of the discrete dependent variable on $\log_2$ (initial dioxin) including covariate and interactions in the adjusted model. Based on the multiple logistic regression model, the adjusted relative risk for the $\log_2$ (initial dioxin) term and its associated 95 percent confidence interval are reported for each assumption. The p-value for testing whether the adjusted relative risk is equal to 1 also is presented under both assumptions. Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple regression model after implementing the modeling strategy are presented under covariate remarks, along with the associated p-values. If the multiple logistic regression model contains a significant initial dioxin-by-covariate interaction with an associated p-value less than or equal to 0.01, then the adjusted relative risk, 95 percent confidence interval, and associated p-value generally are not reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained in the model are, however, reported under covariate remarks. For some clinical assessments, an analyst may exercise discretion and report an adjusted relative risk, 95 percent confidence interval, and an associated p-value from a model that excludes the interaction having a p-value less than 0.01. When these discretionary followup analyses are performed, the results are reported along with three asterisks (***) and are explained by a table footnote. If the multiple logistic regression model contains a significant initial dioxin-by-covariate interaction with a p-value between 0.01 and 0.05, then the adjusted relative risk, 95 percent confidence interval, and associated p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case (i.e., $p \leq 0.01$ or $0.01 < p \leq 0.05$), stratified analyses are undertaken and the results are reported in an appropriate appendix.

Subpanels (e) and (f) of Table 13-4, for example, report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association of the discrete dependent variable with current dioxin and time since tour without adjusting for covariate information. Multiple logistic regression techniques are used to generate the statistics provided in both panels. In the multiple logistic regression model, current dioxin is treated as a continuous variable and time since tour as a discrete variable. The interaction of current dioxin and time since tour also is included in the model. For the logistic regression model, time since tour is dichotomized and separate statistics are presented for the association between the dependent variable and current dioxin within each time stratum. For each subpanel, the aggregate sample size (n) is presented under each specified assumption for the multiple logistic regression model. For presentation purposes, current dioxin and time since tour both are categorized. The numerical values defining the current dioxin categories are specified in a table footnote. The low, medium, and high categories are based on the lower 25th percent, the 25th to 75th percent, and the upper 25th percent of the measured current dioxin for the cohort corresponding to the specified assumption. The value of 18.6 years for time since tour corresponds to approximately the median value in the Ranch Hand cohort. The percentage of Ranch Hands with the specified dichotomous characteristic (as cited in the column heading) is calculated from the data and presented, along with sample size, for the combinations of trichotomized current dioxin and dichotomized time since tour. Each panel also contains a p-value (i.e., the first p-value in each subpanel) for the interaction of the multiple logistic regression using current dioxin in continuous form and time since tour in discrete form. The p-value for the interaction term provides a test of the equality of the relative risks for the two time strata. For each time stratum, the logistic regression on current dioxin ($\log_2$ scale) provides an estimated relative risk, associated 95 percent confidence interval, and p-value for testing the significance of the relative risk.

Incorporating covariate and interaction information into the analysis, subpanels (g) and (h) report summary statistics (for the minimal and maximal assumptions, respectively) assessing the association of the discrete dependent variable with current dioxin, time since tour, and the current dioxin-by-time interaction. Multiple logistic regression techniques are used to generate the statistics provided. In the multiple logistic regression model, current dioxin is included as a continuous variable and time since tour as a discrete variable. The interaction of current dioxin and time since tour also is included. The test of the interaction of current dioxin and time since tour (i.e., the first p-value in each subpanel) determines whether the adjusted relative risks of the two time strata differ significantly.

Immediately below the specified assumption, the aggregate sample size (n) is presented for the multiple logistic regression of the continuous dependent variable on $\log_2$ (current dioxin), time since tour, the current dioxin-by-time interaction, covariates, and other interactions retained in the model. For each time stratum (≤18.6 years or >18.6 years), separate statistics relating the dependent variable to current dioxin ($\log_2$ scale) are presented. Based on the multiple logistic regression analysis, the adjusted relative risk for the $\log_2$ (current dioxin) term, its associated 95 percent confidence interval, and a p-value for testing the significance of the adjusted relative risk are reported.

Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple logistic regression model after implementing the modeling strategy are presented under covariate remarks, along with the associated p-values. If the multiple logistic regression model contains a significant current dioxin-by-time-by-covariate interaction term such that the associated p-value is less than or equal to 0.01, then the adjusted relative risk, associated 95 percent confidence interval, and p-value generally are not reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained in the model, however, are reported under covariate remarks. For some clinical assessments, an analyst may exercise discretion and report an adjusted relative risk, 95 percent confidence interval, and an associated p-value from a model that excludes the interaction having a p-value less than 0.01. When these discretionary followup analyses are performed, the results will be reported along with three asterisks (***) and are explained by a table footnote. If the multiple logistic regression model contains a significant current dioxin-by-time-by-covariate interaction such that the interaction lies between 0.01 and 0.05, then the adjusted relative risk, 95 percent confidence interval, and p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case ($p \leq 0.01$ or $0.01 < p \leq 0.05$), stratified analyses are undertaken and reported in the appropriate appendix.

Subpanels (i) and (j) of Table 13-4, for example, show the results of unadjusted and adjusted analyses that compare Ranch Hands with high, low, and unknown current dioxin levels and Comparisons having background current dioxin levels on the relative frequency for a specified discrete dependent variable (e.g., percent of participants in a current dioxin category with an abnormal condition). The note at the bottom of the table defines the four categories. Sample sizes for each category and across the four categories are reported.

For the unadjusted analysis, a relative frequency is presented for each current dioxin category. The simultaneous equality of the four category relative frequencies is evaluated by the first p-value cited. For the individual contrasts of the three Ranch Hand categories versus Comparison background category, relative risks, associated 95 percent confidence intervals for the relative risks, and p-values to evaluate if the risks differ significantly from 1 are presented.

Results may exhibit a significant ($p \leq 0.05$) p-value associated with testing whether the relative risk is equal to 1.00, while the corresponding 95 percent confidence interval on the relative risk contains the number 1.00. Similarly, the results may exhibit a 95 percent confidence interval of a relative risk that does not contain the number 1.00, while the corresponding p-value is not significant (p>0.05). These patterns are due to the use of the normal distribution in calculating an approximate 95 percent confidence interval and the use of Fisher's exact test for unadjusted analyses in the determination of the corresponding p-values in the event of sparse data.

For an adjusted analysis, the table presents adjusted relative risks, 95 percent confidence intervals on the adjusted relative risks, and covariates and interactions retained in the adjusted model along with their associated p-values.

Discrete Variable With More Than Two Categories

Log-linear analysis techniques were used to analyze discrete dependent variables having more than two levels (e.g., low, normal, high—see Table 13-6). For the unadjusted and adjusted analyses relating such discrete dependent variables to initial dioxin, summary tables present sample sizes, relative frequencies, relative risks, 95 percent confidence intervals for the relative risks, and associated p-values. For the adjusted analyses, any covariates and interactions retained in the model along with their associated p-values also are presented. One difference between the table presentations for dichotomous dependent variables and discrete dependent variables with more than two levels is that relative frequencies of Ranch Hands belonging to each of the dependent variable categories are summarized with respect to each initial dioxin category (i.e., low, medium, and high initial dioxin). Therefore, for each initial dioxin level, the relative frequencies sum to 100 percent across the dependent variable categories. Also, for specified pairs of dependent variable levels (e.g., low and normal or high and normal for the discrete dependent variable), contrasts for high initial dioxin versus low initial dioxin, and medium initial dioxin versus low initial dioxin, are constructed with relative risks, 95 percent confidence intervals, and associated contrast p-values. Contrasts are based on a categorized form (i.e., low, medium, and high) of initial dioxin rather than $\log_2$ (initial dioxin). A p-value for an overall test of independence between the dependent variable and initial dioxin also is reported.

Similar to the log-linear analysis using initial dioxin, unadjusted and adjusted analyses of discrete dependent variables with more than two categories were performed using current dioxin and time since tour. For the unadjusted analysis, sample sizes, relative frequencies (within each current dioxin level), current dioxin contrasts for specified pairs of dependent variable levels with relative risks, 95 percent confidence intervals on the relative risks, and associated contrast p-values were reported for each time since tour stratum. For these analyses a categorized form of current dioxin (i.e., low, medium, and high), rather than the continuous form of $\log_2$ (current dioxin), is used. For the adjusted analysis, contrast-specific adjusted relative risks with 95 percent confidence intervals, associated contrast p-values, and covariates and interactions retained in the model along with associated p-values are presented. For both the unadjusted and the adjusted analyses, a p-value is provided that tests the significance of the interaction between current dioxin and time since tour and, for each time stratum, another p-value is reported as an overall test of independence between the discrete dependent variable and current dioxin.

For log-linear analyses of initial dioxin, and those concerning current dioxin and time since tour, the cutpoints between the three dioxin categories (i.e., between low and medium dioxin, and between medium and high dioxin) are the same under both the minimal and maximal assumptions. The actual cutpoints are relevant for log-linear analyses, and this standardization was done to permit a more valid comparison of category contrasts between the minimal and maximal assumptions.

Unadjusted and adjusted analyses comparing relative frequencies for discrete dependent variables of more than two categories also were performed to compare the four current dioxin categories. For the unadjusted analysis, sample sizes, relative frequencies (within each of the four categories), Ranch Hand versus Comparison contrasts for specified pairs of dependent variable levels with relative risks, 95 percent confidence intervals on the relative risks, and associated contrast p-values were reported. For the adjusted analysis, sample sizes, contrast-specific adjusted relative risks with 95 confidence intervals, associated contrast p-values, and covariates and interactions retained in the model along with associated p-values are presented. For both the unadjusted and the adjusted analyses, an all categories p-value is provided that tests the independence of the categories and the discrete dependent variable.

GRAPHICS

The analytic activities for the serum dioxin analyses were supplemented by two sets of graphic displays: data plots/histograms and interaction plots/histograms. These graphics were produced using the SYSTAT® graphics procedure (16).

Data Plots/Histograms

As part of the serum dioxin analyses, graphic displays were produced describing the relationship between each dependent variable and serum dioxin level, as well as relevant covariates and serum dioxin level. Evaluations of the relationships between dioxin and the covariates were carefully made because such relationships particularly are important in the interpretation of dioxin effects for this study (see Chapter 5, Covariate Associations). Initial and current dioxin levels were used in continuous form. Transformations used in statistical analyses also were incorporated into the graphic presentations.

For initial dioxin, dependent variable and covariate relationships were displayed separately for Ranch Hands under the minimal and maximal assumptions. In addition, graphic relationships between dependent health variables and current dioxin level, as well as relevant covariates and current dioxin level, were presented separately for all Comparisons and Ranch Hands.

For continuous dependent variables, bivariate scatterplots were produced. For binary or categorical dependent variables, bar charts with percentages of participants classified as abnormal for common interval groupings of dioxin were generated for each of the clinical areas. For the covariate associations section, relative frequency histograms were produced for each level of the covariate.

Figure 4-5 presents an illustration of the bar charts seen in the appendix for each clinical area. Figures 4-5(a), (b), and (c) display a positive relationship, no relationship, and a negative relationship between the percentage of participants classified as abnormal and dioxin. These displays were generated assuming equal sample sizes for each bar; inference based on unequal sample sizes is not straightforward. Figures 4-6(a), (b), and (c) illustrate

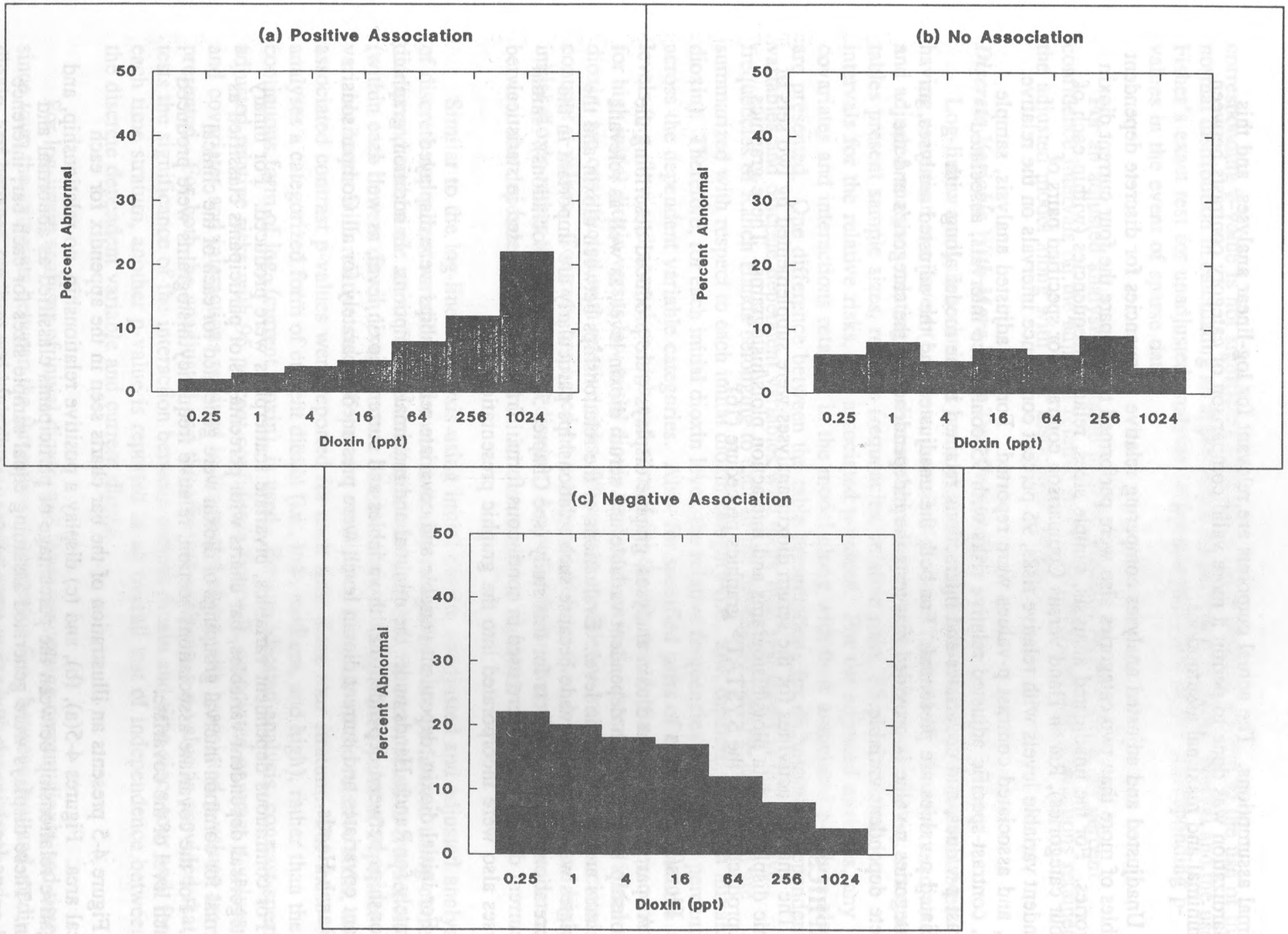

FIGURE 4-5. Hypothetical Data (Discrete Dependent Variable) versus Dioxin

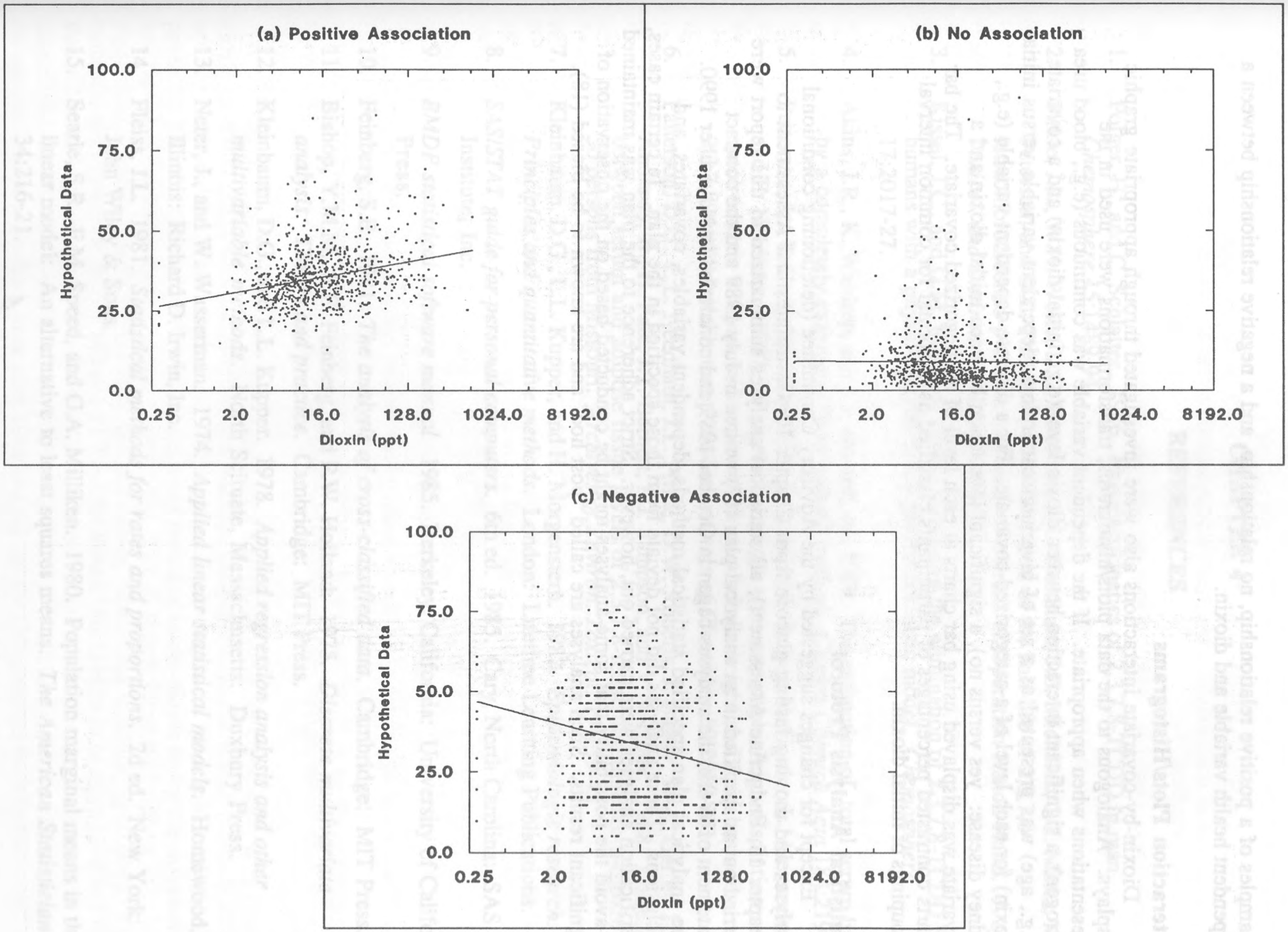

FIGURE 4-6. Hypothetical Data (Continuous Dependent Variable) versus Dioxin

examples of a positive relationship, no relationship, and a negative relationship between a dependent health variable and dioxin.

Interaction Plots/Histograms

Dioxin-by-covariate interactions also were investigated through appropriate graphic displays. Analogous to the data plots/histograms, transformations were used in the presentations when appropriate. If the dependent variable was continuous (e.g., blood urea nitrogen), a significant interaction between dioxin level (e.g., initial dioxin) and a covariate (e.g., age) was presented as a set of bivariate scatterplots (dependent variable versus initial dioxin) for each level of a categorized covariate. For a discrete dependent variable (e.g., kidney disease: yes versus no), a significant interaction between initial dioxin and a covariate was displayed using bar charts at each level of a categorized covariate. The bar charts contrasted percentages of participants classified as abnormal for common interval groupings of initial dioxin.

Statistical Analysis Protocol

Except for changes suggested by the Advisory Committee (deletioning conditional analyses and moving fasting glucose from Chapter 10, Gastrointestinal Assessment to Chapter 15, Endocrine Assessment), all statistical analyses summarized in this report were carried out as specified in an analytical plan (17) written in July 1989 and the contract Statement of Work; the analyses began in October 1989 and concluded in November 1990. The analytical plan specified statistical methods, dependent variables, covariates, and exclusions. These analyses did not deviate from those specified in the plan. In certain cases, clarification analyses were carried out, however. Strict adherence to the plan was maintained to avoid the possibility that some analyses might be conducted based on the observation of significant results. Such analyses are called "post hoc" and are known to be biased (18).

CHAPTER 4

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CHAPTER 5

COVARIATE ASSOCIATIONS

INTRODUCTION

This chapter evaluates the covariates used in adjusted statistical analyses for significant associations with initial dioxin levels for the Ranch Hand participants and current dioxin levels for the Ranch Hands and the Comparisons. The evaluation, with respect to initial dioxin levels for the Ranch Hand participants, was performed under both the minimal and the maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively; see Chapter 4, Statistical Methods, for a further discussion of these assumptions). Associations between the covariates and the health status variables are documented in the previous Air Force Health Study report of the 1987 examination data (1).

Table 5-1 presents geometric mean dioxin levels (transformed from the logarithm base 2 scale) and sample sizes by covariate category under both assumptions for initial dioxin and under both group classifications (i.e., Ranch Hands and Comparisons) for current dioxin. Mean dioxin levels, expressed in parts per trillion (ppt), were evaluated for statistical significance across the defined categories of a particular covariate (e.g., under both assumptions, initial dioxin means of Black and non-Black Ranch Hand participants were compared for a statistically significant difference). The aggregate sample size and the significance probability associated with comparing dioxin means across covariate levels are included in the table. Aggregate sample sizes may differ from covariate to covariate because of missing covariate information. The significance probability was determined from statistics calculated on the logarithm base 2 scale of the serum dioxin concentration. For covariates on a continuous scale, the correlation coefficient and the associated significance probability are presented in the table. The correlation coefficient is based on the association between the covariate and the logarithm base 2 of the serum dioxin concentration. Dioxin levels equal to zero were assigned a value of 0.1 ppt due to the logarithmic transformation used in the analyses of all Ranch Hands and all Comparisons.

MATCHING VARIABLES (AGE, RACE, AND OCCUPATION)

The variables age, race, and military occupation were used in the design of the Air Force Health Study to match Ranch Hand participants with Comparisons and thus reduce the association between these variables and group status. It was not possible to eliminate the association of these variables with serum dioxin through the study design, however.

In general, age at Baseline (1982) exhibited a significant negative correlation with initial dioxin ($p<0.001$ under both the minimal and maximal assumptions). For Ranch Hands born in or after 1942, and for those born before 1942, initial dioxin means were 226.6 ppt and 148.5 ppt under the minimal assumption. Corresponding means of initial dioxin under the maximal assumption were 149.9 and 101.6 ppt, respectively. For all Ranch Hand participants a significant negative correlation between age and current dioxin was exhibited ($p<0.001$). The current dioxin means were 19.3 ppt and 11.7 ppt for Ranch Hands born in or after 1942 and Ranch Hands born before 1942. For the Comparisons the correlation between age and current dioxin was also significant, but positive ($p<0.001$). The current dioxin means were 3.0 ppt for Comparisons born in or after 1942 and 4.0 ppt for Comparisons born before 1942.

TABLE 5-1.

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Matching Variables					
Age (continuous)	n	521	742	866	804
	Correlation	-0.240	-0.200	-0.205	0.155
	p-Value	<0.001	<0.001	<0.001	<0.001
Age (year of birth) (discrete)	n	521	742	866	804
	Mean (n)				
	Born≥1942	226.6 (237)	149.9 (314)	19.3 (355)	3.0 (330)
	Born<1942	148.5 (284)	101.6 (428)	11.7 (511)	4.0 (474)
	p-Value	<0.001	<0.001	<0.001	<0.001
Race	n	521	742	866	804
	Mean (n)				
	Black	134.5 (32)	114.7 (38)	14.6 (44)	2.9 (49)
	Non-Black	183.5 (489)	120.0 (704)	14.4 (822)	3.6 (755)
	p-Value	0.011	0.701	0.904	0.288
Occupation	n	521	742	866	804
	Mean (n)				
	Officer	91.7 (108)	61.4 (246)	7.7 (319)	4.0 (291)
	Enlisted Flyer	172.3 (108)	134.7 (132)	16.3 (148)	3.7 (127)
	Enlisted Groundcrew	232.1 (305)	180.2 (364)	23.2 (399)	3.2 (386)
	p-Value	<0.001	<0.001	<0.001	0.007
Alcohol Variables					
Current Alcohol Use (continuous)	n	518	737	861	804
	Correlation	0.043	0.014	0.039	0.023
	p-Value	0.326	0.703	0.255	0.523
Current Alcohol Use (drinks/day) (discrete)	n	518	737	861	804
	Mean (n)				
	0-1	181.8 (420)	121.4 (594)	14.3 (696)	3.6 (630)
	>1-4	158.4 (83)	105.5 (124)	13.6 (143)	3.2 (143)
	>4	276.6 (15)	182.2 (19)	22.3 (22)	4.5 (31)
	p-Value	0.051	0.049	0.171	0.100

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

		Initial Dioxin (Ranch Hands) Assumption		Current Dioxin	
Variable	Statistic	Minimal	Maximal	Ranch Hand	Comparison
Lifetime Alcohol History (continuous)	n	515	733	857	802
	Correlation	0.044	0.057	0.012	0.005
	p-Value	0.318	0.125	0.728	0.894
Lifetime Alcohol History (drink-years) (discrete)	n	515	733	857	802
	Mean (n)				
	0	233.7 (57)	163.7 (73)	18.7 (85)	3.8 (61)
	>0-40	167.5 (345)	110.1 (507)	13.4 (599)	3.5 (547)
	>40	192.8 (113)	134.3 (153)	15.8 (173)	3.6 (194)
	p-Value	0.012	0.001	0.021	0.810
Current Wine Use (continuous)	n	517	737	861	803
	Correlation	-0.111	-0.110	-0.054	-0.007
	p-Value	0.011	0.003	0.110	0.853
Current Wine Use (drinks/day) (discrete)	n	517	737	861	803
	Mean (n)				
	0	197.2 (349)	139.9 (459)	16.7 (526)	3.6 (458)
	>0	148.5 (168)	92.1 (278)	11.3 (335)	3.5 (345)
	p-Value	<0.001	<0.001	<0.001	0.656
Lifetime Wine History (continuous)	n	517	736	860	802
	Correlation	-0.160	-0.107	-0.059	0.018
	p-Value	<0.001	0.004	0.086	0.603
Lifetime Wine History (drink-years) (discrete)	n	517	736	860	802
	Mean (n)				
	0	207.4 (301)	144.2 (398)	16.9 (458)	3.6 (403)
	>0-10	151.9 (191)	97.1 (302)	11.8 (363)	3.5 (367)
	>10	117.9 (25)	87.5 (36)	12.9 (39)	4.3 (32)
	p-Value	<0.001	<0.001	<0.001	0.482

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Smoking Variables					
Current Cigarette Smoking (continuous)	n	521	742	866	804
	Correlation	0.013	0.034	-0.067	-0.074
	p-Value	0.758	0.355	0.049	0.035
Current Cigarette Smoking (cigarettes/ day) (discrete)	n	521	742	866	804
	Mean (n)				
	0-Never	189.0 (135)	114.1 (207)	15.2 (236)	4.3 (223)
	0-Former	169.1 (196)	113.6 (282)	14.5 (323)	3.5 (336)
	>0-20	187.9 (101)	137.4 (131)	14.5 (159)	2.9 (128)
	>20	182.7 (89)	126.6 (122)	12.9 (148)	3.1 (117)
	p-Value	0.603	0.208	0.587	<0.001
Lifetime Cigarette Smoking History (continuous)	n	521	742	866	804
	Correlation	-0.064	-0.010	-0.094	-0.013
	p-Value	0.147	0.783	0.006	0.719
Lifetime Cigarette Smoking History (pack-years) (discrete)	n	521	742	866	804
	Mean (n)				
	0	187.7 (136)	113.8 (208)	15.1 (237)	4.3 (223)
	>0-10	180.6 (152)	124.5 (206)	15.3 (237)	2.9 (218)
	>10	175.3 (233)	120.7 (328)	13.5 (392)	3.6 (363)
	p-Value	0.749	0.621	0.297	<0.001
Sun Exposure-Related Variables					
Average Lifetime Residential Latitude[a]	n	489	704	821	750
	Mean (n)				
	Latitude <37°	196.5 (205)	126.1 (295)	14.8 (344)	3.7 (385)
	Latitude ≥37°	174.6 (284)	115.8 (409)	14.2 (477)	3.6 (365)
	p-Value	0.128	0.247	0.596	0.786

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Ethnic Background[a,b]	n	476	687	801	738
	Mean (n)				
	AB	179.8 (447)	116.5 (654)	14.0 (767)	3.7 (701)
	CDE	260.4 (29)	214.8 (33)	29.1 (34)	2.9 (37)
	p-Value	0.022	<0.001	<0.001	0.115
Skin Color[a]	n	489	703	821	755
	Mean (n)				
	Peach	183.3 (395)	122.5 (559)	14.7 (651)	3.6 (615)
	Non-Peach	184.3 (94)	111.5 (144)	13.4 (170)	3.5 (140)
	p-Value	0.952	0.293	0.354	0.582
Hair Color[a]	n	489	704	822	754
	Mean (n)				
	Black/Dark Brown	196.7 (332)	129.0 (467)	15.7 (541)	3.6 (524)
	Other	158.4 (157)	104.2 (237)	12.2 (281)	3.7 (230)
	p-Value	0.008	0.005	0.004	0.486
Eye Color[a]	n	488	703	821	753
	Mean (n)				
	Brown	206.2 (150)	135.4 (211)	16.4 (242)	3.4 (227)
	Hazel/Green	167.8 (144)	113.5 (205)	13.3 (241)	3.4 (188)
	Grey/Blue	179.6 (194)	114.4 (287)	13.8 (338)	3.9 (338)
	p-Value	0.101	0.097	0.103	0.072
Reaction of Skin to Sun After at Least 2 Hours, After First Exposure[a]	n	489	704	822	755
	Mean (n)				
	Burned Painfully	182.6 (35)	123.3 (48)	14.8 (56)	5.0 (48)
	Burned	170.1 (63)	117.6 (87)	14.9 (102)	3.7 (90)
	Became Red	192.8 (195)	120.1 (292)	14.2 (345)	3.5 (326)
	No Reaction	179.1 (196)	120.1 (277)	14.3 (319)	3.5 (291)
	p-Value	0.720	0.995	0.997	0.062

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

		Initial Dioxin (Ranch Hands) Assumption		Current Dioxin	
Variable	Statistic	Minimal	Maximal	Ranch Hand	Comparison
Reaction of Skin to Sun After Repeated Exposure[a]	n	489	704	822	754
	Mean (n)				
	Freckled-No Tan	202.4 (11)	138.1 (15)	15.9 (18)	5.6 (18)
	Tanned Mildly	207.2 (74)	149.4 (95)	16.1 (119)	3.4 (109)
	Tanned Moderately	178.3 (246)	113.8 (366)	14.5 (417)	3.8 (393)
	Tanned Deep Brown	179.9 (158)	118.2 (228)	13.4 (268)	3.4 (234)
	p-Value	0.565	0.094	0.507	0.088
Composite Sun Reaction Index[a,c]	n	489	704	822	754
	Mean (n)				
	Low	180.7 (358)	116.5 (526)	14.0 (609)	3.5 (557)
	Medium	194.3 (90)	134.5 (121)	15.8 (147)	3.4 (139)
	High	184.9 (41)	124.4 (57)	15.1 (66)	5.1 (58)
	p-Value	0.764	0.319	0.496	0.008
Carcinogen Exposure Variables					
Asbestos Exposure	n	521	742	866	804
	Mean (n)				
	Yes	183.6 (129)	121.3 (185)	14.6 (212)	3.7 (195)
	No	178.8 (392)	119.3 (557)	14.3 (654)	3.5 (609)
	p-Value	0.754	0.832	0.802	0.580
Ionizing Radiation Exposure	n	521	742	866	804
	Mean (n)				
	Yes	160.6 (105)	115.7 (143)	12.3 (175)	3.5 (212)
	No	185.2 (416)	120.8 (599)	15.0 (691)	3.6 (592)
	p-Value	0.118	0.626	0.070	0.833
Industrial Chemical Exposure	n	521	742	866	804
	Mean (n)				
	Yes	196.8 (311)	138.8 (408)	16.6 (470)	3.4 (443)
	No	157.8 (210)	100.0 (334)	12.1 (396)	3.8 (361)
	p-Value	0.003	<0.001	<0.001	0.043

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Herbicide Exposure	n	521	742	866	804
	Mean (n)				
	Yes	180.5 (493)	119.7 (703)	14.6 (816)	3.8 (263)
	No	170.6 (28)	121.3 (39)	11.9 (50)	3.5 (541)
	p-Value	0.728	0.933	0.227	0.151
Insecticide Exposure	n	521	742	866	804
	Mean (n)				
	Yes	173.0 (381)	118.0 (537)	14.1 (626)	3.7 (454)
	No	200.5 (140)	124.6 (205)	15.2 (240)	3.5 (350)
	p-Value	0.074	0.484	0.391	0.430
Degreasing Chemical Exposure	n	521	742	866	804
	Mean (n)				
	Yes	196.0 (353)	137.3 (471)	17.1 (529)	3.6 (496)
	No	150.5 (168)	94.5 (271)	10.9 (337)	3.6 (308)
	p-Value	0.001	<0.001	<0.001	0.926
Anthracene Exposure	n	521	742	866	803
	Mean (n)				
	Yes	83.4 (1)	83.4 (1)	15.0 (1)	4.0 (3)
	No	180.3 (520)	119.8 (741)	14.4 (865)	3.6 (800)
	p-Value	0.357	0.704	0.971	0.832
Arsenic Exposure	n	521	741	865	803
	Mean (n)				
	Yes	156.0 (11)	100.5 (18)	12.9 (21)	3.1 (13)
	No	180.6 (510)	120.4 (723)	14.4 (844)	3.6 (790)
	p-Value	0.567	0.426	0.669	0.557
Benzene Exposure	n	521	742	866	804
	Mean (n)				
	Yes	226.2 (21)	162.6 (27)	16.9 (33)	3.7 (21)
	No	178.3 (500)	118.4 (715)	14.3 (833)	3.6 (783)
	p-Value	0.201	0.089	0.522	0.893

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Benzidine Exposure	n	521	742	866	802
	Mean (n)				
	Yes	127.5 (5)	93.8 (7)	7.5 (9)	3.7 (9)
	No	180.6 (516)	120.0 (735)	14.5 (857)	3.6 (793)
	p-Value	0.355	0.495	0.313	0.929
Chromate Exposure	n	519	739	863	804
	Mean (n)				
	Yes	232.5 (36)	159.2 (47)	17.8 (55)	3.3 (39)
	No	176.6 (483)	117.5 (692)	14.2 (808)	3.6 (765)
	p-Value	0.057	0.034	0.160	0.593
Coal Tar Exposure	n	521	742	866	804
	Mean (n)				
	Yes	137.0 (18)	121.7 (20)	9.7 (27)	4.1 (27)
	No	181.8 (503)	119.7 (722)	14.6 (839)	3.6 (777)
	p-Value	0.158	0.940	0.207	0.459
Creosote Exposure	n	521	742	866	804
	Mean (n)				
	Yes	175.7 (47)	125.6 (62)	13.8 (76)	3.2 (63)
	No	180.4 (474)	119.2 (680)	14.4 (790)	3.6 (741)
	p-Value	0.837	0.683	0.752	0.381
Aminodiphenyl Exposure	n	521	742	866	802
	Mean (n)				
	Yes	83.2 (2)	83.2 (2)	14.4 (2)	4.4 (4)
	No	180.5 (519)	119.9 (740)	14.4 (864)	3.6 (798)
	p-Value	<0.001	<0.001	0.998	0.649
Chloromethyl Ether Exposure	n	520	740	864	804
	Mean (n)				
	Yes	144.3 (3)	65.4 (8)	6.0 (10)	4.2 (11)
	No	180.1 (517)	120.5 (732)	14.5 (854)	3.6 (793)
	p-Value	0.648	0.070	0.015	0.267

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Mustard Gas Exposure	n	521	742	866	804
	Mean (n)				
	Yes	126.3 (3)	126.3 (3)	10.2 (4)	3.8 (4)
	No	180.4 (518)	119.7 (739)	14.4 (862)	3.6 (800)
	p-Value	0.461	0.923	0.553	0.633
Naphthylamine Exposure	n	521	741	865	803
	Mean (n)				
	Yes	219.1 (23)	179.5 (26)	19.9 (30)	3.3 (20)
	No	178.4 (498)	118.2 (715)	14.2 (835)	3.6 (783)
	p-Value	0.249	0.028	0.217	0.759
Cutting Oils Exposure	n	521	742	866	804
	Mean (n)				
	Yes	174.1 (76)	118.8 (107)	13.9 (124)	3.0 (102)
	No	181.0 (445)	119.9 (635)	14.5 (742)	3.7 (702)
	p-Value	0.706	0.924	0.693	0.076
Trichloroethylene Exposure	n	518	738	862	804
	Mean (n)				
	Yes	207.5 (57)	142.4 (76)	15.5 (91)	3.3 (71)
	No	176.7 (461)	117.3 (662)	14.2 (771)	3.6 (733)
	p-Value	0.170	0.092	0.547	0.386
Ultraviolet Light (Not Sun) Exposure	n	521	742	866	803
	Mean (n)				
	Yes	142.7 (13)	101.1 (18)	13.8 (20)	4.2 (17)
	No	181.1 (508)	120.3 (724)	14.4 (846)	3.6 (786)
	p-Value	0.311	0.445	0.808	0.232
Vinyl Chloride Exposure	n	520	741	865	803
	Mean (n)				
	Yes	209.1 (10)	144.1 (13)	17.0 (15)	4.1 (11)
	No	179.5 (510)	119.3 (728)	14.3 (850)	3.6 (792)
	p-Value	0.568	0.478	0.564	0.363

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Composite Carcinogen Exposure	n	515	731	855	796
	Mean (n)				
	Yes	192.9 (155)	134.2 (208)	16.4 (236)	3.3 (179)
	No	174.3 (360)	114.7 (523)	13.6 (619)	3.6 (617)
	p-Value	0.209	0.045	0.038	0.157
Personal and Family Health Variables					
Cholesterol (continuous)	n	521	742	866	804
	Correlation	0.054	0.046	0.051	0.046
	p-Value	0.217	0.215	0.137	0.196
Cholesterol (mg/dl) (discrete)	n	521	742	866	804
	Mean (n)				
	≤200	168.4 (163)	112.0 (238)	13.0 (287)	3.4 (281)
	>200-230	175.8 (177)	120.7 (244)	15.2 (275)	3.4 (244)
	>230	195.6 (181)	126.4 (260)	15.1 (304)	3.9 (279)
	p-Value	0.227	0.362	0.175	0.139
HDL (continuous)	n	521	742	866	804
	Correlation	-0.074	-0.142	-0.136	-0.099
	p-Value	0.090	<0.001	<0.001	0.005
HDL (µg/dl) (discrete)	n	521	742	866	804
	Mean (n)				
	≤40	182.7 (206)	138.6 (261)	17.5 (289)	3.9 (264)
	>40-50	188.6 (173)	121.7 (251)	14.5 (294)	3.7 (294)
	>50	166.5 (142)	99.6 (230)	11.6 (283)	3.1 (246)
	p-Value	0.400	<0.001	<0.001	0.008
Cholesterol-HDL Ratio (continuous)	n	521	742	866	804
	Correlation	0.078	0.146	0.148	0.109
	p-Value	0.076	<0.001	<0.001	0.002

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

		Initial Dioxin (Ranch Hands) Assumption		Current Dioxin	
Variable	Statistic	Minimal	Maximal	Ranch Hand	Comparison
Cholesterol-HDL Ratio (discrete)	n	521	742	866	804
	Mean (n)				
	≤4.2	158.1 (138)	97.0 (222)	11.3 (274)	3.0 (264)
	>4.2-5.5	187.9 (199)	124.5 (283)	15.2 (322)	3.9 (286)
	>5.5	189.3 (184)	139.3 (237)	17.2 (270)	3.9 (254)
	p-Value	0.104	<0.001	<0.001	0.001
Diabetic Class[d]	n	519	740	863	802
	Mean (n)				
	Normal	174.4 (371)	112.8 (548)	13.5 (648)	3.4 (620)
	Impaired	176.2 (82)	123.7 (110)	14.8 (130)	4.0 (115)
	Diabetic	221.9 (66)	169.9 (82)	21.9 (85)	4.5 (67)
	p-Value	0.095	0.001	0.001	0.028
Differential Cortisol Response (continuous)	n	509	721	839	770
	Correlation	-0.024	-0.059	-0.076	-0.052
	p-Value	0.583	0.112	0.027	0.152
Differential Cortisol Response (mg/dl) (discrete)	n	509	721	839	770
	Mean (n)				
	≤0.6	191.7 (185)	132.0 (251)	15.7 (288)	3.6 (275)
	>0.6-4.0	189.0 (192)	127.5 (265)	16.4 (299)	3.8 (262)
	>4.0	155.5 (132)	101.4 (205)	11.5 (252)	3.3 (233)
	p-Value	0.056	0.007	<0.001	0.315
Percent Body Fat (continuous)	n	521	742	866	804
	Correlation	0.139	0.210	0.300	0.154
	p-Value	0.001	<0.001	<0.001	<0.001
Percent Body Fat (discrete)	n	521	742	866	804
	Mean (n)				
	Lean/Normal: ≤25%	170.4 (389)	110.2 (579)	12.9 (693)	3.3 (608)
	Obese: >25%	211.4 (132)	161.1 (163)	22.4 (173)	4.4 (196)
	p-Value	0.018	<0.001	<0.001	<0.001

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

		Initial Dioxin (Ranch Hands) Assumption		Current Dioxin	
Variable	Statistic	Minimal	Maximal	Ranch Hand	Comparison
Family History of Heart Disease	n	521	742	866	804
	Mean (n)				
	Yes	176.9 (125)	118.5 (178)	13.9 (208)	3.5 (177)
	No	181.0 (396)	120.2 (564)	14.6 (658)	3.6 (627)
	p-Value	0.793	0.867	0.591	0.765
Family History of Heart Disease Before Age 50	n	521	742	866	804
	Mean (n)				
	Yes	179.0 (17)	106.5 (27)	14.5 (30)	2.3 (26)
	No	180.0 (504)	120.3 (715)	14.4 (836)	3.6 (778)
	p-Value	0.979	0.515	0.970	0.134
Other Variables					
Education	n	517	737	860	799
	Mean (n)				
	High School	198.0 (322)	153.1 (395)	18.2 (448)	3.5 (400)
	College	153.4 (195)	89.8 (342)	11.1 (412)	3.7 (399)
	p-Value	0.001	<0.001	<0.001	0.378
Blood Type	n	519	738	861	802
	Mean (n)				
	A	182.4 (224)	125.0 (307)	15.0 (351)	3.6 (311)
	AB	171.9 (18)	111.8 (27)	14.6 (31)	4.3 (24)
	B	184.5 (54)	128.5 (72)	14.9 (87)	3.8 (98)
	O	177.3 (223)	114.4 (332)	13.8 (392)	3.4 (369)
	p-Value	0.973	0.593	0.773	0.469
Presence of Pre-SEA Acne	n	521	742	866	804
	Mean (n)				
	Yes	193.0 (53)	133.6 (71)	15.1 (88)	2.8 (88)
	No	178.6 (468)	118.4 (671)	14.3 (778)	3.4 (716)
	p-Value	0.523	0.309	0.819	0.246

TABLE 5-1. (Continued)

Relationship of Covariates to Initial and Current Dioxin

Variable	Statistic	Initial Dioxin (Ranch Hands) Assumption: Minimal	Initial Dioxin (Ranch Hands) Assumption: Maximal	Current Dioxin: Ranch Hand	Current Dioxin: Comparison
Personality Type	n	506	717	834	769
	Mean (n)				
	Type A	173.9 (222)	112.3 (331)	13.6 (381)	3.5 (325)
	Type B	185.2 (284)	128.3 (386)	15.3 (453)	3.6 (444)
	p-Value	0.401	0.061	0.148	0.685

[a]Blacks excluded.

[b]Ethnic Background – A: English, Welsh, Scottish, or Irish
B: Scandinavian, German, Polish, Russian, Other Slavic, Jewish, or French
C: Spanish, Italian, or Greek
D: Mexican, American Indian, or Asian
E: African
AB: A or B
CDE: C, D, or E.

[c]Composite Sun Reaction Index (from reaction of skin after at least 2 hours after first exposure and reaction of skin after repeated exposure) – High: Burns painfully and/or freckles with no tan
Medium: Burns and/or tans mildly
Low: All other reactions.

[d]Diabetic Class – Normal: <140 mg/dl 2-hour postprandial glucose
Impaired: ≥140-<200 mg/dl 2-hour postprandial glucose
Diabetic: Verified past history of diabetes or ≥200 mg/dl 2-hour postprandial glucose.

Note: All means expressed in parts per trillion and have been transformed from the logarithm (base 2) scale.

Under the minimal assumption, the Black and non-Black Ranch Hand categories had significantly different initial dioxin means (134.5 ppt versus 183.5 ppt, p=0.011). Under the maximal assumption, the initial dioxin means were not significantly different between the race categories (p=0.701). The current dioxin means were also not significantly different between the race categories for all Ranch Hand participants and for all Comparisons (Ranch Hands, p=0.904; Comparisons, p=0.288).

As expected, the initial dioxin means differed significantly, under both assumptions, among the Ranch Hands who served as officers, enlisted flyers, and enlisted groundcrew (minimal, p<0.001; maximal, p<0.001). The initial dioxin means, under the minimal assumption, were 91.7 ppt for the officers, 172.3 ppt for the enlisted flyers, and 232.1 ppt for the enlisted groundcrew. The corresponding means under the maximal assumption were 61.4, 134.7, and 180.2 ppt, respectively. The current dioxin means also differed significantly for all Ranch Hands (p<0.001) and for all Comparisons (p=0.007). However, for the Ranch Hands, the enlisted groundcrew had the highest current dioxin mean (officers: 7.7 ppt; enlisted flyers: 16.3 ppt; enlisted groundcrew: 23.2 ppt), whereas, for the Comparisons, the officers had the highest current dioxin mean (officers: 4.0 ppt; enlisted flyers: 3.7 ppt; enlisted groundcrew: 3.2 ppt). (See Chapter 2, Dioxin Assay, for a further discussion of these results.)

DRINKING HABITS

Drinking habits were analyzed on the basis of current alcohol use, lifetime alcohol history, current wine use, and lifetime wine history.

Under the minimal assumption, the mean initial dioxin levels for Ranch Hands with current alcohol use values categorized as zero to one drink per day, over one but no more than four drinks per day, and over four drinks per day were marginally significant (p=0.051; 0-1 drink per day: 181.8 ppt; >1-4 drinks per day: 158.4 ppt; >4 drinks per day: 276.6 ppt). Under the maximal assumption, the mean initial dioxin levels differed significantly (p=0.049) with corresponding means of 121.4 ppt, 105.5 ppt, and 182.2 ppt for increasing current alcohol use categories. However, when current alcohol use was treated as a continuous variable, the correlation between current alcohol use and initial dioxin was not significant under both assumptions (minimal, p=0.326; maximal, p=0.703).

For all Ranch Hand participants, the mean current dioxin levels did not differ significantly among the current alcohol use categories (p=0.171). The differences were marginally significant for all Comparisons (p=0.100; 0-1 drink per day: 3.6 ppt; >1-4 drinks per day: 3.2 ppt; >4 drinks per day: 4.5 ppt). The correlation between current alcohol use, when treated as a continuous variable, and current dioxin was nonsignificant for both groups (Ranch Hands, p=0.255; Comparisons, p=0.523).

Under both assumptions, mean initial dioxin levels differed significantly among Ranch Hands who had lifetime alcohol history values of 0 drink-years, over 0 but no more than 40 drink-years, and over 40 drink-years (minimal, p=0.012; maximal, p=0.001). (See Chapter 7, Malignancy Assessment, for a definition of drink-years.) For these lifetime alcohol history categories, the mean initial dioxin levels for the minimal cohort were 233.7, 167.5, and 192.8 ppt, respectively. For the maximal cohort, the corresponding mean initial dioxin levels were 163.7, 110.1, and 134.3 ppt, respectively. Under both assumptions, however, the correlation between lifetime alcohol history and initial dioxin was not significant when lifetime alcohol history was treated as a continuous variable (minimal, p=0.318; maximal, p=0.125).

The mean current dioxin levels were significantly different among the lifetime alcohol categories for all Ranch Hand participants (p=0.021). The current dioxin means for the categories of 0 drink-years, over 0 but no more than 40 drink-years, and over 40 drink-years were 18.7, 13.4, and 15.8 ppt. For all Comparisons, the differences in the mean current dioxin levels were not significant (p=0.810). When lifetime alcohol history was treated as a continuous variable, the correlation between lifetime alcohol history and current dioxin was not significant for both groups (Ranch Hands, p=0.728; Comparisons, p=0.894).

Under both the minimal and maximal assumptions, the mean initial dioxin levels differed significantly between Ranch Hands who reported they did not drink wine and Ranch Hands who reported they drank wine at the time of the 1987 examination (minimal, p<0.001; maximal, p<0.001). The mean initial dioxin levels for the minimal cohort were 197.2 ppt for Ranch Hands with zero drinks per day and 148.5 ppt for Ranch Hands with more than zero drinks per day. For the maximal cohort, the corresponding mean initial dioxin levels were 139.9 ppt and 92.1 ppt. When current wine use was treated as a continuous variable, a significant negative correlation between current wine use and initial dioxin was exhibited under both assumptions (minimal, p=0.011; maximal, p=0.003).

For all Ranch Hand participants, the mean current dioxin level was significantly higher for Ranch Hands who reported they did not drink wine than for Ranch Hands who reported they drank wine at the time of the 1987 examination (p<0.001). The current dioxin means were 16.7 ppt and 11.3 ppt for the two current wine use strata (i.e., 0 drinks per day and >0 drinks per day). However, the correlation between current wine use, when treated as a continuous variable, and current dioxin was nonsignificant for all Ranch Hand participants (p=0.110). For all Comparisons, the current dioxin means did not differ significantly between the two current wine use categories (p=0.656). The correlation between current wine use and current dioxin was also nonsignificant for the Comparisons (p=0.853).

The mean initial dioxin levels differed significantly among the lifetime wine history categories (0 drink-years, >0-10 drink-years, and >10 drink-years) under both assumptions (minimal, p<0.001; maximal, p<0.001). Under the minimal assumption, the mean initial dioxin levels were 207.4, 151.9, and 117.9 ppt for the lifetime wine history categories (0 drink-years, >0-10 drink-years, and >10 drink-years). Under the maximal assumption, the corresponding means were 144.2, 97.1, and 87.5 ppt, respectively. When lifetime wine history was treated as a continuous variable, a significant negative correlation between lifetime wine history and current dioxin was exhibited under both assumptions (minimal, p<0.001; maximal, p=0.004).

There was a significant difference in the mean current dioxin levels for all Ranch Hand participants with lifetime wine history values of 0 drink-years, greater than 0 but no more than 10 drink-years, and greater than 10 drink-years (p<0.001). The mean current dioxin levels were 16.9, 11.8, and 12.9 ppt for the lifetime wine history categories, respectively. For all Ranch Hand participants, there was a marginally significant negative correlation between lifetime wine history, when treated as a continuous variable, and current dioxin (p=0.086). For all Comparisons, the difference in mean current dioxin levels among the lifetime wine history categories was not significant (p=0.482). In contrast to the Ranch Hands, the correlation between lifetime wine history and current dioxin was positive, but nonsignificant for all Comparisons (p=0.603).

SMOKING HABITS

The covariates used to evaluate smoking habits were current cigarette smoking and lifetime cigarette smoking history.

Under the minimal and maximal assumptions, the mean initial dioxin levels were not significantly different for Ranch Hands with current cigarette smoking habits categorized as follows: never smoked, formerly smoked, smoked no more than 20 cigarettes per day, and smoked over 20 cigarettes per day (minimal, p=0.603; maximal, p=0.208). Similarly, the mean current dioxin levels were not significantly different among the defined current cigarette smoking categories for all Ranch Hand participants (p=0.587). However, for all Comparisons, there was a significant difference in the mean current dioxin levels among the current cigarette smoking categories (p<0.001). The mean current dioxin levels were 4.3 ppt for those who never smoked, 3.5 ppt for those who formerly smoked, 2.9 ppt for those who smoked no more than 20 cigarettes per day, and 3.1 ppt for those who smoked over 20 cigarettes per day.

When current cigarette smoking was treated as a continuous variable, the correlation between initial dioxin and current cigarette smoking was not significant under both assumptions (minimal, p=0.758; maximal, p=0.355). However, for all Ranch Hand participants, the correlation between current dioxin and current cigarette smoking was significantly negative (p=0.049). For all Comparisons, there was also a significant negative association between current dioxin and current cigarette smoking (p=0.035).

Mean initial dioxin levels were compared for Ranch Hands who had categorized lifetime cigarette smoking history values of 0 pack-years, up to 10 pack-years, and over 10 pack-years. (See Chapter 7 for a definition of pack-years.) Under both assumptions, the means were not significantly different (minimal, p=0.749; maximal, p=0.621). In addition, mean current dioxin levels also did not differ significantly among all Ranch Hand participants for the categorized lifetime cigarette smoking history values (p=0.297). However, there was a significant difference in mean current dioxin levels for all Comparisons (p<0.001; 0 pack-years: 4.3 ppt; >0-10 pack-years: 2.9 ppt; >10 pack-years: 3.6 ppt).

The correlation between initial dioxin and lifetime cigarette smoking, when treated as a continuous variable, was not significant under both assumptions (minimal, p=0.147; maximal, p=0.783). Likewise, the correlation between current dioxin and lifetime cigarette smoking was not significant for all Comparisons (p=0.719). However, for all Ranch Hand participants, there was a significant negative correlation between current dioxin and lifetime cigarette smoking (p=0.006).

SUN EXPOSURE CHARACTERISTICS

The following covariates characterize sun exposure and reaction to sun exposure: average lifetime residential latitude, ethnic background, skin color, hair color, eye color, reaction of skin to sun after at least 2 hours of exposure after first exposure, reaction of skin to sun after repeated exposure, and a composite sun-reaction index. These variables were candidate covariates for the skin neoplasm analyses. Since Blacks were excluded in the analyses of skin neoplasms, they were also excluded in these analyses.

A line connecting San Francisco, California, and Richmond, Virginia, approximates 37 degrees North latitude. Participants were classified into two categories depending on whether their average lifetime residential latitude was above or below 37 degrees North latitude. The determination of each participant's average lifetime residential latitude is discussed in Chapter 7. Under both the minimal and maximal assumptions, the initial dioxin means did not differ significantly between Ranch Hands who resided in the northern latitudes ($\geq$37° N. latitude) and those who resided in the southern latitudes (<37° N. latitude) (minimal, p=0.128; maximal, p=0.247). The current dioxin means also did not differ significantly between the north and the south for all Ranch Hand participants (p=0.596) and for all Comparisons (p=0.786).

For this study, ethnic background was divided into five categories (A: English, Welsh, Scottish, or Irish; B: Scandinavian, German, Polish, Russian, Other Slavic, Jewish, or French; C: Spanish, Italian, or Greek; D: Mexican, American Indian, or Asian; E: African). These five categories were combined into two categories for this analysis (A and B in one category; C, D, and E in the other). Under the minimal assumption, there was a significant difference in the mean initial dioxin levels between these two categories (p=0.022; AB: 179.8 ppt, CDE: 260.4 ppt). The mean initial dioxin levels also differed significantly under the maximal assumption (p<0.001; AB: 116.5 ppt; CDE: 214.8 ppt). For all Ranch Hand participants there was a significant difference in the mean current dioxin levels (p<0.001; AB: 14.0 ppt; CDE: 29.1 ppt), but, for all Comparisons, the difference in the current dioxin means was not significant (p=0.115). For the Ranch Hands, the current dioxin mean was greater for the CDE category, whereas, for the Comparisons, the AB category had the larger current dioxin mean.

There were no significant differences, under either assumption, in the mean initial dioxin levels between Ranch Hands with skin color categorized as peach and those whose skin color was not peach (minimal, p=0.952; maximal, p=0.293). The difference in the mean current dioxin levels was nonsignificant for all Ranch Hand participants (p=0.354) and for all Comparisons (p=0.582).

Under both assumptions, the initial dioxin means were significantly different between Ranch Hands with black or dark brown hair and other Ranch Hands (minimal, p=0.008; maximal, p=0.005). The means, under the minimal assumption, were 196.7 ppt for black or dark brown hair and 158.4 ppt for other hair colors. Under the maximal assumption, the corresponding means were 129.0 and 104.2 ppt. The difference in the current dioxin means was significant for all Ranch Hand participants (p=0.004), but not for all Comparisons (p=0.486). For the Ranch Hands, the current dioxin means were 15.7 ppt (black/dark brown) and 12.2 ppt (other); whereas, for the Comparisons, the current dioxin mean was lower for the black/dark brown hair category than for the other category.

No significant association was found between eye color and initial dioxin under the minimal assumption (p=0.101). However, under the maximal assumption, there was a marginally significant difference in the initial dioxin means among the eye color categories of brown, hazel/green, and grey/blue (p=0.097). The initial dioxin means were 135.4, 113.5, and 114.4 ppt, respectively. For all Ranch Hand participants, the association between eye color and current dioxin was nonsignificant (p=0.103). There was, however, a marginally significant association for all Comparisons (p=0.072). The current dioxin means for the Comparisons were 3.4, 3.4, and 3.9 ppt for the brown, hazel/green, and grey/blue categories.

The reaction of one's skin after at least 2 hours of exposure to the sun, after the first exposure, was not significantly associated with initial dioxin under either assumption (minimal, p=0.720; maximal, p=0.995). There was also no significant association with current dioxin for all Ranch Hand participants (p=0.997). For all Comparisons, however, there was a marginally significant difference in the current dioxin means among the skin reaction categories (p=0.062). The means were 3.5 ppt for Comparisons who reported they experienced no reaction, 3.5 ppt for those who became red, 3.7 ppt for those who burned, and 5.0 ppt for those who burned painfully.

The reaction of one's skin, after repeated exposure to the sun, was not significantly associated with initial dioxin under the minimal assumption (p=0.565). However, under the maximal assumption, there was a marginally significant association (p=0.094). The initial dioxin means were 118.2 ppt for those who reported they tanned deep brown, 113.8 ppt for those who tanned moderately, 149.4 ppt for those who tanned mildly, and 138.1 ppt for those who freckled with no tan. For all Ranch Hand participants, there was no significant association between current dioxin and skin reaction to repeated sun exposure (p=0.507). For all Comparisons, however, the differences in the current dioxin means among the skin reaction categories (tanned deep brown, tanned moderately, tanned mildly, and freckled with no tan) were marginally significant (p=0.088). The current dioxin means were 3.4, 3.8, 3.4, and 5.6 ppt, respectively.

A composite sun-reaction index was formed from the two skin reaction measures and categorized as follows: high (burns painfully and/or freckles with no tan), medium (burns and/or tans mildly), and low (all other reactions). The mean initial dioxin levels for these categories did not differ significantly under both the minimal and the maximal assumptions (minimal, p=0.764; maximal, p=0.319). There were also no significant differences in the mean current dioxin levels for all Ranch Hand participants (p=0.496). However, for all Comparisons, the current dioxin means differed significantly (p=0.008) with means of 3.5, 3.4, and 5.1 ppt for the low, medium, and high sun reaction categories.

EXPOSURE TO CARCINOGENS

Information was gathered on each participant's exposure to 21 different carcinogens. (See Chapter 7 for a discussion of these carcinogens.) These carcinogens were divided into two sets. The first set consisted of asbestos, ionizing radiation, industrial chemicals, herbicides, insecticides, and degreasing chemicals. The other set contained anthracene, arsenic, benzene, benzidine, chromate, coal tar, creosote, aminodiphenyl, chloromethyl ether, mustard gas, naphthylamine, cutting oils, trichloroethylene, ultraviolet light, and vinyl chloride. A composite carcinogen exposure variable was created from the second set. The response was coded as "yes" if the individual had been exposed to any of the 15 carcinogens.

The mean initial dioxin levels did not differ between those Ranch Hands who had been exposed to ionizing radiation and those who had not been exposed (minimal, p=0.118; maximal, p=0.626). There was also no significant difference in the current dioxin means for all Comparisons (p=0.833). However, for all Ranch Hands, there was a marginally significant difference in the current dioxin means between those who had been exposed to ionizing radiation and those who had not been exposed (p=0.070; exposed: 12.3 ppt, not exposed: 15.0 ppt).

Under both the minimal and maximal assumptions, Ranch Hands who had been exposed to industrial chemicals had a significantly higher mean initial dioxin level than those who had not been exposed (minimal, p=0.003; maximal, p<0.001). Under the minimal assumption, the mean initial dioxin levels were 196.8 ppt for those who had been exposed and 157.8 ppt for those who had not been exposed. Under the maximal assumption, the means were 138.8 ppt and 100.0 ppt. Ranch Hand participants who had been exposed to industrial chemicals also had a higher mean current dioxin level than those who had not been exposed (p<0.001; exposed: 16.6 ppt; not exposed: 12.1 ppt). There was also a significant difference for all Comparisons (p=0.043), but the exposed category had a lower current dioxin level mean than the nonexposed category (exposed: 3.4 ppt; not exposed: 3.8 ppt).

Under the minimal assumption, there was a marginally significant difference in the mean initial dioxin levels between Ranch Hands who had been exposed to insecticides and those who had not been exposed (173.0 ppt versus 200.5 ppt; p=0.074). Under the maximal assumption, the difference was not significant (p=0.484). For all Ranch Hand participants and for all Comparisons, the mean current dioxin levels did not differ between the two insecticide exposure categories (Ranch Hands, p=0.391; Comparisons, p=0.430).

Under both assumptions, the Ranch Hands who reported being exposed to degreasing chemicals had a higher mean initial dioxin level than those who had not been exposed (minimal, p=0.001; maximal, p<0.001). The means, under the minimal assumption, were 196.0 ppt for those who had been exposed and 150.5 ppt for those who had not been exposed. Under the maximal assumption, the corresponding means were 137.3 ppt and 94.5 ppt, respectively. The mean current dioxin level was also higher for all Ranch Hand participants who reported exposure to degreasing chemicals than for those who reported no exposure (17.1 ppt versus 10.9 ppt; p<0.001). For all Comparisons, the difference was nonsignificant (p=0.926).

For the other two carcinogens in the first set (asbestos and herbicides), no significant differences in the initial dioxin means were found between the exposed category and the nonexposed category, under both assumptions. There were also no significant differences in the current dioxin means for all Ranch Hands and all Comparisons (see Table 5-1 for the associated significance probabilities).

There was no significant difference, under the minimal assumption, between the initial dioxin mean for those who had been exposed to benzene and the initial dioxin mean for those who had not been exposed (p=0.201). However, under the maximal assumption, those who had been exposed to benzene had a marginally higher initial dioxin mean than those who had not been exposed (162.6 ppt versus 118.4 ppt; p=0.089). The current dioxin means did not differ significantly for all Ranch Hand participants and for all Comparisons (Ranch Hands, p=0.522; Comparisons, p=0.893).

Ranch Hands who had been exposed to chromate had a marginally higher initial dioxin mean, under the minimal assumption, and a significantly higher initial dioxin mean, under the maximal assumption, than those who had not been exposed (minimal, p=0.057; maximal, p=0.034). The means under the minimal assumption were 232.5 ppt for the exposed category and 176.6 ppt for the nonexposed category. Under the maximal assumption, the corresponding means were 159.2 ppt and 117.5 ppt, respectively. For all Ranch Hand participants and for all Comparisons, the current dioxin means did not differ significantly (Ranch Hands, p=0.160; Comparisons, p=0.593).

The mean initial dioxin levels differed significantly between Ranch Hands who had been exposed to aminodiphenyl and those who had not been exposed, under both assumptions (minimal, p<0.001; maximal, p<0.001). Those who had been exposed had a lower mean than those who had not been exposed (minimal, 83.2 ppt versus 180.5 ppt; maximal, 83.2 ppt versus 119.9 ppt). For all Ranch Hand participants and for all Comparisons, the mean current dioxin levels did not differ significantly (Ranch Hands, p=0.998; Comparisons, p=0.649). However, there were only two Ranch Hand participants and four Comparisons who had been exposed to aminodiphenyl.

Under the minimal assumption, there was no significant difference between the initial dioxin mean for Ranch Hands who had been exposed to chloromethyl ether and the mean for those who had not been exposed (p=0.648). Under the maximal assumption, the difference was marginally significant (p=0.070). The means were 65.4 ppt for those who reported being exposed to chloromethyl ether and 120.5 ppt for those who reported no exposure. There were, however, only three Ranch Hands in the minimal cohort and eight in the maximal cohort who had been exposed to chloromethyl ether. The current dioxin means for the two exposure categories did not differ significantly for all Comparisons (p=0.267), but did differ significantly for all Ranch Hand participants (p=0.015; exposed: 6.0 ppt, not exposed: 14.5 ppt).

Under the maximal assumption, the mean initial dioxin level for those Ranch Hands who had been exposed to naphthylamine was significantly higher than for those who had not been exposed (179.5 ppt versus 118.2 ppt; p=0.028). The difference was not significant under the minimal assumption (p=0.249). For all Ranch Hand participants and for all Comparisons, there was no significant difference between the naphthylamine exposure categories (Ranch Hands, p=0.217; Comparisons, p=0.759).

Under both assumptions, there was no significant difference in the initial dioxin means for Ranch Hands who were exposed to cutting oils and those who were not (minimal, p=0.706; maximal, p=0.924). There was also no significant difference in the current dioxin means for all Ranch Hand participants (p=0.693). For all Comparisons, however, the current dioxin mean was marginally lower for those who had been exposed to cutting oils than for those who had not been exposed (3.0 ppt versus 3.7 ppt; p=0.076).

Ranch Hands in the maximal cohort who had been exposed to trichloroethylene had a marginally higher initial dioxin mean than those who had not been exposed (142.4 ppt versus

117.3 ppt; p=0.092). The difference was not significant under the minimal assumption (p=0.170). There was also no significant difference in the current dioxin means for all Ranch Hand participants and for all Comparisons (Ranch Hands, p=0.547; Comparisons, p=0.386).

With respect to the remaining carcinogens in the second set (anthracene, arsenic, benzidine, coal tar, creosote, mustard gas, ultraviolet light, and vinyl chloride), the initial dioxin means did not differ significantly between the exposed and nonexposed categories. Similarly, for all Ranch Hand participants and all Comparisons, the current dioxin means were not significantly different between the exposed and nonexposed categories. Table 5-1 presents the associated significance probabilities.

For the composite carcinogen exposure variable, under the minimal assumption, there was no significant difference between the initial dioxin mean of the exposed category and the initial dioxin mean of the nonexposed category (p=0.209). Under the maximal assumption, those Ranch Hands who had been exposed to any of the carcinogens in the second set had a significantly higher initial dioxin mean than those who had not been exposed (134.2 ppt versus 114.7 ppt; p=0.045). The mean current dioxin level was also significantly higher for all Ranch Hands who had been exposed, as compared to those who had not been exposed (16.4 ppt versus 13.6 ppt; p=0.038). In contrast, for all Comparisons, those who had not been exposed to any of the carcinogens had a higher current dioxin mean (3.6 ppt) than those who had been exposed (3.3 ppt), but the difference was not significant (p=0.157).

PERSONAL AND FAMILY HEALTH

The personal health covariates used in this study were cholesterol, high-density lipoprotein (HDL), cholesterol-HDL ratio, diabetic class, differential cortisol response, and percent body fat. Family health was also taken into account by means of family history of heart disease and family history of heart disease before the age of 50. No participants were excluded from the association analyses for these variables.

The correlation between cholesterol and initial dioxin was not significant under either assumption (minimal, p=0.217; maximal, p=0.215). The differences in the initial dioxin means for the three cholesterol categories (≤200 mg/dl; >200-230 mg/dl; >230 mg/dl) were also nonsignificant under both assumptions (minimal, p=0.227; maximal, p=0.362). For all Ranch Hand participants and for all Comparisons, the correlation between current dioxin and cholesterol was not significant (Ranch Hands, p=0.137; Comparisons, p=0.196). The current dioxin means also did not differ significantly among the cholesterol categories (Ranch Hands, p=0.175; Comparisons, p=0.139).

Under the minimal assumption, there was a marginally significant negative correlation between HDL and initial dioxin (p=0.090). However, the initial dioxin means for the three HDL categories (≤40 mg/dl; >40-50 mg/dl; >50 mg/dl) did not differ significantly (p=0.400). Under the maximal assumption, there was a significant negative correlation between HDL and initial dioxin (p<0.001), and the differences in the initial dioxin means among the HDL categories was also significant (p<0.001; ≤40 mg/dl: 138.6 ppt; >40-50 mg/dl: 121.7 ppt; >50 mg/dl: 99.6 ppt). The correlation between current dioxin and HDL was significant for all Ranch Hand participants (p<0.001) and for all Comparisons (p=0.005). The mean current dioxin levels also differed significantly among the HDL categories for both groups (Ranch

Hands, p<0.001; Comparisons, p=0.008). For all Ranch Hand participants, the means were 17.5, 14.5, and 11.6 ppt for the HDL categories (≤40 mg/dl, >40-50 mg/dl, and >50 mg/dl). For all Comparisons, the corresponding means were 3.9, 3.7, and 3.1 ppt, respectively.

The results for the cholesterol-HDL ratio were similar, but in the opposite direction, to the HDL results. Under the minimal assumption, there was a marginally significant positive correlation between initial dioxin and the cholesterol-HDL ratio (p=0.076), but the initial dioxin means did not differ significantly among the cholesterol-HDL categories (p=0.104). Under the maximal assumption, there was a significant correlation between initial dioxin and the cholesterol-HDL ratio (p<0.001) and there was a significant difference in the initial dioxin means (p<0.001; ≤4.2: 97.0 ppt; >4.2-5.5: 124.5 ppt; >5.5: 139.3 ppt). For all Ranch Hand participants and for all Comparisons, there was a significant positive correlation between current dioxin and the cholesterol-HDL ratio (Ranch Hands, p<0.001; Comparisons, p=0.002). The current dioxin means for the cholesterol-HDL categories also differed significantly for both groups (Ranch Hands, p<0.001; Comparisons, p=0.001). For the cholesterol-HDL ratio categories (≤4.2, >4.2-5.5, and >5.5), the current dioxin means were 11.3, 15.2, and 17.2 ppt for the Ranch Hands and 3.0, 3.9, and 3.9 ppt for the Comparisons.

Under the minimal assumption, there was a marginally significant difference in the mean initial dioxin levels for Ranch Hands classified as normal, impaired, and diabetic (p=0.095). The mean initial dioxin levels were 174.4, 176.2, and 221.9 ppt for the normal, impaired, and diabetic classes. Under the maximal assumption, the mean initial dioxin levels differed significantly among the three diabetic classes (p=0.001; normal: 112.8 ppt; impaired: 123.7 ppt; diabetic: 169.9 ppt).

For all Ranch Hand participants, a significant difference in the mean current dioxin levels was exhibited among the three diabetic classes (p=0.001). The means were 13.5, 14.8, and 21.9 ppt for the normal, impaired, and diabetic classifications. For all Comparisons, there was also a significant difference in the mean current dioxin levels for the three diabetic classes (p=0.028). The means were 3.4, 4.0, and 4.5 ppt, respectively.

The correlation between initial dioxin and differential cortisol response was not significant under either the minimal or maximal assumptions (minimal, p=0.583; maximal, p=0.112). However, the differences in the initial dioxin means among the differential cortisol response categories (≤0.6 µg/dl; >0.6-4.0 µg/dl; >4.0 µg/dl) were marginally significant under the minimal assumption (p=0.056) and significant under the maximal assumption (p=0.007). The initial dioxin means were 191.7, 189.0, and 155.5 ppt under the minimal assumption and 132.0, 127.5, and 101.4 ppt under the maximal assumption. For all Ranch Hand participants, there was a significant negative correlation between current dioxin and differential cortisol response (p=0.027) and a significant difference in the current dioxin means among the differential cortisol response categories (p<0.001; ≤0.6 µg/dl: 15.7 ppt; >0.6-4.0 µg/dl: 16.4 ppt; >4.0 µg/dl: 11.5 ppt). For all Comparisons, neither the correlation between current dioxin and differential cortisol response (p=0.152) nor the difference in the current dioxin means among the differential cortisol response categories (p=0.315) was significant.

Percent body fat and initial dioxin exhibited a significant positive correlation under both assumptions (minimal, p=0.001; maximal, p<0.001). There was also a significant positive correlation between percent body fat and current dioxin for all Ranch Hand participants and for all Comparisons (Ranch Hands, p<0.001; Comparisons, p<0.001).

Under both the minimal and maximal assumptions, Ranch Hands who had been classified as obese had a significantly higher mean initial dioxin level than those who had been classified as normal or lean (minimal, p=0.018; maximal, p<0.001). The means, under the minimal assumption, were 211.4 ppt for the obese category and 170.4 ppt for the normal/lean category. Under the maximal assumption, the corresponding means were 161.1 ppt and 110.2 ppt, respectively. Similarly, for current dioxin levels, all Ranch Hands who had been classified as obese had a higher mean current dioxin level than those who had been classified as normal or lean (p<0.001; obese: 22.4 ppt; normal/lean: 12.9 ppt). The mean current dioxin level for all Comparisons who had been classified as obese was also higher than the mean for all Comparisons who had been classified as normal or lean (p<0.001; obese: 4.4 ppt; normal/lean: 3.3 ppt).

Under both the minimal and the maximal assumptions, there was no significant association between initial dioxin and either family history of heart disease (minimal, p=0.793; maximal, p=0.867) or family history of heart disease before the age of 50 (minimal, p=0.979; maximal, p=0.515). For all Ranch Hand participants and for all Comparisons, the association with current dioxin was also nonsignificant for family history of heart disease (Ranch Hands, p=0.591; Comparisons, p=0.765) and for family history of heart disease before the age of 50 (Ranch Hands, p=0.970; Comparisons, p=0.134).

OTHER CHARACTERISTICS

The relationship with initial and current dioxin was also examined for education, blood type, presence of pre-Southeast Asia (SEA) acne, and personality type.

Ranch Hands with only a high school education had a significantly higher mean initial dioxin level than those with a college education, under both assumptions (minimal, p=0.001; maximal, p<0.001). Under the minimal assumption, the means were 198.0 ppt and 153.4 ppt for the high school and college categories. Under the maximal assumption, the means were 153.1 ppt and 89.8 ppt, respectively. The mean current dioxin level for all Ranch Hand participants with only a high school education was significantly greater than the mean for all Ranch Hand participants with a college education (18.2 ppt versus 11.1 ppt; p<0.001). For all Comparisons, the college graduates had a larger current dioxin mean than those with only a high school education, but the difference was not significant (p=0.378).

No significant differences in the mean initial dioxin levels were found among the four blood types (A, B, AB, and O) under either the minimal or the maximal assumption (minimal, p=0.973; maximal, p=0.593). For all Ranch Hand participants and for all Comparisons the differences in the mean current dioxin levels among the four blood types were also nonsignificant (Ranch Hands, p=0.773; Comparisons, p=0.469).

Under the minimal and maximal assumptions, the initial dioxin mean for the Ranch Hands with acne prior to their first SEA tour was not significantly different from the mean for those without acne before their first SEA tour (minimal, p=0.523; maximal, p=0.309). The current dioxin means also did not differ significantly between the Ranch Hand participants with pre-SEA acne and those without (p=0.819) nor between the Comparisons with and without pre-SEA acne (p=0.246).

Under the minimal assumption, the mean initial dioxin levels for individuals classified as either type A or type B (by the Jenkins Activity Survey administered at the 1985 followup examination) were not significantly different (p=0.401). However, under the maximal assumption, the mean initial dioxin levels for Ranch Hands classified as type A (112.3 ppt) and Ranch Hands classified as type B (128.3 ppt) were marginally different (p=0.061). For all Ranch Hand participants, the difference in the mean current dioxin levels between type A and type B individuals was not significant (p=0.148). For all Comparisons, there was also no significant difference in the mean current dioxin levels (p=0.685).

SUMMARY

Among the matching variables, age and occupation exhibited a significant association with dioxin in one direction for Ranch Hands and in the opposite direction for Comparisons. Age had a negative correlation with initial dioxin for Ranch Hands under the minimal and maximal assumptions and a negative correlation with current dioxin for all Ranch Hands; whereas, for all Comparisons, age and current dioxin were positively correlated. In the analysis of occupation, the dioxin means were greatest for Ranch Hands in the enlisted groundcrew, but for Comparisons, the officers had the greater dioxin means, although all Comparison means were below generally accepted background levels (10 ppt).

For most of the alcohol variables, a significant association was exhibited with initial dioxin for the minimal and maximal cohorts, and with current dioxin for all Ranch Hands. However, for all Comparisons, the association with current dioxin was not significant. For Ranch Hands, the correlations between alcohol use and dioxin, when significant, tended to be negative.

For both smoking variables (current cigarette smoking and lifetime cigarette smoking history), the current dioxin means differed significantly among the smoking categories for all Comparisons. In both cases the correlation between smoking and dioxin was negative. In contrast, for the minimal and maximal cohorts and for all Ranch Hands, the dioxin means did not differ significantly.

The only sun exposure-related variables that had a significant association with dioxin were ethnic background and hair color for Ranch Hands and the composite sun reaction index for Comparisons.

In the analyses of the carcinogen exposure variables—degreasing chemicals, chromate, and naphthylamine—the exposed category had a higher dioxin mean than the nonexposed category, when the dioxin means differed significantly. In the analyses of aminodiphenyl and chloromethyl ether, the nonexposed category had a higher mean than the exposed category. Ranch Hands (including those in the minimal and maximal cohorts and all Ranch Hands) who had been exposed to industrial chemicals had higher dioxin means than those who had not been exposed; whereas, Comparisons who had been exposed to industrial chemicals had a lower dioxin mean than those who had not been exposed. For the composite carcinogen exposure variable, Ranch Hands with an affirmative response had a higher dioxin mean than those who had not been exposed to any of the 15 specific carcinogens.

Among the personal and family health variables, percent body fat and the cholesterol-HDL ratio showed a significant positive correlation with dioxin for Ranch Hands and Comparisons, and HDL showed a significant negative correlation with dioxin. For both Ranch Hands and Comparisons, diabetic class also exhibited a significant association with dioxin, in which the dioxin means were greatest for the diabetic category.

Education was the only other variable to be significantly associated with dioxin. This association, in which college graduates had a lower dioxin mean than high school graduates, was only significant for Ranch Hands.

CONCLUSION

Many of the significant associations between dioxin and the covariates in the Ranch Hand group can be attributed to an indirect effect of occupational rank, which is highly associated with current serum levels of dioxin. For example, the decreasing relationship between age and dioxin occurred because enlisted groundcrew, who have the highest current dioxin levels of the Ranch Hands, were also the youngest occupational category, while officers, who have the lowest levels, were the oldest occupational category. Adjusting for occupation, the association between dioxin and age became nonsignificant under both the minimal (p=0.138) and maximal (p=0.712) assumptions. By contrast, the reason for the significant positive association with age in the Comparison group is not as apparent, but may be due to accumulation of normal background levels with time.

Significant associations in the Ranch Hand group between dioxin and education, industrial chemical exposure, degreasing chemical exposure, and wine consumption can also be explained by occupational differences (officers were more likely to be college educated, less likely to have been exposed to industrial or degreasing chemicals, and more likely to drink wine than the enlisted personnel). As with age, these associations (except for lifetime wine consumption under the minimal assumption) became nonsignificant after adjusting for occupation.

More difficult to understand are the associations in the Comparison group between current levels of dioxin with several of the covariates. Most of the Comparison group are assumed to have background levels (97.8% are less than 10 ppt) and there is no obvious related factor (such as occupation) that could explain the associations. Of the 51 covariates (discrete and continuous versions counted as one), 9 were significant at or below the 0.05 level. By chance alone, one would expect about two significant associations. The interrelatedness of some of the covariates may have inflated the number of significant results observed. Most of the significant associations were for the health variables (HDL, cholesterol-HDL ratio, diabetes, and percent body fat) that were also associated significantly with dioxin in the Ranch Hand group.

CHAPTER 5

REFERENCES

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CHAPTER 6
GENERAL HEALTH ASSESSMENT

INTRODUCTION

Background

Most of the published reports on the effects of herbicides on human health have been based on studies of Vietnam veterans and on civilian populations exposed to trichlorophenols by occupation or as a consequence of industrial accidents. Though potentially lethal effects of extreme phenoxyherbicide intoxication recently have been reported (1, 2), the long-term health effects of low-dose exposure remain uncertain.

In laboratory animals, dioxin toxicity is species- and strain-specific and appears to correlate with the presence of the "Ah receptor," a stereospecific protein receptor found in the cytosol of selected organs capable of binding aromatic hydrocarbons (3-7). Though the relevance of these observations to dioxin toxicity in humans remains to be proven, epidemiologic studies nonetheless have focused on biologic endpoints that have been defined in animal models including immunotoxicity, carcinogenicity, genetic/reproductive outcomes, hepatotoxicity, and neurotoxicity. Each of these are considered in detail in subsequent chapters or in other reports from the Air Force Health Study (AFHS).

Prior to the AFHS serum dioxin analysis, the inability to estimate dioxin exposure accurately has led to criticism and caution in the interpretation of all previous studies on the effects of herbicides on human health. Techniques have been developed that permit the accurate detection of minute (in parts per trillion) amounts of dioxin in humans, first in adipose tissue (8, 9, 10), and more recently, in blood (11, 12). Based on the serum dioxin level, the current body burden can thus be determined and, employing a half-life of 7.1 years (13), the extent of past exposure can be estimated objectively.

The importance of the serum dioxin assay to this and other epidemiologic studies cannot be overemphasized. The Centers for Disease Control (CDC) study of serum dioxin levels in Vietnam veterans established that previously employed indices of exposure based on military records were invalid and, secondly, that there was no significant difference between Vietnam and non-Vietnam veterans in the current body burden of dioxin when military records were used as the basis for determining exposure (14). Several preliminary reports on the levels of serum dioxin in AFHS participants have been published (15-18). These studies leave no doubt that, of the close to 3 million members of the armed forces who served in Southeast Asia (SEA), the 1,300 Ranch Hand personnel were among those most highly exposed to dioxin and that, within this group, the enlisted groundcrew responsible for handling the herbicide and maintaining the herbicide spray equipment were most exposed.

In addition to the first examination report of the current study (19), the results of several investigations have been reported focusing on the incidence of selected cancers in veterans (20, 21). From these results, the CDC Selected Cancer Study established a link between Vietnam experience and an increased risk of non-Hodgkins lymphoma (22) and the

AFHS found an increased risk of basal cell skin cancer among Ranch Hands. None of the results established a link between herbicide exposure and malignant disease.

As summarized in the comprehensive literature reviews of Clement and Associates (23, 24), two large-scale epidemiologic studies were published in 1988 that are pertinent to the general health of Vietnam veterans (25-28). The largest of these and the most methodologically sound was the Vietnam Experience Study (VES), which compared the psychosocial (29), physical (30), and reproductive (31) health of close to 20,000 veterans, half of whom served in SEA. Of interest, the Agent Orange component of the VES was canceled when, based on preliminary serum dioxin data from veterans, it became clear that previously employed indices of herbicide exposure in ground troops were invalid and that there was no significant difference between Vietnam and non-Vietnam veterans in the current body burden of dioxin (14) when military records were used to determine the likelihood of individual exposure.

The published results of the VES are similar to other studies. Vietnam veterans perceived themselves to be in worse health than non-Vietnam veterans but data from the medical examination failed to reveal any significant health detriment apart from combat-related hearing loss (30). Semen analysis revealed minor differences in the cohorts with no detectable effect on reproductive outcomes (31). There was a significantly increased incidence of psychological disorders in the Vietnam veterans including depression, anxiety disorders, drug/alcohol abuse, and combat-related post-traumatic stress disorder (29). Consistent with a large-scale, all-cause mortality study of Wisconsin veterans (32), there was no significant difference in overall mortality detected between the cohorts (33).

The second study, the American Legion Study (26, 27, 28), attempted to compare the general health and potential effects of herbicide exposure in 6,810 American Legion veterans, 42 percent of whom served in Vietnam. Design limitations in this study are such that few conclusions can be drawn beyond that, in self-reported questionnaires, Vietnam veterans perceive themselves to be in worse health than non-Vietnam veterans. Furthermore, given the evidence cited above (14) that most Vietnam and non-Vietnam veterans do not differ in the current body burden of dioxin, the exposure indices employed in this study must now be considered invalid.

More detailed summaries of the pertinent scientific literature for the general health assessment can be found in the report of the previous analyses of the 1987 examination data (34).

Summary of Previous Analyses of the 1987 Examination Data

The general health in the Ranch Hand and Comparison groups was assessed by five measures (self-perception of health, appearance of illness or distress, relative age, percent body fat, and the erythrocyte sedimentation rate [ESR]). There were no significant group differences, either unadjusted or adjusted for covariates (age, race, occupation, and, in the case of self-perception of health and sedimentation rate, personality type), nor any significant group-by-covariate interactions for self-perception of health, appearance of illness or distress, relative age, or percent body fat. There was little difference in the geometric mean values of ESR in the two groups, but the Ranch Hand group had a significantly higher percentage of individuals with an abnormal sedimentation rate (>20 mm/hr) than the Comparisons. However, only three participants (two Ranch Hands and one Comparison) were found to have rates in excess of 100 mm/hr. One participant (a Comparison) proved to have lung cancer and died in early 1989. For neither of the two Ranch Hands was a diagnosis established during the course of the 1987 examination. Longitudinal analyses revealed a similar decline in both groups over time in the percentage of individuals reporting their health as fair or poor. For sedimentation rate, there was a significant difference between groups in the change from Baseline to the 1987 followup examination, with a relatively greater number of Ranch Hands than Comparisons shifting from normal at Baseline to abnormal at the followup examination. The clinical meaning of this observation is unknown.

Parameters of the General Health Assessment

Dependent Variables

The serum dioxin analysis general health assessment was based on data from the 1987 questionnaire, physical examination, and laboratory examination data. The variables analyzed were identical to those in the 1982 and 1985 examinations.

Questionnaire Data

During the questionnaire health interview, each study participant was asked, "Compared to other people your age, would you say your health is excellent, good, fair, or poor?" This self-reported perception was analyzed as a measure of the general health status of each participant, though susceptible to varying degrees of conscious and subconscious bias. This variable was dichotomized as excellent/good and fair/poor for statistical analyses.

No participants were excluded for medical reasons from the analysis of this variable.

Physical Examination Data

Three variables derived from the physical examination were analyzed in the assessment of general health. The physician at the examination recorded the appearance of illness or distress (yes/no) of the study participant. The physician also noted the appearance of the subject as younger than, older than, or the same as his stated age. To the degree that the examining physicians were kept blind to the participant's group membership, these assessments were less subject to bias than the self-perception of health.

Percent body fat, a measure of the relative body mass of an individual and calculated from height and weight recorded at the physical examination, was also analyzed. Percent body fat was calculated from a metric body mass index (35); the formula was

$$\text{Percent Body Fat} = \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2} \times 1.264 - 13.305.$$

This variable was analyzed in both the discrete and continuous forms. For purposes of discrete analyses, percent body fat was dichotomized as lean/normal (≤25 percent) and obese (>25 percent). Lean participants were analyzed with normal participants due to the sparse number of people in this study considered lean (<1%). This variable does not reflect changes in weight since service in SEA.

No participants were excluded for medical reasons from the analyses of these three variables.

Laboratory Examination Data

The ESR (mm/hr), measured at the laboratory examination, was analyzed. Although nonspecific, a high sedimentation rate is a generally accepted indicator of an ongoing disease process. This variable was analyzed in both the discrete and continuous forms. The logarithmic transformation was used to enhance statistical normality for continuous analyses.

No participants were excluded for medical reasons from the analysis of this variable.

Covariates

The effects of the covariates age, race, and personality type were examined in the assessment of general health in adjusted statistical analyses. Age and race were used for analyses with all dependent variables. Age was used in its continuous form for all adjusted analyses. Personality type was used in the analysis of self-perception of health and sedimentation rate only. Personality type was determined from the Jenkins Activity Survey administered during the 1985 followup examination. This variable was derived from a discriminant-function equation based on questions that best discriminate men judged to be type A from those judged as type B (36). Positive scores reflect the type A direction and negative scores the type B direction. Personality type was dichotomized as type A and type B for all analyses. Because the Jenkins Activity Survey was not administered at the 1987 followup examination, participants at the 1987 followup examination who had not attended the 1985 followup examination had missing information for personality type.

Relation to Baseline, 1985, and 1987 Studies

As noted above, the same variables were analyzed for the serum dioxin analysis as for the Baseline, 1985, and 1987 studies.

For longitudinal analyses, sedimentation rate was analyzed as a discrete variable. The normal range for sedimentation rate for the Baseline examination was less than or equal to 12 mm/hr; the Scripps Clinic and Research Foundation (SCRF) normal range for sedimentation rate for the 1987 examination was less than or equal to 20 mm/hr. Self-perception of health was also analyzed in the longitudinal analyses.

Statistical Methods

Chapter 4, Statistical Methods, describes the basic statistical analysis methods used in this chapter.

Table 6-1 summarizes the statistical analyses performed for the general health assessment. The first part of this table describes the dependent variables, the source of the data used for the analysis, the form(s) of the data (discrete and/or continuous), and cutpoints.

TABLE 6-1.

Statistical Analysis for the General Health Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Self-Perception of Health	Q-SR	D	Fair/Poor Excellent/Good	AGE,RACE, PERS	U:LR A:LR L:LR
Appearance of Illness or Distress by Physician	PE	D	Yes No	AGE,RACE	U:LR A:LR
Relative Age	PE	D	Older Same/Younger	AGE,RACE	U:LR A:LR
Percent Body Fat	PE	D/C	Obese: >25% Lean/Normal: ≤25%	AGE,RACE	U:LR,GLM A:LR,GLM
Sedimentation Rate (mm/hr)	LAB	D/C	Abnormal: >20 Normal: ≤20	AGE,RACE, PERS	U:LR,GLM A:LR,GLM L:LR

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Personality Type (PERS)	PE (1985)	D	A Direction B Direction

TABLE 6-1. (Continued)

Statistical Analysis for the General Health Assessment

Abbreviations

Data Source:	LAB--1987 SCRF laboratory results MIL--Air Force military records PE (1985)--1985 SCRF physical examination PE--1987 SCRF physical examination Q-SR--1987 NORC questionnaire (self-reported)
Data Form:	D--Discrete analysis only D/C--Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates
Statistical Analyses:	U--Unadjusted analyses A--Adjusted analyses L--Longitudinal analyses
Statistical Methods:	GLM--General linear models analysis LR--Logistic regression analysis

This table also presents candidate covariates examined in adjusted analyses. To conserve space, abbreviations are used extensively in the body of the table and are defined in footnotes.

The second part of this table provides a further description of candidate covariates. Standard abbreviations for these variables, which will be used subsequently in this chapter, are presented, as well as data source, data form, and cutpoints.

Table 6-2 provides a list of the number of participants with missing data for the dependent variables and covariates described in Table 6-1.

Appendix E contains graphic displays of individual dependent variables versus initial dioxin for the minimal and maximal Ranch Hand cohorts, and individual dependent variables versus current dioxin for Ranch Hands and Comparisons. Appendix E also presents graphics for dioxin-by-covariate interactions determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

Three statistical analysis approaches were used to examine the association between a health status dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (34). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

RESULTS

Exposure Analysis

Questionnaire Variable

Self-Perception of Health

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

An unadjusted analysis revealed no significant association between self-perception of health and initial dioxin under the minimal assumption (Table 6-3 [a]: p=0.471). Under the maximal assumption, the estimated relative risk was of borderline significance (Table 6-3 [b]: p=0.058, Est. RR=1.23). Under the maximal assumption, the associated relative frequencies for a fair or poor self-perception of health at low, medium, and high initial dioxin levels were 4.9, 5.9, and 7.0 percent.